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Epidemiologie, Begleitsymptome und Familienhistorie von Brustwanddeformitäten im Kindesalter

Dissertation

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– For my parents –

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1. Introduction

1.1 General

This doctoral thesis is about deformities of the anterior chest wall. It focuses on three isolated forms of chest wall deformities (CWDs), including pectus excavatum (PE), pectus carinatum (PC) and cleft sternum (SC). They are caused by malformation of osseous and cartilaginous structures. This work examines their epidemiology, demographics, concomitant clinical features, associated comorbidities, and family history. Analysis of family history extends to chest wall, spine, and connective tissue disorders. The dissertation is based on a retrospective clinical study with patients recruited from the children's hospital of the University Medical Center Hamburg Eppendorf (Kinder UKE) and the Altona Children's Hospital (AKK).

CWDs are common, but present in a wide phenotypic spectrum. They can be classified into two major classes: isolated and syndromic. Syndromic CWDs are present in a minority of cases.[3] There are a variety of different syndromes associated with CWDs (Tables 11-16 in the appendix). For example, there are: Marfan, Noonan, Loeys-Dietz, Poland, Moebius, Cantrell, and PHACE syndrome.[5] This research aims to find out whether signs of syndromic PE are also present in isolated CWD. In some of these syndromes (e.g., Marfan, Noonan, or Loeys-Dietz syndrome), different CWDs such as PE and PC co-occur. CT imaging studies have compared the sternal curvature pattern in CWDs. They showed similar sternal curvature abnormalities in PE and PC.[6] Both of these findings suggest that the pathological mechanisms for PE and PC are inter-connected. There are several research groups that assume the genes causing both diseases are identical, but their quantitative expression is critical to whether patients develop PE or PC.[7,8] This study aims to support such ideas of a common cause. It attempts to prove the accumulation of different CWD phenotypes within families.

The majority of CWD cases involve isolated CWDs. Even though etiology is largely unknown, there are only a few research groups focused on that topic. The current evidence gathered in families with isolated chest wall anomalies suggests that they are characterized as a genetic disorder.[9,10] However, there are several limitations in such evidence. Those limitations are: large variability in results between different papers, not based on large-scale population, and quality issues such as syndromic forms that were not thoroughly ruled out.[5,9,11,12] There is also a limitation in the information gathering phase. It exists because the affected relatives of CWD patients are not recorded in patient files. Specifically, those with mild phenotypes are rarely registered. This can be related to the lack of time, motivation, and resources at the medical institutes. Overall, the underlying inheritance pattern of isolated CWD is debatable.[5,11] Skewed ratios of males to females have been observed. Despite that, there has bee no identifiable gene linked to the X or Y chromosome.[13] This work is designed to characterize such an imbalance between the sexes more precisely. The large study population of this doctoral thesis provides

many pedigrees. They help clarify the heritability of isolated CWD. There has been not much research conducted on causative mutations in isolated deformities.[11] The experiments in mice have shown that G protein-coupled receptor 126 (*Gpr126*) gene mutations are important in PE formation. This gene is also found in humans. GPR126 binds collagen V and the collagen-like glycoprotein laminin. It is associated with hypersulfation.[14] Honke and Taniguchi[15] studied the sulfation of proteoglycans. They showed that sulfation is critical to the normal development of cartilage and bone, which suggest that it may play a role in the pathogenesis of CWDs. Various enzymes and transporters are involved in the formation and degradation of such sulfate esters. These include sulfurylase kinase (SK)1 and SK2. *SK* genes result in the expression of transmembrane transporters of sulphate. They also result in the expression of enzymes that synthesize phosphoadenosine phosphosulfate (PAPS). PAPS is responsible for the development of the postnatal skeletal and cartilage matrix. There are various hereditary skeletal deformities caused by *SK1* and *SK2* mutations.[15-17] The aim of this study is to identify candidate genes for isolated CWD by analyzing clinical features of target population.

1.2 Structure and biology of cartilage and bone matrix

Ribs and sternum develop by differentiation of mesenchymal cells into hyaline cartilage, which consists mainly of an extracellular matrix with sparsely distributed chondrocytes in between. The extracellular matrix of hyaline cartilage contains collagen II and proteoglycans such as aggrecan, decorin, and biglycan (Fig. 1). Subsequently, endochondral ossification occurs. The ossification process of the ribs and sternum begins in the ninth gestational week. It continues until the age of 28.[19] The extracellular matrix of bones is composed of collagen type I, minerals, osteocalcin, and osteopontin.

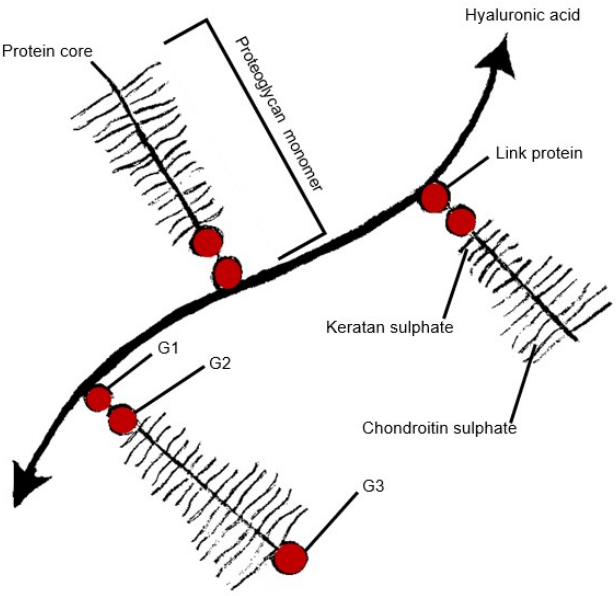


Fig. 1 Extracellular matrix components of rib cartilage including proteoglycans[18]

Crucial molecules in this differentiation process are: Sox proteins, BMP, TGFβ, RUNX2, Hox proteins, TIMP1, PDK1, FGF, AKT1, PBX1, CGRP, alkaline phosphatase, and calcitonin. The PTH/PTHrP signalling, TSH/T3 axis, and hedgehog signaling are also important.[20-30]

Ribs have a large inter-individual, -age and -gender dependent variability. This is shown by evidence of different ossification patterns, length, and angulation of ribs. The composition of collagen and proteoglycan also changes with age.[31-36]

Anterior CWDs involve abnormal patterns of cartilage growth and endochondral ossification.[37] Incomplete fusion of sternal bars or maldevelopment of ossification centers can lead to sternal defects.

1.2 Pectus excavatum

Pectus excavatum, also called funnel chest, is the most common CWD.[4,13] It occurs in about 1:300 to 1:400 children.[8,10] Mild CWD phenotypes that do not necessarily require surgical correction can occur in up to 1:100 Germans [38]. Male to female ratios for PE reported so far are 3:1 and 4:1.[8,9,11,13,39-41] Mild phenotypes in females would explain such extreme underrepresentation. Studies indicate that females with mild phenotypes avoid doctor visits.[42,43] PE is a common congenital anomaly, but also can occur later in childhood.[8,44] There are different opinions on the age of manifestations. Historically, this medical condition was considered congenital. Later, it was observed that it was present in only a minority of patients at birth. Its progression in infancy and childhood is low. Therefore, PE is rare in the first decade of life. It tends to become prominent during the teenage growth spurt. This is paralleled by the accelerated bone growth and cartilage growth.[10,13,41]

PE shows a variable phenotypic manifestation. It ranges from mild to severe. The severity can be quantified by the Haller index.[45] This disorder involves developmental abnormalities of the sternum and adjacent costal cartilage that cause a concave intrusion of the anterior chest wall.[4] It can also be associated with rib hypoplasia, which results in a smaller hemithorax.[8] Four distinct types of phenotypic manifestations have been declared (Fig. 2). The associated narrowing of the sternovertebral space can lead to pulmonary and cardiac compression (Fig. 3).[46] Our study quantifies cardiopulmonary dysfunction in CWD.

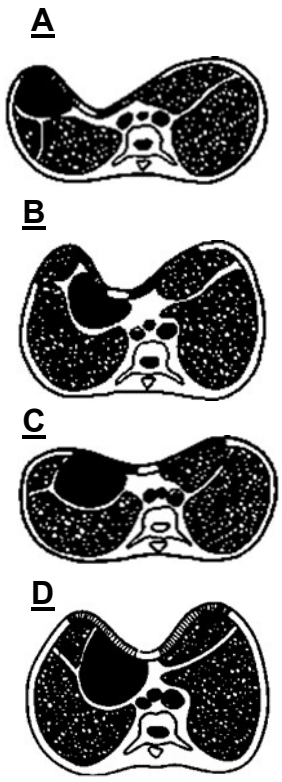


Fig. 2 Phenotypes of PE[47]
A: Flat asymmetric chest
B: Asymmetric chest
C: Flat symmetric chest
D: Symmetric chest

Therea are various theories about the pathophysiology of PE, which have been developed. In the past, researchers suspected non-genetic causes. Eggel[48] suggested weakness of the anterior chest wall as the cause. He claimed underlying malnutrition or developmental failure. Rickets was assumed as a possible cause by Kelley.[49] At the beginning of the twentieth century, another leading theory was intrauterine pressure on the sternum. Schmaus and Herxheimer[50] claimed that oligohydramnios led to compression of the sternum by the chin. A less common theory involved maldevelopment of the diaphragm and post-sternal bands. Excessive diaphragmatic traction was thought to pull the anterior chest wall inward.[51-53] Recent studies reported iatrogenic PE after sternotomy for cardiothoracic surgery.[54]

A common pathological mechanism to explain sternal deviation is tissue overgrowth. It is thought to occur in the cartilage connecting the ribs to the sternum. Typically, four to five ribs in the parasternal region are affected. There is a lack of space for overgrowth in the coronary plane. This causes an inversion or eversion of the anterior thoracic wall, which supposedly results in PE and PC (Fig. 4).[4,9,55,56] However, this pathological mechanism requires larger rib lengths. These have not yet been convincingly proven in measurements.[57,58] Another pathological mechanism involves structural weakness of the anterior thoracic wall. An analysis of the costal cartilage of PE patients supports this hypothesis. It is assumed that such structural weakness predisposes to chest wall collapse. This is believed to be mediated by respiratory gradients.[59,60]

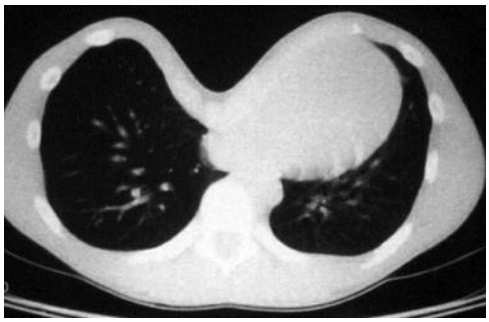


Fig. 3 Computer tomography of a severe case of PE showing narrowing of sternovertebral space with heart and lung compression[1]

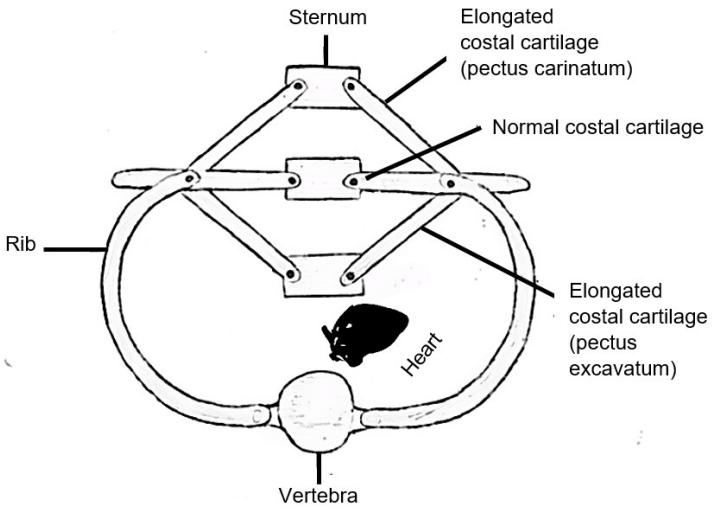


Fig. 4 Mechanical model showing how elongation of costal cartilages produces either PE (depression) or PC (protrusion)[4]

The genes affected by mutations in syndromic forms of PE are: *FBN1, TGFβ and TGFβR, PTPN11* and *PLOD1* genes.[8,61,62] Presuming inheritance patterns for non-syndromic forms of this disorder is difficult. This is due to the small amount of family history information available. Several patterns of inheritance have been proposed. In the past, the most commonly postulated theory was an autosomal dominant disease.[9,12,63] Autosomal recessive and X-linked inheritance have recently been proposed.[8,41] The deviation from the unequal sex ratio could be caused by predominantly X-linked inheritance. Locus heterogeneity and coexistence of different inheritance patterns are also discussed.[8,9] The genetic locus/loci for the isolated familial forms of PE remain unknown.

1.2.2 Treatment of Pectus excavatum

Mild PE can be treated conservatively with breathing and gymnastic exercises.[41] Patients with mild to moderate forms can receive vacuum bell therapy at home. This should be used optimally at a young age when the chest wall is still soft and flexible.[13] Surgical repair is recommended for patients with more severe disorders.

Surgical correction procedures range from purely cosmetic to extensive corrections of the skeletal thorax. Lipofilling, i.e., the autologous transfer of fatty tissue, is an option to fill the cavity.[64] Another technique involves the placement of custom-made 3D silicone pectus implants. These fill the chest wall defect.[65] In most cases, patients undergo minimally invasive repair by the Nuss procedure, which involves placing a bar under the sternum. In rare cases, an open surgical repair with cartilage resection is performed. This includes the Ravitch procedure. The optimal timing of surgical repair is debated. Surgical growth restriction and chances of recurrence during the upcoming growth are weighed against each other. Surgery improves cardiopulmonary dysfunction. It relieves pressure on the cardiac chambers and improves ventilation and oxygenation.[13,66] Some patients develop cardiopulmonary dysfunction if not corrected in time. Previous cases indicate that late treatment can lead to irreversible cardiac damage. Early treatment could prevent such cardiac damage.[67] It is difficult to make a prognosis in cases of congenital or early-onset PE, and to predict who will suffer long-term harm by delayed or omitted treatment.[41,68]

1.3 Pectus carinatum

1.3.1 Epidemiology, phenotypes, and pathophysiology of Pectus carinatum

Pectus carinatum, also called pigeon chest, is the second most common CWD. About 5 to 22% of CWDs are PC. Its prevalence in the population is 0.06% to 1.7%. The range of PC to PE ratio varies from 1:13 to 1:4.[4,13,69] It is a keel-shaped deformity, named after the keel (carina) of ancient Roman ships.[70] Its prevalence in the population depends on ethnicity. According to Hebra[13] it is much more common in Latin American populations. So far, a positive family history has been reported in up to 25%. However, limited data are available.[69,71,72] Reported male to female ratios range from 2:1 to 4:1.[4,69] This medical condition can be congenital, but in most cases occurs later in life. One peak age has been described in early childhood. The other has been described during the growth spurt of puberty. The growth spurt of puberty is also the time when existing deformities often worsen.[4,69]

PC involves protrusion of the anterior chest wall, including the sternum and adjacent ribs. It shows a very variable morphology and severity. All forms are associated with an increased anteroposterior thoracic diameter.[4,11,69] Four distinct types of phenotypic manifestation are classified in the horizontal plane (Fig. 5). A rare form is lateral PC, in which the ribs are unilaterally prominent. It is caused by asymmetric rib overgrowth and has little or no sternal deviation.[4] There are also different phenotypes in the vertical plane (Fig. 6-7). The most common variant is the keel chest. This involves chondrosternal prominence. It is characterized by angulation at the sternoxiphoidal junction. Another variant is the sternum elevatum. In this variant, the caudal end of the xiphoid process forms the vertex.[4] A third rarer form is the pouter pigeon breast, which is also called pectus arcuatum. It involves prominence and angulation of the manubriosternal junction. The paraster-

nal ribs at this level are also prominent. The pouter pigeon breast involves excessive and premature ossification. Such a disorder of ossification affects the manubriosternal joint and adjacent bones. It leads to an increase in the thickness of the sternum.[71,73] Fourth, a combination phenotype of PC and PE can also occur.[47] This can involve a protrusion cranially from a depression. But it can also be a depression lateral to a medial protrusion.[74] The pathological mechanisms of PC are thought to be similar to those of PE. It is believed that they involve overgrowth of costal cartilage. Rarely, PC has occurred secondary to trauma, cardiothoracic surgery, kyphosis, or severe cardiac enlargement.[4,75,76]

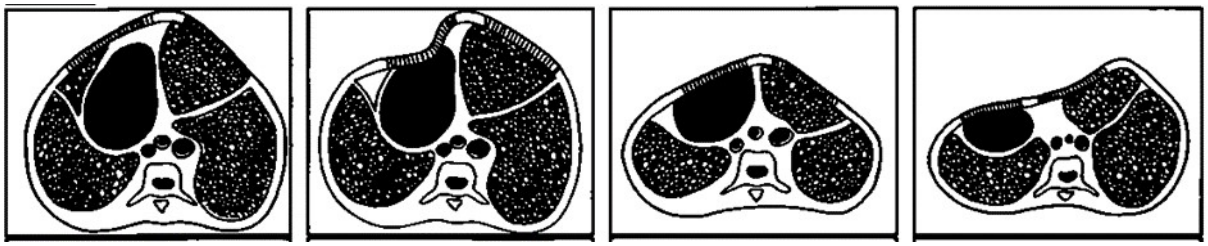
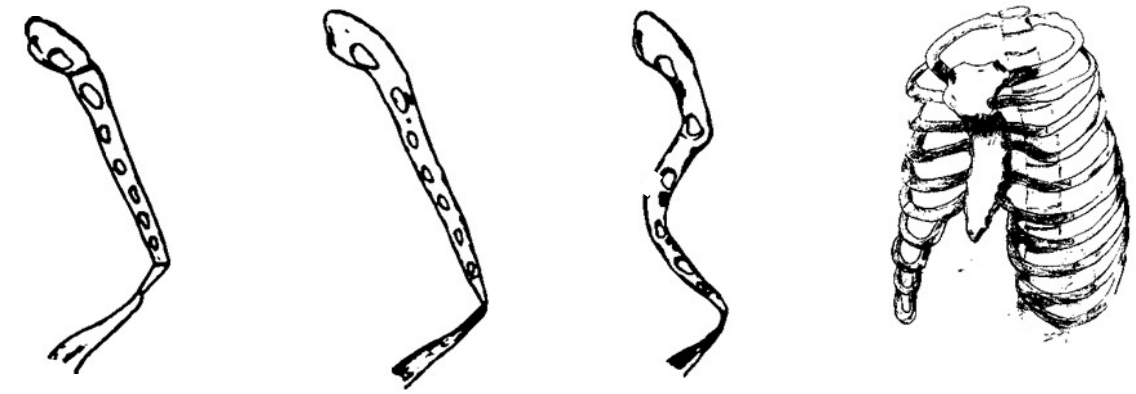


Fig. 5 Phenotypes of PC in the horizontal plane[47]



keel chest sternum elevatum pouter pigeon breast pouter pigeon

Fig. 6 Phenotypes of PC in the sagittal plane[4]

Fig. 7 3D reconstruction of pouter pigeon breast[77]

Data on comorbidities in PC patients are scarce. The clinical study provides information on their comorbidities and cardiopulmonary function. Mutations of syndromic forms of PC affect the genes *FBN1, TGFβ* and *TGFβR, PTPN11, COL1A1, COL1A2* and *CBS* gene.[8,61,78] However, the inheritance of non-syndromic PC remains largely unknown. Apart from two primary studies conducted two decades ago, no family histories in isolated PC have been analyzed to date.[71,72] Due to the lack of family history, no inheritance pattern for isolated PC has been proposed. The genetic locus/loci for the isolated familial forms of PC are unidentified. This study aims to reveal family history in PC.

1.3.2 Treatment of Pectus carinatum

Mild PC can be treated conservatively through physiotherapy. Patients with mild to moderate forms may also be offered non-surgical brace therapy at home. It should be used optimally at a youthful age when the chest wall is still soft and flexible.

Success rates are up to 80%.[69] Surgical repair is recommended for patients with more severe forms. In some cases, open surgical repair with cartilage resection is performed. In other cases, minimally invasive repair techniques are used.[4,69,74]

1.4 Cleft sternum

Cleft sternum, also known as bifid sternum or sternal fissure, is a congenital CWD. It is caused by decreased fusion of sternal elements.[79] Anatomic variations of the Os sternum are common.[80,81] The incidence of SC is relatively unknown. Its proportion of CWDs has been estimated at 0.15% to 0.3%.[47,82] Less than 100 patients have been described in the literature since 1897. Rarely more than two cases were included in a single publication.[83-85] It can be detected prenatally by ultrasound. However, in most cases it is diagnosed in the neonatal period. In some cases, it is missed at birth and diagnosed later through imaging.[83] The disorder develops when bilateral sternal bands of mesenchymal cells fail to fuse into a cartilaginous sternum. Normally, this should occur in the ventral midline during the first trimester.[79] Unlike PE and PC, SC is prominent in the female population. A retrospective analysis of all published series on this deformity was performed. 62% of patients were female and only 38% were male.[83]

There are different subtypes of SC (complete or partial). The partial SC can be either superior, inferior, subtotal, or focal (Fig. 8). The superior form is a non-fusion of the manubrium and upper part of the body of the sternum. It is almost always non-syndromic.[79] The sternal defects have skin covering but no cartilaginous sternum underneath. Isolated SC involves a paradoxical bulging of the mediastinal viscera during expiration. Otherwise, it was described as asymptomatic. Complications include dyspnea and frequent respiratory infections.[4] Few cases can be treated conservatively. Most receive surgical correction by primary closure. This is performed within the first few months of life.[79]

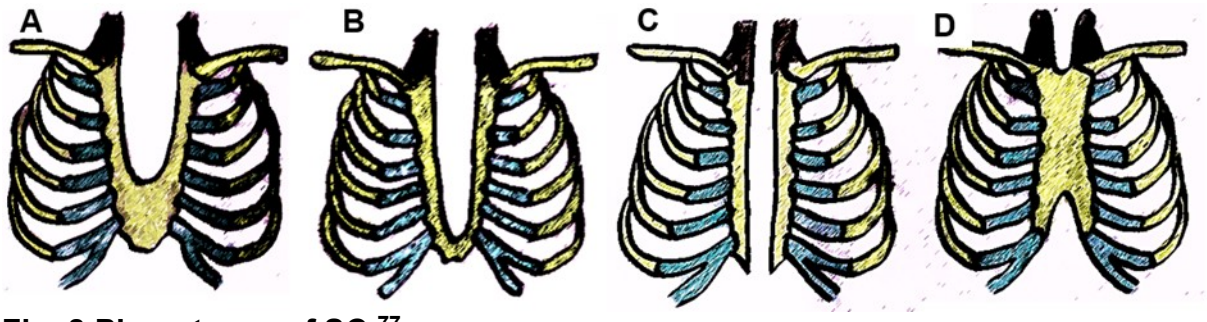


Fig. 8 Phenotypes of SC [77]
A Superior SC **B** Subtotal SC **C** Total SC **D** Inferior SC

In a minority of cases, SC is a part of syndromes. This includes the Pentalogy of Cantrell or PHACES syndrome.[86] Most often, it occurs as an isolated disorder.[87-91] No family histories in isolated SC have been analyzed to date, except for one sibling pair. These were children of consanguineous parents.[92] The deformity was reported to be associated with other defects in up to 72%.[83] Such high rates of

associations contradict current views. They refute the notion that SC is an isolated disease without genetic changes. No associated genes have been reported for SC. This contrasts with PE and PC. Searching for genes in these other two CWDs may be helpful. Analysis of those found genes in SC patients could be revealing. SC has been reported to be associated with PE.[84,87,93-96] Ten percent of SC patients also had PE.[83,97] PE was diagnosed either pre-operatively or post-operatively at follow-up visits. Torre et al.[83] showed that it can occur up to years after surgery. The literature indicates an interconnected etiopathogenesis of the three CWDs. SC is characterized by hypoplasia of sternal cartilage. Pectus deformities also occur in syndromes which are characterized by hypoplasia. These include Poland syndrome and Noonan syndrome.[98] Karner et al.[14] worked with mouse models of PE. The mouse models showed an increased apoptosis of chondrocytes. It was assumed that such apoptosis led to a gradual loss of mechanical properties. This was implicated as causative of pectus deformities. Some see sternal cartilage abnormalities as the primary cause of pectus deformities. They postulate that a posterior angulation of the os sternum occurs first. The sternal angulation causes secondary dorsalward angulation of adjacent ribs.[99] Their idea is supported by radiographic analyses. CTs show that pectus deformities are not just simple linear depressions or anteversions of the sternum. Instead, they involve significantly abnormal sternal curvature. Such curvature abnormalities indicate disturbances in sternal growth in pectus deformities.[100,101] Growth disturbance of cartilage in the anterior thoracic wall seems to be a common feature of pectus deformities and SC. This made it reasonable to include SC in this all-encompassing study.

2. Material and methods

2.1 Literature research strategies

Prior to this dissertation, the literature was searched for systematic reviews and primary studies (cohort studies/individual case studies). The search terms: “pectus excavatum”, “pectus carinatum”, “cleft sternum”, “clinical study”, “syndromes”, “isolated” and “genes” were used in PubMed. The generated results were narrowed down by language (English or German) and presence of an abstract. Appropriate studies were critically evaluated regarding methodology and significance. “OMIM, Online Mendelian Inheritance in Man®”, “GeneCards Suite, MalaCards Human Disease Database”, “Pictures of Standard Syndromes and Undiagnosed Malformation” (POSSUM), “Winter-Baraitser Dysmorphology Database” (WBDD), Human Phenotype Ontology and MalaCards were used as additional sources.

2.2 Methods

The ethics vote was granted by the ethics committee of the Medical Association of Hamburg (number PV5909). The clinical study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. It was registered at https://clinicaltrials.gov/ under the ID NCT04448574.

The data collected were initially pseudonymized. Information from completed questionnaires was transferred to an Excel database. A complete anonymization was performed four weeks after the end of the analysis. The results were quantified and analyzed by gender. The pedigrees were created using the online drawing tool Visual Paradigm Online (VP Online). Initially, Mendelian rules of inheritance were used to identify the pattern of inheritance. Simple descriptive quantitative analyses using simple operators were performed in the Excel program. This included the calculation of percentages, means, and standard deviations (SD). Further quantitative analyses and visualization of datasets were performed using GraphPad Prism 8 software (Graphpad Software, LLC, San Diego, USA). The student's t-test and chi-square test were used to compare measurement variables. $P<0.05$ was chosen as the cut-off value for statistical significance. Somatic percentiles for weight and height were determined using the online tool "Ped(z) — Pediatric Calculator" on the website https://www.pedz.de/en/. Data from the KiGGS (German Health Interview and Examination Survey for Children and Adolescents) study was chosen as the preferred reference data. The z-scores obtained were compared using the General Linear Model (GLM).

The results of this work were successfully submitted to the European Journal of Pediatric Surgery and published in April 2021: The Epidemiology behind Pectus Excavatum: Clinical Study and Review of the Literature (DOI: 10.1055/s-0041-1729898).

2.3 Generation of the patient list

The participants were recruited from the patient collectives of University Medical Center Hamburg-Eppendorf (UKE) and Altona Children's Hospital (AKK). Both inpatient and outpatient individuals who received relevant diagnosis/treatment and presented between January 2013 and April 2019 were selected. All patients recruited had received prior anamnesis interviews and physical examinations for their CWD. Patient data from the AKK were obtained accordingly from the pediatric surgery office of the AKK. Patients who met the study criteria were invited to participate in a multi-stage process.

2.4 Inclusion and exclusion criteria

Inclusion and exclusion were based on written records and diagnoses in patient files. A total of 278 patients met the inclusion criteria. They were contacted during this clinical study. Inclusion criteria were defined as follows:

- patients who presented to the UKE or AKK between January 2013 and April 2019
- diagnosed with the chest wall deformities PE, PC, or SC
- without a diagnosed syndromic disorder
- age between 2 and 26 years
- mailing address current and correct

- existing signed patient consent form; in the case of underage patients, signed declarations of consent from parents or legal guardians

Exclusion criteria were:

- Marfan syndrome, Noonan syndrome, Poland anomaly, Moebius anomaly, Cantrell pentalogy or PHACE association
- no signed patient consent form; in the case of underage patients, no signed declaration of consent from parents or legal guardians

2.5 Study design and survey rounds

This research project was designed as a quantitative cohort study. Patients were first contacted by post. They received a cover letter and two information sheets. Those who were interested could use the answer sheet to make an appointment for a telephone consultation, which lasted about 10 minutes. Patients were asked to inquire about connective tissue diseases (CTDs) among their family members. Any relevant questions were answered. If anyone agreed to participate, informed consent forms were mailed. After acquiring the signed forms, a three-page questionnaire was sent out. Those who failed to respond over the course of the study received reminders. If participants withdrew their consent, they were excluded. The recruitment period lasted six months from March 2019 to August 2019. The analysis period lasted until March 2020. To give an overview, the procedure is briefly outlined in a flow chart in the supplements (Fig. 11).

2.6 Generation of questionnaire

The questionnaire was about clinical features. It focused on frequently reported CWD symptoms. These are based on previous cases and cohort studies of CWD. They are also based on symptoms of related syndromic diseases. Features from the intersection of the most frequently associated syndromes were asked. CTD signs were inquired about as well. Similar analyses of this patient profile have already been carried out, for example by Cullen[102] and Horth et al.[8]. Previous studies suggested an association of isolated CWDs and CTD.[103]

Reported clinical features in PE patients include scoliosis, arachnodactyly, cardiac/dental abnormalities, hernias, joint laxity, history of bruising, flat feet, and arthritis.[2,8,9,104] Data on accompanying comorbidities in PC are scarce. This applies particularly to data on cardiopulmonary function in it. As the disease progresses with age, comorbidities continue to develop. An association of PC with scoliosis and kyphosis has been described.[4,69,105] Accompanying clinical features in SC patients are mostly cardiovascular abnormalities. This includes cardiac defects and aortic malformations. Ocular abnormalities, such as visual impairment, were reported to be also very common in SC patients.[61] Hernias were associated with SC, especially in the incomplete forms of this deformity. Occasionally, thinning of the skin over the defect, supraumbilical raphe, and craniofacial hemangiomas were described

as other comorbidities of SC.[4] In a few cases, disorders of various bones (e.g., clavicular hypoplasia and mandibular cleft) were present in SC.[95,106]

Based on the above knowledge, a questionnaire was created. Its aim was to be comprehensive and completable within 20 minutes.

3 Results

3.1 Response rate

278 families with CWDs had no formally diagnosed syndromic disorder. 274 of them met the inclusion criteria. Of these, 103 families agreed to participate. 28 families had moved away, 24 actively declined to participate, and 119 did not reply. The participation rate was 42% (103/246). Of the 103 patients, 96 patients submitted completed questionnaires, while the other 7 remaining individuals were lost during follow-up. The final response rate was 39% (96/246). A response rate flow chart has been provided below (Fig. 9).

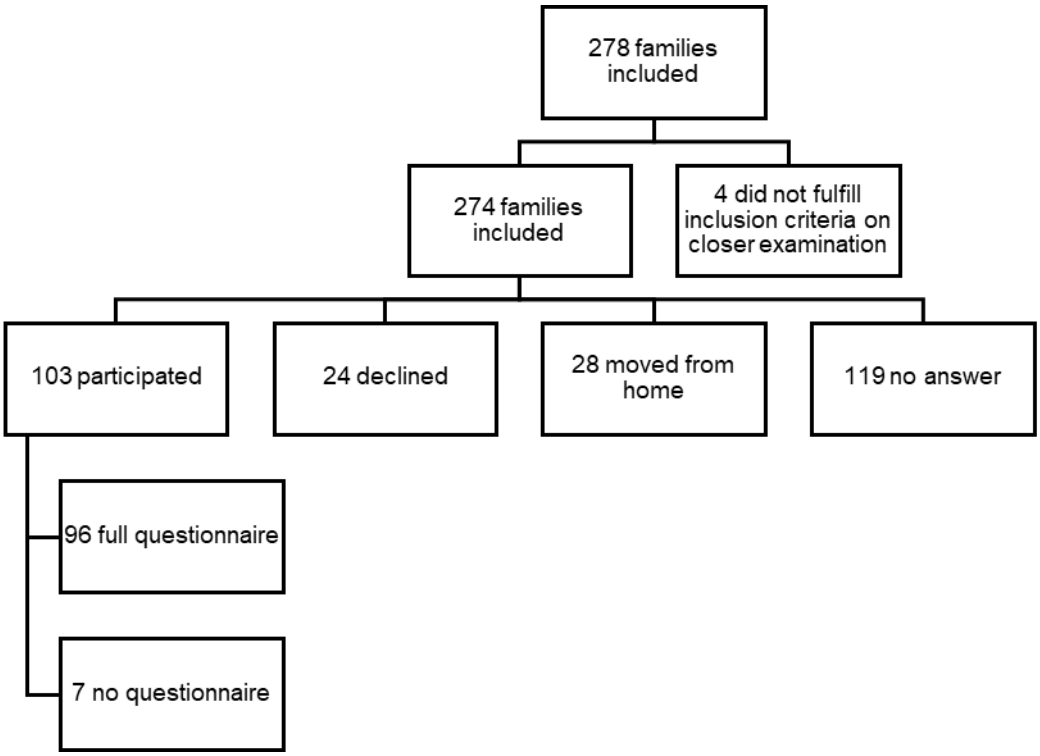


Fig. 9 Flow chart on response rate

3.2 Demographics of the study

The following table shows the demographics (Table 1). The age ranged from 2 to 24 years. The average age was 15.42 years. The median age was 16 years. Of the total patient sample, 8 (only 8.3%) patients were younger than 10 years. One of them was female while the others were boys. Within the female population, 7.1% were younger than 10 years. Within the male population, 11% were younger than 10 years. The overall male to female ratio for CWDs was 5.86:1. Of the participants, 82 (85.4%) were male and 14 (14.6%) were female.

Table 1 Demographics of the study

	Total sample	Male	Female
Absolute number (n)	96	82	14
Relative proportion (in percent)	100%	85.4%	14.6%
Mean age in years at time of study participation +/-(SD)	15.42 +/- 4.53	15.74 +-/ 4.65	13.50 +/- 3.23

3.3 Body measurements and percentiles

Of the 96 patients, 90 provided accurate body measurements. 77 of the 82 male patients reported accurate weight and height. 13 of the 14 female patients reported accurate weight and height. The body mass index (BMI) was calculated if both weight and height were given.

CWD patients' height ranged from 89 centimeters (cm) to 205 cm. Their height z-score showed a significant difference from the height in the general population ($p<0.001$) (Table 2). Every third participant had a height percentile ≥90 (30/90, 33.3%). 26 male participants had a height percentile ≥90 (26/77, 34%). This is significantly higher than the population average of 10% ($p<0.0001$). 11 of them had a height percentile >97, which is defined as giantism (11/77, 14.3%). So about one in seven male patients with CWD is a giant. Within the normal reference population, only 3% are giants ($p<0.0001$). This result suggests that tall height in males is associated with CWDs. The average BMI z-score for this subpopulation of 11 giants was -1.02. Dwarfism, on the other hand, occurred in only two individuals. It is defined as height below the third percentile. Both were male. The proportion found corresponds to 2.2% (2/90). This is below the population average of 3%. One of them was a three-year-old boy. His mother reported reduced oral food intake in her child. The other male patient had severe aortic and bronchus stenosis, reduced lung function, hernia, and partial aniridia. He was in the first percentile for height and weight. Height, weight, and BMI percentiles were below three. The change of all somatic measurements in the same direction indicates a general failure to thrive. Such a correlation differs fundamentally from the body measurements of our other CWD patients. Those had above-average height and below-average weight.

In children, it is crucial to interpret the BMI in an age- and gender-adjusted manner. Therefore, percentiles and corresponding z-scores were calculated. CWD patients were significantly underweight for their age ($p<0.001$). They were also significantly underweight for their height ($p<0.0001$). These observations apply to male and female patients alike (Table 2). A BMI percentile below ten is generally considered underweight. Accordingly, 26 out of 90 patients were underweight. This corresponds to 28.9%. 21 of 77 males (27.3%) and 5 out of 13 females were underweight (38.5%). Large-scale census studies on somatic body parameters have

been conducted in the past. Data from the IOTF (International Obesity Task Force) suggested that 10% of minors are underweight. The WHO (World Health Organization) reported an underweight frequency of 1.6% among minors. KiGGS analyses determined an underweight rate of 10% among German children.[107] The found proportions in this study are above such reference values. In particular, they are significantly higher than those of the German average population. This applies to the found percentages of 28.9% for the entire study population ($p<0.0001$), 38.5% for females ($p<0.01$), and 27.3% for males ($p<0.0001$). Such observations suggest an association between the diagnosis of CWDs and being underweight.

For the male participants, the average z-score was positive for height and negative for weight. The combination of both resulted in a negative z-score for the average BMI. A negative z-score implies below-average gender and age-adjusted weight. 65 of 77 males (84%) had a negative z score for BMI. Six of them had a BMI below the third percentile. This corresponds to 7.8% (6/77 = 7.8%). A BMI percentile below three is generally considered to be extremely underweight. Accordingly, six male patients were extremely underweight. Two additional male patients were exactly on the third percentile. Based on previous census studies, only about 3% of male children in the general population are extremely underweight. The value of 7.8% of male CWD patients significantly exceeds this ($p<0.05$). For female participants, the average z-score for height and weight was negative. However, it was disproportionately lower for height than weight. This resulted in a negative BMI. Consequently, 12 females had a negative z-score for BMI. In three of them it was < -2. The concomitant BMI percentiles of these three were ≤ 2. Their proportion corresponds to 23.1% (3/13 = 23.1%). Accordingly, almost every fourth girl was extremely underweight. Based on previous census studies, only about 3% of female children in the average population are extremely underweight. The value of 23.1% of female CWD patients markedly exceeds this ($p<0.0001$).

The male patient with the highest deviation from age-appropriate height was 11 years old. He was 189 cm tall with no information on his weight. The participant was above the 99th percentile for height. This corresponds to a z-score of over 5.6. He had PE since the onset of puberty. The female with the highest deviation from age-appropriate height was 16 years old. She was 181 cm tall and weighed 57 kilograms (kg), resulting in a BMI of 17.4. The height z score of the participant was 2.39 and the BMI z score was -2.2. Thus, she was also underweight for her age and gender.

None of the 90 included patients were obese. Obesity was defined by a weight percentile >90. Except for two adult participants, all included patients had a BMI below the 70th percentile. Percentiles and z-scores were not applicable to these adult participants anyway. Based on a microcensus in men over the age of 18, BMI is thought to increase with age.[108] According to overweight criteria for adults,

a BMI >25 is considered overweight. The adult participants had an absolute BMI of 26 and 24.9. One of these two adult participants was therefore overweight. He was 20 years old at the time the study was conducted. Overall, our study included only one overweight patient. Height, weight, and BMI are further illustrated in the figures in the appendix (Fig. 49-54). Neither the height nor the BMI curve is normally distributed in the CWD population. This would require an equal proportion of dwarfism and giantism. Normal distribution would also require an even proportion of over and underweight. Instead, the distribution is skewed towards giantism and underweight.

Table 2 Body measurements and z-scores

	Z-score (age/gender adjusted)		
	Total sample (n= 90)	**Male (n=77)**	**Female (n=13)**
Mean z-score for height +/- SD	0.67 +/- 1.63 ***	0.83 +/- 1.28 ****	-0.30+/- 2.89 ns
Median z-score for height	0.78	0.78	0.62
Mean z-score for weight +/- SD	-0.35 +/- 0.91 ***	-0.29 +/- 0.95 **	-0.69 +/- 0.61 **
Median z-score for weight	-0.17	-0.06	-0.67
Mean z-score for BMI +/- SD	-0.89 +/- 0.84 ****	-0.85 +/- 0.85 ****	-1.14 +/- 0.79 ***
Median z-score for BMI	-0.74	-0.69	-1.07

*Analysis was carried out by comparing the determined z scores with established reference values from the KiGGS study. Data are expressed as ns= not significant * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001, with student's t test*

3.4 Age at time of diagnosis

84 patients reported the time at which the diagnosis was made. 12 patients gave no information on this. One in three CWDs was evident at birth. In two-thirds of cases, CWD developed after birth. Age at diagnosis ranged from birth to 18 years. Two age peaks were identified for the time of diagnosis. 58 of 84 patients (69%) had late-onset CWD. Among them were 38 patients diagnosed during puberty (38/84, 45.2%). Puberty was defined as age 12 or older. A closer analysis of the peak of onset was done. It revealed that the peak was at the beginning of puberty rather than towards the end. 26 of 84 patients received the diagnosis immediately after birth (31%). The remaining minority of 20 patients were diagnosed till middle childhood. The median and average age of onset for these 20 patients was 6 years (range: 3 months-11 years).

The median age of onset across the CWD cohort was 7 years. The average age of onset across the CWD cohort was over 7 years. The underlying premise is that patients who reported puberty were at least 12 years old. The latest diagnosis was made in a male patient at the age of 18 years. He was 20 when he participated in the study. The latest diagnosis among the female participants was made in a girl at the age of 15 years. She was 16 when she took part in the study.

In the female subgroup, one patient did not specify the time of diagnosis. Four females reported a congenital diagnosis (4/13, 30.8%). Nine reported late-onset CWD (69.2%). This ratio of about 1:2 is like that of the entire study population. In the male subgroup, 11 patients did not specify the time of diagnosis. 22 males reported a congenital diagnosis (22/71, 31%). 49 declared late-onset CWD (49/71, 69%). This ratio of about 1:2 is like that of the entire study population.

3.5 Chest wall deformities

Of the respondents, 79 had PE, 19 had PC, and 1 had SC. It was permissible to mention multiple CWDs in the questionnaire. Three of the respondents (3.1%) reported a mixture of CWDs.

Table 3 Proportions of chest wall deformities

	Total number
Included patients in total patient sample	**96**
PE including mixed forms	79
PC including mixed forms	19
SC including mixed forms	2
Patients with one isolated CWD	**93**
Patients with isolated PE excluding other CWDs	76
Patients with isolated PC excluding other CWDs	17
Patients with multiple mixed CWDs	**3**
Patients with PE and PC	2
Patients with PE and SC	1

3.6 Comorbidities

11 of 96 patients had no concomitant clinical features. 84 patients with CWDs reported at least one other anomaly (84/96, 87.5%). 66 of them reported several. An average number of 2.9 +/- 2.1 pathologic clinical features was found in our CWD patients. These affected an average number of 2.3 +/- 1.6 organ systems. Skeletal affection was most common among them. The maximum number of clinical features that a single patient had was 10. They affected five different organ systems. A total of 280 anomalies were found. They were grouped into categories. The following table shows the number of anomalies reported from each category (Table 4).

Concomitant anatomic skeletal deformities were common. 25 unspecific malposition of the joints (genu valgum, genu varum, pes cavus, pes planus, pes valgus, lower leg distortion, Sprengel deformity, and rounded shoulders) were reported. Arachnodactyly was present in only a few individuals. The most prominent skeleton deformities were scoliosis (16) (16/96, 16.7%) and kyphosis (6) (6/96, 6.3%). According to the German Scoliosis Network, only about 3-5% of Germans suffer from scoliosis [109]. A found percentage of 16% is significantly above this reference value of 5% ($p<0.0001$). The gender distribution of scoliosis was different than in the general population. 18.3% of participating males had scoliosis (15/82). Only 7.1% of participating females had scoliosis (1/14).

25 of 96 patients showed signs of increased joint mobility. They mentioned a total of 40 different anomalies in the Beighton Scoring System tests. These tests are sensitive for CTD. Such high numbers suggest an association between CWDs and hypermobile joints. Among these 25 patients, 83.3% had a positive family history. Of the patients without joint hypermobility, only 60.6% had positive family history. This data shows that a strong family history is associated with joint abnormalities. 23 patients had 25 skin abnormalities. Pigment disorders (6), especially hypopigmentation (5), were the most common. 11 patients reported non-specific symptoms like neurodermatitis (5), acne (4), or eczema (2). The rates are in the normal range for the German population.[110,111] Remarkably, 4 patients reported skin hyperextensibility. Patients with abnormal skin extensibility and joint anomalies should be tested for connective tissue disorders. One family was particularly interesting in this regard. Its index patient had PE since puberty, hyperextensible skin, and joint hypermobility. His mother, a sibling of his parents, and his maternal grandmother all had connective tissue weakness.

50 dental anomalies were counted in the 96 participants. This corresponds to the data from the KiGGS Wave 2 survey. That survey presented data on the average population in Germany. According to its age-dependent figures, up to 55% of girls and 50.8% of boys receive orthodontic treatment.[112] One patient presented with a dental enamel anomaly. Enamel contains hydroxylapatite and calcium-binding phosphoproteins. This makes enamel similar to bone. Enamel hypoplasia has been reported to be associated with SC.[113] Therefore, a link to CWDs cannot be ruled out. Mutations for enamel disease are either autosomal dominant, autosomal recessive, or X-linked.[114] Strikingly, 33 eye anomalies were mentioned. Ocular anomalies are also common in the general population occurred frequently (i.e., myopia, hyperopia, and astigmatism). Beside these, 8 rare eye defects were reported (8/96, 8.3%). Inguinal hernias were present in 6/96 patients (all males). Accordingly, the rate in our study cohort was 6.3% (6/96, 6,3%). Inguinal hernia is one of the most common diseases in children. The normal prevalence of inguinal hernia is 5% during childhood, with boys being affected more frequently.[115,116] The prevalence within our study cohort is comparable with this. There is no significant

difference between them ($p>0.05$). The lifetime risk of hernias might be increased in CWD patients. That is not covered in this research project.

Ten of 96 participants had cardiac problems (10.4%). This is above the well-known prevalence of 1% for congenital heart disease ($p<0.0001$).[117,118] Eight of these ten patients had cardiac defects other than just displacement within the thoracic cage. Half of these patients had heart valve diseases. These affected the tricuspid, mitral, and pulmonary valves. Further cardiac problems included heart failure, aortic isthmus stenosis, and a ventricular septal defect requiring surgery. 45 participating patients had undergone a heart function test. Among them, six had pathologic echocardiographic results. This corresponds to a rate of 13.3% (6/45) (Fig. 13). Ooshima et al.[119] performed an echocardiographic study in the general pediatric population. It detected a rate of 1.0% for heart malformations at the age of 12 months. The rate of 13.3% is markedly higher than this.

21 participants declared lung disease (21/96, 22%). Their symptoms included recurrent pneumonia and dyspnea. 47 patients received lung function tests. 15 out of the 47 tested showed reduced lung function (15/47, 32%). Of them, 9 explicitly had restrictive lung disease (Fig. 12). Some participants described improvement in lung function after surgery. Such reversibility supports a mechanical cause-effect relationship between pulmonary impairment and CWD. A few reported dyspnea in the questionnaire, but did not have a lung function test. The prevalence of abnormal lung function may therefore be even higher. 13 patients had some form of airway obstruction (13/96, 14%). They mostly had asthma (11/96, 11.5%). A KiGGS census study showed a rate of 6% for asthma in German children.[110] The found rate of 11.5% for asthma is significantly higher than this ($p<0.05$). One participant with PE had a bronchus that was compressed from the outside. Another patient suffered from chronic bronchitis since infancy.

Interestingly, boys (29/82, 35.4%) were significantly more often affected by cardiac, pulmonary, or airway disease than girls (1/14, 7.1%) ($p<0.05$).

Table 4 Numbers of comorbidities and concomitant clinical features

Categories sorted by frequency in descending order	**Number of anomalies reported from this category (n) (percentage)**

Anatomic deformities of the skeleton and locomotor system
• Lower limbs
  ○ Genu valgum
  ○ Genu varum
  ○ Pes planus
  ○ Pes cavus
  ○ Pes valgus
	59
	• 28
	  ○ 6 (6.3%)
	  ○ 5 (5.2%)
	  ○ 5 (5.2%)
	  ○ 3 (3.1%)
	  ○ 3 (3.1%)

○ Long legs ○ Jumper's knee ○ Distorted lower legs ○ Apophysitis calcanei ○ Double digitus pedis • Scoliosis • Kyphosis • Upper limbs ○ Arachnodactyly ○ Long arms ○ Shortened fifth finger • Shoulder deformity ○ Sprengel deformity ○ Rounded shoulders with forward displacement • Pelvic obliquity	○ 2 (2.1%) ○ 1 (1%) ○ 1 (1%) ○ 1 (1%) ○ 1 (1%) • 16 (16.7%) • 6 (6.3%) • 6 ○ 3 (3.1%) ○ 2 (2.1%) ○ 1 (1%) • 2 ○ 1 (1%) ○ 1 (1%) • 1
Natural dentition • Retainer, irregular teeth, abnormality of jaw occlusion • Strong dysplasia of dental enamel of four teeth requiring tooth extraction	**50** • 49 (51%) • 1 (1%)
Increased joint mobility • Thumb extendable till lower arm • Short finger extendable up to 90° towards dorsum of the hand • Hip flexion with straightened legs can lead to palms of the hand touching the ground • Not further specified	**41** • 19 (19.8%) • 16 (16.7%) • 5 (5.2%) • 1 (1%)
Ophthalmologic • Myopia • Astigmatism • Hyperopia • Retinal detachment • Strabismus • Dyschromatopsia • Chronic conjunctivitis • Congenital hypertrophy of the retinal pigmented epithelium	**33** • 18 (18.8%) • 4 (4.2%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%)

• Ptosis • Aniridia • Abnormal curvature of the nervus opticus • Not further specified	• 1 (1%) • 1 (1%) • 1 (1%) • 2 (2.1%)
Dermatologic • Pigmentation abnormalities o Isolated hypopigmentation o Isolated hyperpigmentation o Not specified • Neurodermatitis • Hyperextensibility of the skin • Acne • Eczema • Dry skin • Scaly skin • Keratosis pilaris • Urticaria	**25** • 6 o 4 (4.2%) o 1 (1%) o 1 (1%) • 5 (5.2%) • 4 (4.2%) • 4 (4.2%) • 2 (2.1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%)
Pulmonary • Reduced lung function in performed lung function test o Restrictive lung disease explicitly stated • Recurrent pneumonia • Anomaly not further specified	**20** • 15 (15.6%) o 9 (9.4%) • 2 (2.1%) • 3 (3.1%)
Respiratory tract • Bronchial asthma • Chronic bronchitis • Stenosis of left main bronchus	**13** • 11 (11.4%) • 1 (1%) • 1 (1%)
Cardiologic • Heart valve disease o Tricuspid valve insufficiency o Mitral valve prolapse o Mitral valve insufficiency	**10** • 4 o 1 (1%) o 1 (1%) o 1 (1%)

○ High grade pulmonary valve stenosis requiring balloon valvuloplasty • Displacement of the heart towards left side of the thoracic cavity • Reduced myocardial pumping function • Ventricular septal defect • Aortic isthmus stenosis • Bradycardia	○ 1 (1%) • 2 (2.1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%)
Hernia (All inguinal hernia)	**6** (6.3%)
Miscellaneous anomalies • Allergies • Osteoarthritis • Gastrointestinal disorders ○ Morning vomiting ○ Vomiting, diarrhea, abdominal pain ○ No intake of solid food • Rheumatism • Vitamin D deficiency • Pathologic gait pattern of toe walking • Blood circulation system dysregulation with syncope • Multiple cysts • Bladder dysregulation • Irritable bladder • Obstipation • Abnormal side stitch pain • Rosacea	**23** • 5 (5.2%) • 3 (3.1%) • 3 ○ 1 (1%) ○ 1 (1%) ○ 1 (1%) • 2 (2.1%) • 2 (2.1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%) • 1 (1%)
Total number of anomalies found in the study cohort of patients with CWDs	**280**

The results from the table above are illustrated in the supplemental figures. Data on cardiopulmonary function tests are also illustrated there (Fig. 12-14).

3.7 Family pedigrees

Family history was available for all 96 participants except for one adoption case (95/96). 64 of them reported a positive family history (64/95, 67.4%), which is defined as having at least one relative with PE, PC, SC, scoliosis, and/or connective tissue weakness. These diseases occurred 114 times in relatives. Their average number per family was 1.2 (114/95). In 26 index patients, several relatives were affected. The maximum number of affected patients within a family was seven. Altogether, this study identified 204 diseased individuals. They are all potential candidates for further genetic analysis. Family history is further quantified in the following tables (Table 5-7). Every fifth patient had a family history of spinal deformities (19/95, 20%). In 16 of them (16/95, 17%), it included scoliosis.

Table 5 Index patients with positive family histories

Disease in affected family members	**Number of index patients (n) (percentage)**
Patients with family history of PE	44 (49%)
Patients with family history of PC	5 (6%)
Patients with family history of SC	0
Patients with family history of abnormal curvature of the spine • Patients with family history of scoliosis • Patients with family history of kyphosis • Patients with family history of flat back syndrome	19 (21%) • 16 (18%) • 2 (2%) • 1 (1%)
Patients with family history of connective tissue weakness	10

Table 6 Affected relatives

Disease in affected family members	**Number of affected family members (n=114)**
Relatives with PE	59
Relatives with PC	7
Relatives with SC	0
Relatives with abnormal curvature of the spine • Relatives with scoliosis • Relatives with kyphosis • Relatives with flat back syndrome	24 • 20 • 2 • 2
Relatives with connective tissue weakness	18

Relatives with disease that is not sufficiently specified	6

As shown in the table below, the relatives most affected were first-degree relatives (Table 7). These include fathers, mothers, and siblings. In 51 families, multiple generations were affected. 14 families had at least three affected generations. Two of them had four affected ones. Further analysis is based on data from precisely specified kin. It shows similar frequencies of all five diseases (CWDs, CTD, spine abnormalities) in maternal and paternal family lines. In 21 patients, these diseases occurred only in paternal relatives (20/52, 38%). 22 patients had only affected maternal relatives (22/52, 42%). Both family lines were diseased in 10 patients (10/52, 19%). Mothers (24) and fathers (27) were involved almost equally often. 17 anomalies were identified in siblings. Six of them occurred in sisters and eight in brothers. The gender of three siblings was not specified.

Table 7 Relationships of affected family members

Relationship to family members with anomaly	**Number of affected family members (n=114) (percentage)**

First degree relatives (percentage)
• Parents
  ○ Father
  ○ Mothers
• Siblings
	68 (60%)
	• 51 (45%)
	  ○ 27 (24%)
	  ○ 24 (21%)
	• 17 (15%)

Second degree relatives (percentage) • Grandparents • Aunts/uncles • Nephews/nieces	36 (32%) • 24 (21%) • 11 (10%) • 1 (1%)
Third degree relatives (percentage) • Great-grandparents • Cousins • Son of nephew	7 (6%) • 1 (1%) • 5 (4%) • 1 (1%)
Fourth degree relatives (percentage) • Great-uncle • Cousin of mother	2 (2%) • 1 (1%) • 1 (1%)

A family history analysis for pectus deformities was also performed. A total of 61 relatives with pectus deformities were reported. 50 of them were male and 11 females. 21 patients mentioned pectus deformities on their paternal side. 19 of the 21 pedigrees contained affected fathers (19/21, 90%). 18 patients declared pectus deformities on their maternal side. Only eight of the 18 pedigrees contained diseased mothers (8/18, 44%). This difference between fathers and mothers is statistically highly significant (90% vs. 44%, $p<0.01$). All affected mothers had PE. They

were all mothers of index patients with PE. Strikingly, 38% (3/8) of these mothers reportedly had only a very mild CWD phenotype. Our data showed equal rates of pectus deformities on maternal and paternal sides. However, mothers were skipped more often than fathers. Most mothers in affected families were linking mothers, i.e., conductors. They themselves were asymptomatic. Even if mothers themselves were symptomatic, they often had only a mild phenotype. In contrast, most fathers of affected families were diseased themselves. They were not just mere conductors. This suggests the idea of mothers as carriers of the genetic load for CWD. It seems as if they carry this genetic load while being free of CWD symptoms. Apparently, such mothers pass on this genetic load to subsequent generations. However, they must have additional genetic factors that prevent phenotypical manifestation in themselves. An analysis of the transmission of pectus deformities to male index patients was performed. Of these, 18 had pectus deformities on their paternal side (18/84, 21%) and 15 on their maternal side (15/84, 18%). Their family history for pectus deformities was more often paternal (18/33, 55%) than maternal (15/33, 45%). Among them, 16 had fathers with pectus deformities (16/84, 19%).

3.7.1 Subgroup analysis of girls within the study cohort

Family history was obtained from 13 of 14 participating girls. One female participant was adopted. 10 of 13 female index patients had a positive family history (10/13, 77%). The percentage found was slightly higher than in index male patients. Of those, 66% had a positive family history (54/82). In all, the females had 13 anomalies in their relatives. It corresponds to one anomaly per relative. Male participants had 101 anomalies in their families. This corresponds to 1.2 anomalies per relative. Siblings were affected in 15% of females (2/13, 15%). The rate of diseased siblings was the same as in males (12/82 male patients, 15%).

The given family histories of the ten index female patients were analyzed further. Relatives with chest, spine, and tissue anomalies were counted. Only data from precisely specified kin were used for this. Paternal relatives were diseased in six cases and maternal relatives in four. This is like the ratio of affected fathers to mothers. Fathers were diseased in half of the female patients (5/10) and mothers in only one fifth (2/10). The data on the parents are presented in the tables below (Tables 8-9). For girls, the biological father was the most frequently sick relative. Despite the small number of female participants, previous data show differences between male and female participants. They had the same overall amount of genetic load. However, the genetic load was markedly shifted towards the paternal side in females.

Table 8 Parental affection by CWD, spine abnormalities, or CTD in male index patients

Relationship of family members to index patient	Number of affected parents (percentage of index patients with affected relative)
• All parents • Father • Mother	• 40 (40/82 = 49%) • 21 (21/82 = 26%) • 19 (19/82 = 23%)

Table 9 Parental affection by CWD, spine abnormalities, or CTD in female index patients

Relationship of family members to index patient	Number of affected parents (percentage of index patients with affected relative)
• All parents • Father • Mother	• 7 (7/13 = 54%) • 5 (5/13 = 38%) • 2 (2/13 = 15%)

3.7.2 Special families

One family was particularly interesting. It included male monozygotic twins. Both had PE. Another male index patient's family showed associations of PE and PC. He had a mixed form of PE and PC since he was eight years old. His maternal grandmother also had both diseases since puberty. The linking mother between them had abnormal curvature of the spine. A third interesting family is that of an 18-year-old male participant with PE. PE affected the paternal grandfather, the father, and his three sons. The older brothers of the index patient were aged 21 and 25. The grandfather and father only suffered from mild PE. The index patient had a severe form of late-onset PE. It became apparent during his 11th to 12th year of life. He had concomitant scoliosis and restrictive lung disease. One of his older brothers also suffered from severe PE. Additionally, his maternal side was affected by scoliosis and CTD. This case involved the merging of different genetic loads. The paternal line contained mild PE. The maternal line presented CTD and scoliosis. Their merging resulted in a stronger PE phenotype in common offspring.

3.8 Genetic testing on detail

Of the 96 included patients, only six had already had some kind of genetic testing (6/96, 6.3%). One patient received genetic testing for Marfan syndrome. Another received a whole exome analysis (trio whole exome sequencing (WES)). It showed a variant in the *GINS4* gene of unclear significance. Still another received a chromosomal analysis in the context of birth via in vitro fertilization treatment. A fourth patient had participated in a study on birth via intracytoplasmic sperm injec-

tion. He was genetically tested as part of this study. Two other patients suffered from rare diseases. They were genetically tested to look for specific disease-causing genes. One of them was genetically tested for having a stepper gait. The other was genetically tested for manifest aniridia and suspected WAGR syndrome. The genes *PAX6* and *WT1* were tested for this. None of the above genetic tests yielded relevant results for our study on CWDs.

3.9 Pectus excavatum

79 patients had PE, including those with mixed CWDs. Their main results are shown in the following table (Table 10). Among them, the gender ratio was 5.6. It corresponds to 85% boys and 15% girls (67:12). Several of their families had pectus deformities that were passed on over multiple generations. They included family members who were skipped. The gender of these skipped family members was imbalanced. It was female in 11 cases and male in only 3 cases. Linking female relatives were affected many times less than linking male relatives. Other than that, family history analysis revealed seven relatives with PC in PE patients.

Table 10 Subanalysis of PE patients

	Total sample (n=79)	**Male (n=67)**	**Female (n=12)**
Gender in percent	100%	84.8%	15.2%
Mean age in years +/- SD	15.48 +/- 4.7	15.84 +/- 4.82	13.5 +/- 3.45
Mean z-score for height +/- SD	0.79 +/- 1.66 ****	0.97 +/-1.22 ****	-0.24 +/- 3.11 ns
Mean z-score for weight +/- SD	-0.27 +/- 0.89 ***	-0.21 +/- 0.93 ns	-0.61 +/- 0.55 **
Mean z-score for BMI +/- SD	-0.85 +/- 0.87 ****	-0.8 +/- 0.87 ****	-1.17 +/- 0.86 ***
Positive family history in percent	72% (56/78)	72% (48/67)	73% (8/11)
Family history for other pectus deformities in percent	56% (44/78)	57% (38/67)	55% (6/11)
Family history of PE	51.3% (40/78)	51% (34/67)	55% (6/11)
Total number of relatives with PE specialized according to degree of relationship (in percent)	55 - 1st: 26 (47%) - 2nd: 16 (29%) - 3rd: 10 (18%) - 4th: 2 (36%) - 5th: 1 (3%)	47 - 1st: 18 (38%) - 2nd: 17 (36%) - 3rd. 10 (21%) - 4th: 2 (4%) - 5th: 0	8 - 1st: 5 (63%) - 2nd: 2 (25%) - 3rd: 0 - 4th: 0 - 5th: 1 (13%)

Patients with more than one relative with PE	13	12	1
Patients with three relatives with PE	2	1	1
Family history of at least three continuous generations with PE	5 • 4 on the maternal line • 1 on the paternal line	4 • 3 families with three continuous generations in the maternal line • 1 family with three continuous generations in the paternal line	1 (three continuous generations in the maternal line)
Family history of PC	4	4	0
Total number of relatives with PC	7	7	0
Abnormal lung function, if tested, in percent	28.6% (12/42)	31.4% (11/35)	14.3% (1/7)
Abnormal heart function, if tested, in percent	11.9% (5/42)	13.2% (5/38)	0% (0/4)

*Analysis was carried out by comparing determined z scores with established reference values from the KiGGS study. Data are expressed as ns= not significant * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001, with student's t test*

3.10 Pectus carinatum

19 patients had PC, including those with mixed CWDs. Their main results are shown in the following table (Table 11). Among them, the gender ratio was 8.5. This corresponds to 89.5% boys and 10.5% girls (17:2). Family history analysis revealed five PE relatives in PC patients.

Table 11 Subanalysis of PC patients

	Total sample (n=19)	**Male (n=17)**	**Female (n=2)**
Gender in percent	100%	89.5%	10.5%
Mean age in years +/- SD	15.3 +/- 3.6	15.5 +/- 3.7	13.5 +/- 2.1

Mean z-score for height +/- SD	0.27 +/- 1.41 ns	0.37 +/- 1.39 ns	-0.63 +/- 1.8 ns
Mean z-score for weight +/- SD	-0.66 +/- 0.93 **	-0.6 +/- 0.94 *	-1.1 +/- 1.01 ns
Mean z-score for BMI +/- SD	-1.03 +/- 0.65 ****	-1.03 +/- 0.69 ****	-1 +/- 0.27 ns
Positive family history in percent	59% (10/17)	47% (8/17)	100% (2/2)
Family history for other pectus deformities in percent	37% (7/19)	78% (6/17)	50% (1/2)
Family history of PC in percent	11% (2/19)	12% (2/17)	0% (0/2) = 0%
Total number of relatives with PC	2	2 (father and maternal grandmother)	0
Family history of PE	5	4	1
Total number of relatives with PE	5	4	1
Abnormal lung function, if tested, in percent	42.8% (3/7)	60% (3/5)	0% (0/2)
Abnormal heart function, if tested, in percent	16.7% (1/6)	25% (1/4)	0% (0/2)

*Analysis was carried out by comparing determined z scores with established reference values from the KiGGS study. Data are expressed as ns= not significant * p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001, with student's t test*

3.11 Cleft sternum

Only one male patient with the disease SC was identifiable within both hospitals. His case study suggests that SC is indeed associated with other bone and cartilage disorders. The patient had a mixed form of PE and SC. The father of the affected patient suffered from PE. SC might run in the family like PE and PC. Further surveys and genetic analysis of index patients and their affected relatives are required. Associations of these three CWDs should be further analyzed. A possible connection, such as jointly affected genes, may be found. The corresponding pedigree of the male index patient is shown below (Fig. 10).

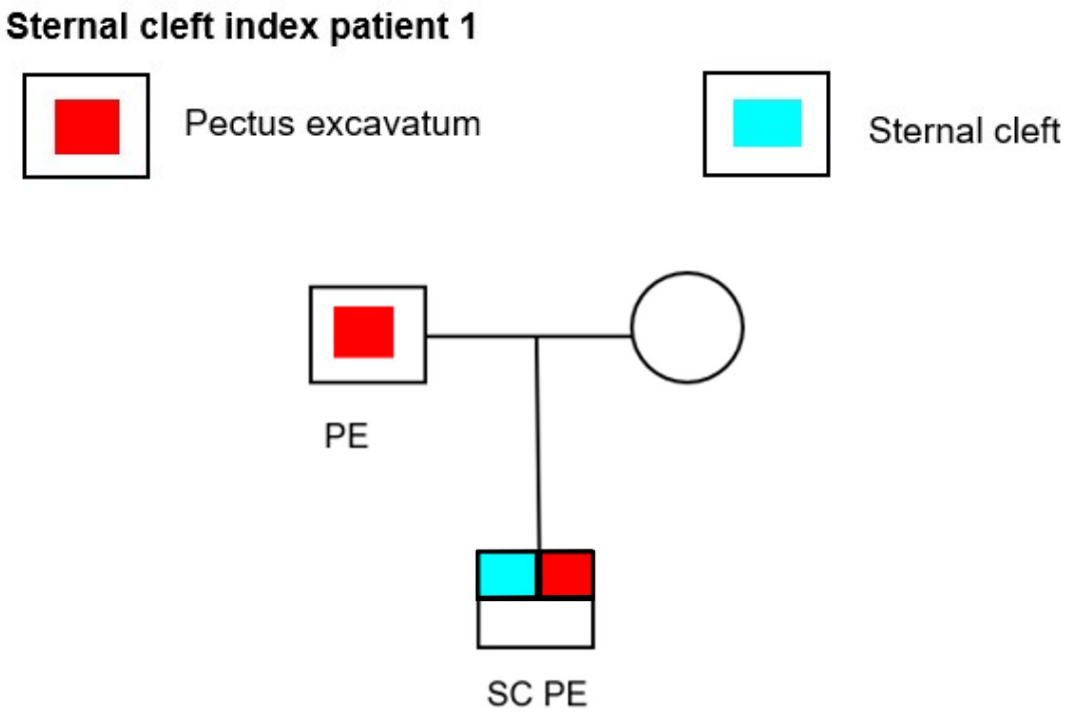


Fig. 10 Pedigree of family with SC

The amount of SC patients included in this research work is very low. This can be explained by the fact that this condition is rare. Only 100 patients have been reported in SC series in the literature yet.[83] Consistent with our study, the largest series included fewer than three cases.[83]

4. Discussion

4.1 Comorbidities

Previous small studies suggested associations between isolated CWDs and other clinical features. Such associations were verified and further specified in this work. One of them was cardiopulmonary disease. 30 of 96 patients had cardiac, pulmonary, or airway disease. The found rate of 31.3% probably underestimates actual cardiac and pulmonary dysfunction. A considerable proportion of the 96 participants received no cardiopulmonary testing (Fig. 13-14). Undertesting contributes to underdiagnosis. The literature suggests a reduced cardiopulmonary function even in supposedly normal patients.[4] Systematic measurements of cardiovascular and pulmonary function were done in previous studies. They found impairment in up to 95% of PE patients.[120,121] In addition, this research project was a cross-sectional study of a young cohort. Many participants were before or amid a growth spurt. Pulmonary symptoms reportedly worsen during growth spurt and teenage years.[13] Surgeries also contributed to the underestimated rate. Previous clinical research showed that corrective surgery reduced cardiopulmonary dysfunctions. Our cohort included patients who had undergone corrective surgeries. In the absence of those surgeries, these participants would have experienced more cardiopulmonary impairment.[66,122] Recall bias further skews the rate. It is difficult to recall diagnosis of past, mild, or asymptomatic dysfunction.[123]

Our analyses showed a strong association with obstructive airway diseases such as asthma. This phenomenon has been described previously. Godfrey[124] reported an association of CWD with bronchial malacia. There are other hereditary diseases with concomitant anomalies of the tracheobronchial and costal cartilage (e.g., Keutel syndrome and chondrodysplasia punctata). Such associations could be due to similar biochemical deficiencies in costal and respiratory cartilage tissue.[125-127] Another linking hypothesis is that of mechanical traction. According to this theory, structural weakness in the thoracic cage leads to deformability. It assumes that breathing movements deform the anterior chest wall. Airway obstruction results in more forceful respirations. They cause increased traction forces during breathing, which are believed to deform the chest.[59,128,129] Morphometric analyses support this etiopathogenetic theory. Their measurements showed reduced tissue strength of the cartilage in CWD.[59]

Our study also indicated an association with skeletal deformities. Some of them were also probably undetected. The data of this study were based on self-report instead of objective physical exam reports. Past research on self-reporting has been done. It suggests a large discrepancy between self-report and diagnoses by health professionals. This is due to a lack of skills to self-diagnose orthopedic deformities. In a previous study, many adolescents denied having scoliosis. In subsequent physical examinations, many of them were diagnosed with this medical condition. Their examinations were carried out by experienced health professionals.[130] Such a bias also applies to our study. Our clinical research verified the association between scoliosis and CWD. This association was previously reported in the literature.[9,72,105] Radiographic CT analyses confirmed it.[131] In our study, 23% of patients had spinal curvature disorders (22/96). Scoliosis was the most frequent form. It is known to progress during growth. Many participants in this study had yet to complete their growth. Therefore, under-reporting of this deformation is possible.[132] Males had scoliosis more than twice as often. Such a gender ratio is inverse to that in the general population.[133] Most scoliosis in the general population is idiopathic, which mainly affects females. The inverse gender relation suggests that the cause of scoliosis in CWD is distinct. Different explanations for the association of spine and rib cage deformities are conceivable. The literature suggested a non-genetic explanation. It was hypothesized that heart dislocation mechanically deforms the spinal curvature.[134] However, the results of this dissertation indicate the presence of a genetic link. Other forms of scoliosis are hereditary.[135-137] The same is conceivable for the abnormal lateral curvature of the spine in CWD. This is supported by family history analysis in our cohort. 38% of patients had an abnormal curvature in themselves or their relatives (36/96). Some relatives with scoliosis linked index patients to other relatives with pectus deformities. These linking family members included parents. Most relatives with abnormal spinal curvature had no concomitant pectus deformity (20/24, 83%). Families with associated scoli-

osis could be helpful to genetic research. They could help identify the pathways and genetic mutations for CWDs. The proposed genetic link is consistent with results from experimental studies in mice. Knockout mice with deletion of the *Gpr126* gene in cartilage developed thoracic scoliosis and PE.[14] Our observation is also consistent with human genetic studies. Genome-wide-linkage analysis mapped adolescent idiopathic scoliosis (AIS) and PE to a common genetic locus on chromosome 18q.[138]

Our data showed that CWDs are also associated with further anomalies. These include hypermobile joints (25/96, 26%), skin anomalies (23/96, 24%), underweight (26/90, 28.9%), and tall height (30/90, 33.3%). The most common skin abnormality was a pigmentation disorder, particularly hypopigmentation. This corresponds to the findings of a previous paper in which light eyes, fair skin, and light hair were more common in PE patients.[8] Our CWD patients were significantly underweight. In developed countries, being underweight is usually caused by an underlying disease. CWD may cause a failure to thrive.[139] Another striking finding is that the patients were taller than expected for their age. Tall height was more pronounced in male than female patients. Such increased height in CWD has been suggested previously.[8,140] Increased height has been similarly observed in Marfan syndrome.[141,142] Tall stature may be caused by the same gene as CWD. Our statistical analyses make a common causal genetic driver more probable.

4.2 Inheritance of isolated CWD

A quantified analysis of 95 family histories up to fifth degree relatives was done. All known distant relatives were included. This distinguished our work from previous publications. 56% of PE and 37% of PC patients had a positive family history of other pectus deformities. The percentages found are among the highest reported in the literature to date.[9,10] These high numbers at specialized surgical centers are consistent with previous observations by Willital et al.[38] They noticed that severe cases requiring surgery had higher positive family history rates. Such high rates verify the previous hypothesis that isolated CWDs are genetic disorders. Our study cohort included a pair of monozygotic twins with PE. Both twin brothers presented to the clinic with moderate non-syndromic PE. This further supports the hypothesis that non-syndromic PE is a genetic condition.

4.2.1 Inheritance patterns

Data on family history from our study disprove primary autosomal recessive inheritance. This inheritance pattern requires a genetic load from paternal and maternal sides. Most of our index patients did not have concomitant affection of both. CWD incidences are estimated at 1:350 of all live births. The rate of heterozygous carrier status calculated from this using the Hardy-Weinberg equation 10.1% (e.g., 1 in 9.9 persons). Given this frequency, most parents of CWD patients would have to be asymptomatic.[143] Among our participants, parents were the most frequently

affected relatives. Autosomal recessive inheritance usually involves horizontal patterns rather than vertical transmission.[144] Vertical transmission accounted for 66.7% of cases (76/114) and an exclusively horizontal pattern (i.e., affected sibling) for 14.9% (17/114).

Analysis of data also disconfirms a purely autosomal dominant inheritance. Only 67.4% of the patients reported a positive family history. Spontaneous mutations, which usually occur at a rate of only 10^{-5} to 10^{-6} cannot explain the 32.6% de-novo occurrences.[8] Autosomal dominant inheritance requires at least one affected parent in every index patient.[143] A parental affection applied to only 60% of our patients. It also requires 50% affection among siblings.[143] This is not the case with our participants. Altogether, an autosomal dominant inheritance with reduced penetrance seems more likely than purely autosomal dominant inheritance.

The male to female ratios among our index patients are higher than in previous publications (i.e., 5.6 for PE and 8.5 for PC). Such a skewed gender ratio can only be explained by involvement of sex-determining chromosomes.[143] A Y-chromosomal inheritance pattern is very unlikely. There are no diseases with this heredity pattern.[8] The affection of females and maternal transmission in this study further refute this pattern.[145,146] A more likely cause of this sex dependency is X-linked inheritance as it can explain the higher penetrance in males and milder phenotypes in females.[147,148] Its typical feature is skewed X-inactivation. It allows excessive inactivation of the mutated X chromosome.[143,149] This could explain mild phenotypes in females.[150,151] X-linked dominant inheritance is disproved as an explanation for the gender disbalance. Only a few diseases are caused by this inheritance pattern. The male predominance and frequent father-to-son transmission refute this pattern (Table 1 and 8).[150,152] A purely X-linked recessive inheritance can also be excluded. It requires almost every index girl to have an affected father.[153] Most girls did not have them. The observed father-to-son transmission and high transmission rates are other reasons against it. Despite the likely involvement of X chromosomes, autosomes must also play a role. Male-to-male transmissions cannot occur via the X chromosome. Their high rates can only be explained by autosomal inheritance of the causative gene.[143] Models of partial X-linked inheritance are also conceivable. These involve additional pathological mutations or physiological modifiers on the X chromosome.[8,9]

The high number of first-degree relatives with pectus deformities make an autosomal dominant pattern seem more probable. Many families had transmission of pectus deformities over several generations with skipped generations in between. This suggests an autosomal inheritance pattern with reduced penetrance. Reduced penetrance can be explained by one or a few modifying factors.[154-156]

This research work reveals variability in age of onset, phenotypes, expressivity, family history, and concomitant clinical traits. Such variability suggests more than one allele for pectus disease and a more complex inheritance model. Coexisting inheritance patterns are conceivable. These are already known for other diseases.[157-159] A polygenetic inheritance, however, is invalidated by our pedigrees. This is due to the inapplicability of the Carter effect. The Carter effect is a characteristic feature of polygenetic inheritance. The high rate of affected fathers is not compatible with this effect (Table 8). High transmission rates within families disprove a strongly multifactorial inheritance further.[2,160] According to this CWDs could be monogenic or oligogenic conditions. Oligogenic inheritance involves modifying genes. These can be on autosomes or gonosomes. Such modifying genes are able to explain qualitative and quantitative variability in phenotypical manifestation and age of onset.[154,161,162] Therefore, the genetic inheritance of CWDs cannot be answered in this study. There needs to be further genetic analyses in future studies to help clarify the inheritance patterns.

4.2.2 Idea of female carriers

The data of this dissertation indicate that females express less severe CWD phenotypes. Female index patients had a lower percentage of abnormal lung, airway, and heart function than males (7.1% vs. 35.4%, $p<0.05$). Similar observations were made in Marfan patients. Female Marfan patients had lower rates of aortic complications (e.g., aortic root dilations, aortic regurgitation, aortic dissections). As a result, they needed aortic replacement less often.[163] The pedigree analysis of our clinical research also indicates less severe female affection. This study generated multigenerational pedigrees showing relatives with CWD. In them, paternal and maternal relatives were equally affected. Maternal transmission was therefore frequent. Until now, the common belief was that CWD primarily involves males. The identification of frequent maternal transmission refutes this. An observation like this implies skipped female carriers. It suggests that mothers transmit the genetic load for CWD without expressing it themselves. They pass it on to the following generations with no or mild symptoms. Such transmission via asymptomatic or mildly affected females has so far been undetected.

The literature reports low proportions of female CWD cases.[8,41] Their proportion in this study was even lower than those previously described. Several explanations are conceivable for this. The research was carried out in clinics specializing in CWD surgery. Specialized clinics treat more severe cases. Mild phenotypes in females would explain their extreme underrepresentation at surgical centers. Taber et al.[42] have analyzed healthcare seeking behavior. They evaluated mildly affected persons without health deterioration. Their study showed that such people frequently avoid doctor visits. Such a phenomenon could partially explain the lower number of females in epidemiologic CWD studies. Additional genetic factors may prevent or attenuate phenotypical manifestation in females. Hormonal factors

might play a role.[164,165] There are also other explanations for the lower frequency of affected females. Exogenous factors affect perceptibility. CWD is concealed by brassieres or covering breast tissue in females. This allows female CWD to be masked. It creates a referral bias to evaluate male patients.[43]

4.3. Practical benefits

Translating scientific knowledge improves health outcomes.[166] It guides clinicians on what to expect, ask, and specifically search for.[167,168] CWD patients should have a full skeletal examination and early screening for cardiopulmonary anomalies. Previous publications on isolated CWD reported many patients with cardiac abnormalities.[169-172] These were identified by echocardiography and stress electrocardiography.[121,173] Respiratory impairment was identified by spirometry and body plethysmography.[174] Consistently, our data justify echocardiographic, electrocardiographic, and pulmonary tests in CWD patients. Occult lesion could be identified earlier.

A practical benefit is the synchronized correction of CWD and concomitant defects. In the past simultaneous corrections of cardiac or aortic malformations and CWD have been performed.[4,170,172,175-177] One-stage repair is advisable as redo cardiothoracic surgery in CWD is technically challenging.[4,171] Simultaneous surgery for CWD and kyphoscoliosis, hernias, and breast hypoplasia are also possible.[4,178-183]

Clinical and genetic profiling could help predict disease progression. This would assist pediatricians, primary care physicians, and pediatric surgeons. Their goal is to prevent progression towards a severe complex deformity and permanent cardiopulmonary impairment. Predictability assists in determining the treatment and its timing. It could help them advise whether a patient requires surgical, interventional, or conservative therapy. Furthermore, it would help them decide whether to refer for early prepubertal or late repair. Individuals would be offered customized treatment recommendations.[41,184] Early screening and subsequent early treatment may help prevent somatic complications (e.g., irreversible heart failure, irreversibly reduced pulmonary function, weight faltering).[184,185] It may also reduce related future psychological distress.[186-189]

Understanding CWD inheritance aids in genetic counselling (e.g., risk for offspring, alternative reproduction options, prenatal and preimplantation genetic testing, predictive testing). This is already carried out for Marfan syndrome.[190] Clinical data helps with this. Our study showed higher rates of CWD transmission in families with joint hypermobility (83.3% vs. 60.6%). Knowledge of genetic causes of CWD would aid in referral to genetic analysis.[191-193] Typical genetic loci should be tested for their nucleotide sequence and methylation pattern. By determining the altered genetic loci, individual genetic profiles can be created. These could be correlated

with the chest wall phenotype, penetrance, and age of onset. Such genotype-phenotype correlations are attempted in Marfan syndrome and scoliosis.[194-196] One exemplary approach is that aggrecan gene polymorphisms correlate with cartilage strength.[197,198]

4.4 Next steps

This doctoral thesis provides appropriate family histories for further research. Genetic analyses in them might be useful. Technologies are whole genome sequencing or single nucleotide polymorphism arrays. Human genetic studies seem to be the most promising tool. They would help to understand the exact etiopathogenesis of CWD.[99] Once pathogenic genetic loci have been identified, animal models must be attempted. These would help to understand the molecular and cellular effects of such loci.

Some research groups have attempted to identify genes in isolated CWD. None have found promising results yet. Suggestions so far include a genetic locus on chromosome 18, *GAL3ST4, TINAG*, and *TIMP1.*[10,14,138,199,200] Further studies on this are required in the future. Our work showed that candidate genes are those of cartilage, bone, and connective tissue.[8,99,138,201] This study found several concomitant symptoms such as tall stature and bone overgrowth (e.g., long arms, long legs, arachnodactyly). Genes for them are on chromosome 5, 11, 17 and the X chromosome.[202-204] Our results suggested a gender-specific association between height and CWD. The causative gene for this is likely on the sex chromosomes. A detailed analysis of the X chromosome seems particularly promising. Candidate genes are also those for scoliosis. Such genes are on chromosome 3, 5, 9, 12, 17, 19 and the X chromosome.[136] *CHL1* and *LBX1* are putative susceptibility genes for scoliosis and PE.[14,205,206]

It is advisable to genetically analyze more affected families first. These include families of index patients with multiple affected relatives. 26 such families were found in our study. 15 families had multiple relatives with pectus deformity. One family had monozygotic twin brothers with PE. Its genetic assessment seems promising. Then, families with different CWD types should be analyzed. There were 10 such families in our study. These suggest pleiotropy. Family members affected differently likely have the same mutations. The genes found are likely the common cause of several CWDs. X-linked attenuating alleles should also be sought. For this, families with skipped females should be analyzed. The presence of autosomal recessive alleles should be determined. For this, specific families should be analyzed. These are families with multiple affected siblings, but absent affection in parents and grandparents. Parents would be heterozygous carriers of these alleles.

In further studies, multivariate logistic regression analyses must be performed. These could specify which clinical signs (e.g., gender, associated features, family history) and genes predict CWD progression. This clinical research work illustrates that future research is interdisciplinary. It requires cooperation between human geneticists, radiology, pediatricians, pediatric pulmonology, pediatric cardiology, and pediatric surgeons. Genetic, radiologic, echocardiographic, and pulmonological exams should be carried out. These should be performed in index patients and their relatives.

4.5 Limitations

This study did not have high power. Established counteracting techniques (e.g., reminders, telephone calls) were used to improve response.[207-209] However, the final response rate remained below the average of previous mail health surveys.[210,211] The low rate is in line with a general trend of decreasing response for health surveys over recent years.[212] A high number of outdated postal addresses can partially explain it.[213,214] The high proportion of male teenage participants explains it as well. Past studies suggested a low response among them.[210,215,216] The extensive length of the used questionnaire likely also lowered response.[217] This research project is subject to various sources of bias (i.e., nonresponse, incomplete response, reduced accuracy of self-report, recall bias, and selection bias). Non-response and incomplete response were marked. They lead to nonresponse bias and reduced validity.[212,218-221] Recall bias must also be considered. The long-time span between presentation at the hospital and this study compounded it. Lower accuracy due to self-reporting is also probable. Previous research revealed a reduced understanding of medical information in patients.[222,223] There may also be a selection bias. It results from data collection at specialized centers, which treat more severe cases. Selection bias reduces generalizability. The results of this work are not projectable onto all other CWD patients, especially not onto those with mild forms. Another limitation is the restricted international applicability of the results. Our study population consisted primarily of Caucasian males. However, genetics and environmental factors vary in different ethnicities.[13,43]

5. Summary

This study addresses the epidemiology and clinical features of chest wall deformities. To this end, three isolated forms of anterior chest wall deformities were examined (i.e., pectus excavatum, pectus carinatum, cleft sternum). The results showed an association between chest wall deformities, underweight, and tall height. There was also an association between chest wall deformities and cardiopulmonary diseases. Cardiac disease was ten times more common than in the general population. Lung and asthma diseases also occurred more frequently than average. In addition, a close association between chest wall deformities and scoliosis was confirmed. This study also showed a strong familial predisposition to chest wall

deformities. About 60-70% of cases had a positive family history. Pedigree analyses support an autosomal dominant inheritance with reduced penetrance. They suggest mothers as asymptomatic carriers of chest wall deformity genes. The pedigrees also showed an association of PE and PC within families.

Zusammenfassung:
In dieser Studie geht es um die Epidemiologie und klinischen Merkmale von Brustwanddeformitäten. Hierfür werden drei Arten von isoliert auftretenden anterioren Brustwanddeformitäten (Pectus Excavatum, Pectus Carinatum, Sternumspalte) untersucht. Die Ergebnisse zeigen eine Assoziation von Brustwanddeformitäten, Körpergewicht und Körperlänge. Es zeigte sich auch eine Assoziation von Brustwanddeformitäten zu kardiopulmonalen Erkrankungen. Herzerkrankungen waren zehnmal häufiger als in der Allgemeinbevölkerung. Lungenerkrankungen und Asthmaerkrankungen waren ebenfalls überdurchschnittlich häufig. Zudem bestätigte sich eine enge Assoziation von Brustwanddeformitäten zur Skoliose. Diese Studie zeigte auch eine starke familiäre Disposition für Brustwanddeformitäten. Etwa 60-70% der Fälle hatten eine positive Familienanamnese. Stammbaumanalysen deuten auf autosomal dominante Vererbung mit reduzierter Penetranz hin. Sie legen nahe, dass Mütter asymptomatische Träger von Genen für Brustwanddeformitäten sind. Die Stammbäume zeigten auch eine Assoziation von PE und PC in Familien.

6. List of abbreviations

AKK: Altona Children's Hospital
AIS: adolescent idiopathic scoliosis
BMI: body mass index
cm: centimeter
CT: computer tomography
CTD: connective tissue disease
CWD: chest wall deformity
HOX: Homeobox
ICD: International Statistical Classification of Diseases and Related Health
KiGGS: German Health Interview and Examination Survey for Children and Adolescents
kg: kilogram
Kinder UKE: children’s hospital of the University Medical Center Hamburg Eppendorf
ns: not significant
PAPS: phosphoadenosine phosphosulfate
PE: pectus excavatum
PC: pectus carinatum
SC: cleft sternum
SK: sulfurylase kinase
SD: standard deviation
UKE: University Medical Center Hamburg-Eppendorf
WES: whole exome sequencing

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8. List of figures

9. List of tables

10. Supplement material
10.1 Flow chart on study design

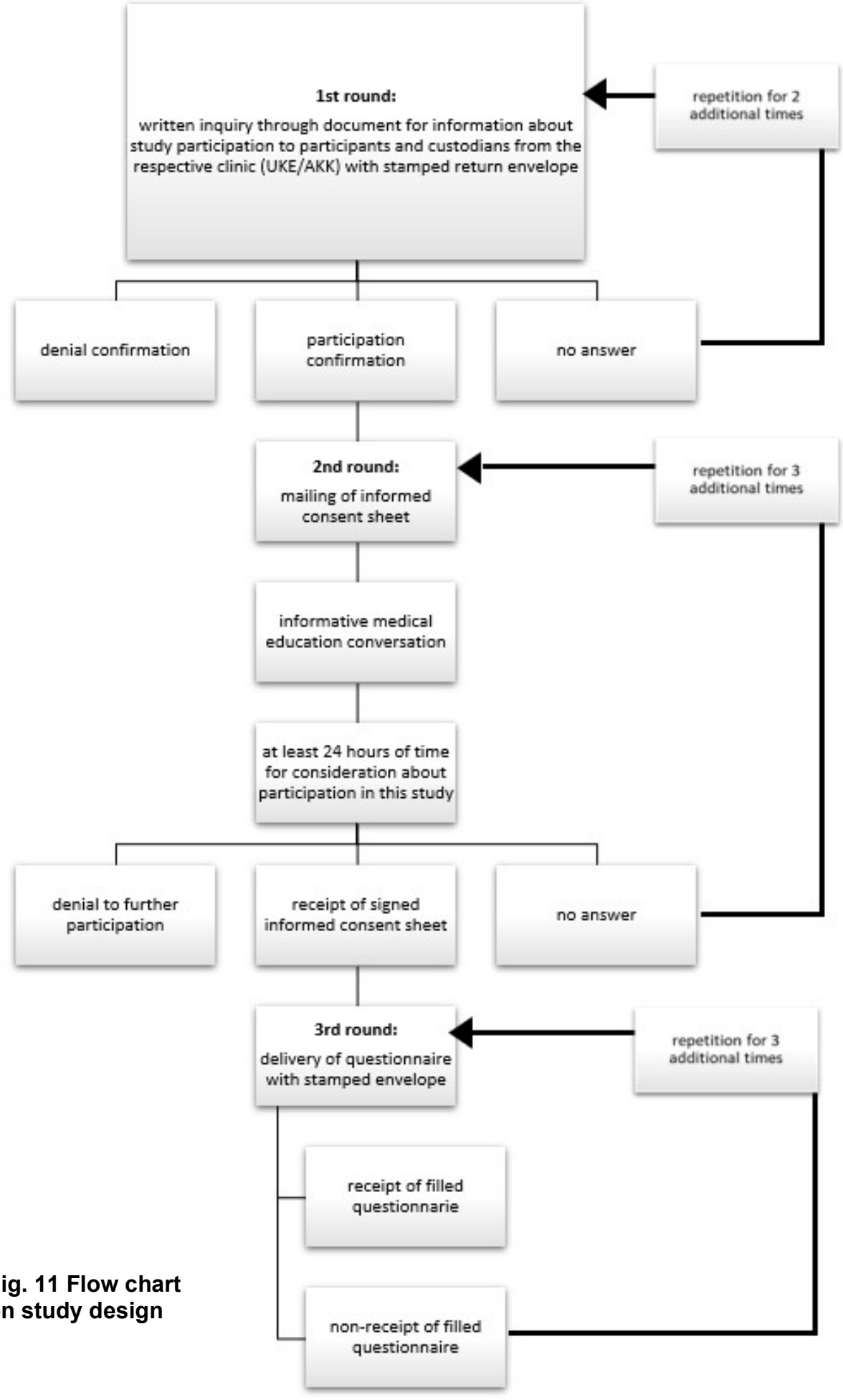

Fig. 11 Flow chart on study design

10.2 Comorbidities in CWD in absolute numbers

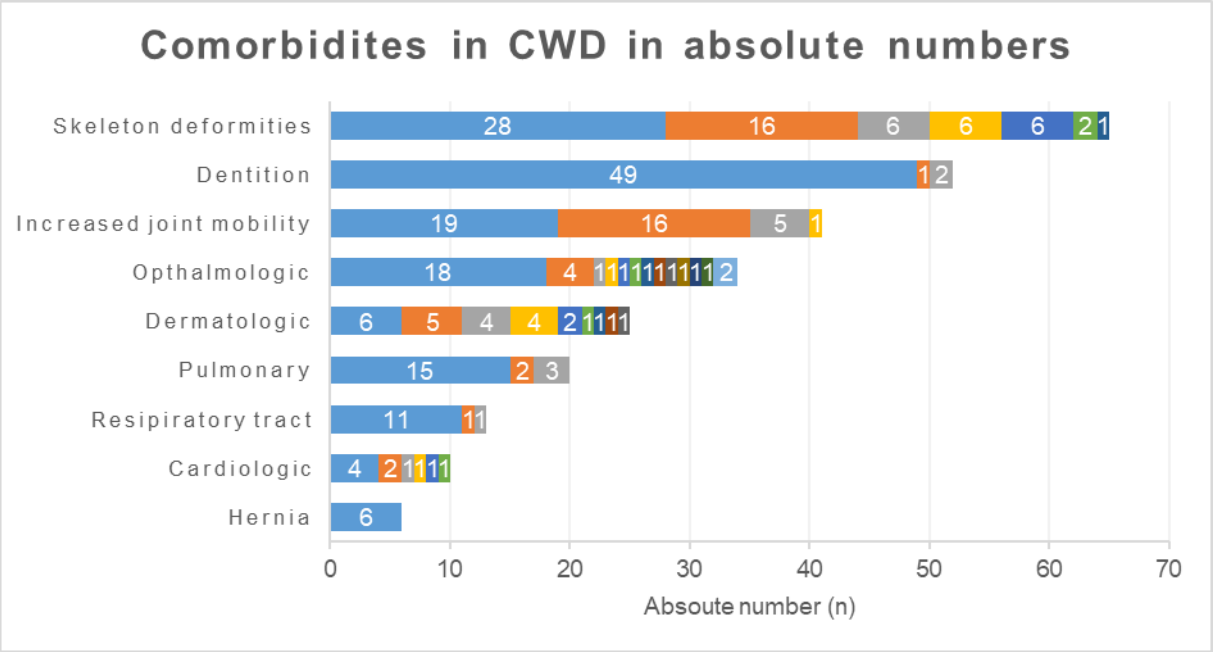

Fig. 12 Comorbidities in CWD in absolute numbers

10.3 Flow chart for pulmonal function testing in CWD patients

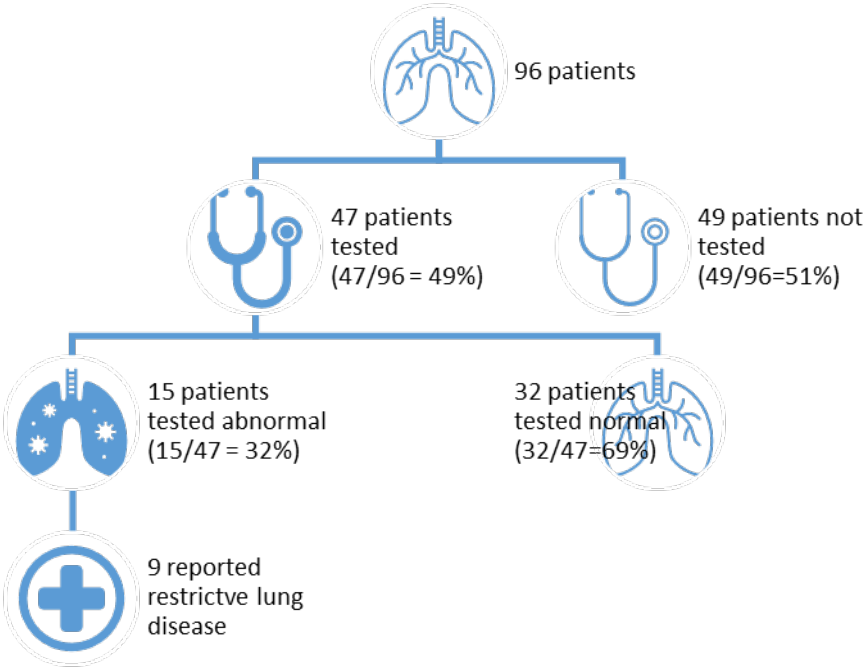

Fig. 13 Flow chart for pulmonal function testing in CWD patients

10.4 Flow chart for cardiac function testing in CWD patients

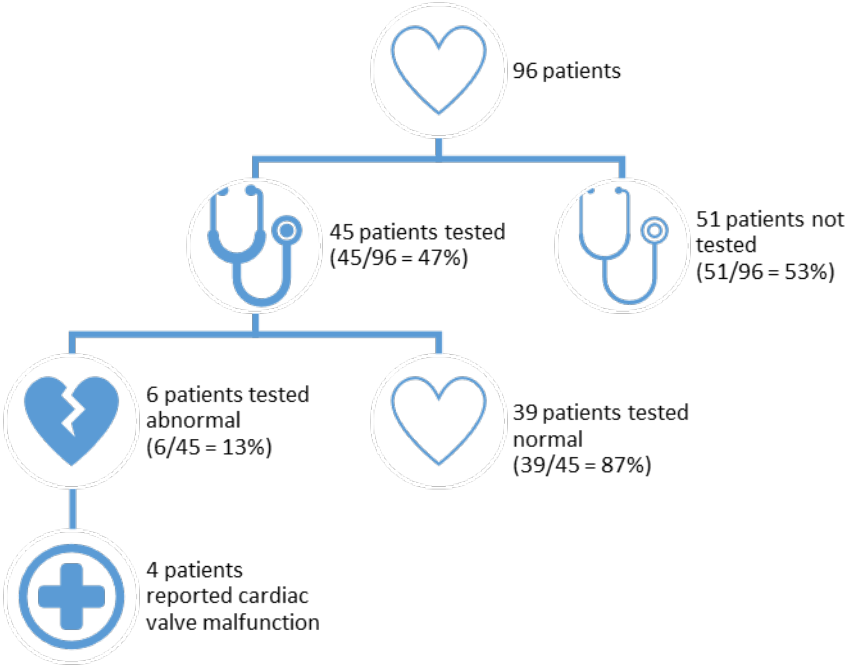

Fig. 14 Flow chart for cardiac function testing in CWD patients

10.5 Cover letter

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Ihre Einladung zur Studie über "Brustwanddeformitäten im Kindesalter"

Hamburg, XX.XX.XXXX

Sehr geehrter Herr Zink,

vor einiger Zeit sind Sie aufgrund einer Trichterbrust am Universitätsklinikum Hamburg-Eppendorf in Behandlung gewesen.

Sie sind nicht allein! Auch andere Menschen leiden unter dieser Erkrankung. Die Ursachen dieser Krankheit sind nicht klar. Wir wollen mehr darüber herausfinden. Hiermit laden wir Sie herzlich ein an einer Studie über Brustwand-deformitäten im Kindesalter teilzunehmen. Ziel ist es familiäre Häufungen, klinische Faktoren und Begleiterkrankungen zu erfassen. Durch Ihren Einsatz kann möglicherweise das Leben anderer Patienten in Zukunft verbessert werden. Damit können Sie etwas ganz Besonderes leisten!

Wir freuen uns, wenn Sie mitmachen. Die Teilnahme ist freiwillig und kostenlos. Es erwartet Sie lediglich ein Fragebogen per Post. Gemäß Ethikantrag der Studie erfolgt vor Zusenden des Fragebogens ein kurzes Telefongespräch mit dem Patient/der Patientin und bei Minderjährigkeit auch mit einem Elternteil.

Zur Terminvereinbarung bitten wir Sie den beiliegenden Antwortbrief portofrei im beigefügten Rückumschlag an uns zurückzusenden!

Ihre Angaben werden streng vertraulich und nach den Bestimmungen des Bundesdatenschutzgesetzes behandelt.
Wir freuen uns auf Ihre Rückmeldung! Bei Fragen wenden Sie sich gerne an die Studienleitung Dr. Trah (jtrah@uke)

Mit freundlichen Grüßen

Prof. Dr. med. K. Reinshagen
Ärztlicher Direktor Kinderchirurgie

Dr. med. Julian Trah
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Doktorandin

Vorstandsmitglieder:
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Fig. 15 Cover letter

10.6 Information sheet

Universitätsklinikum Hamburg-Eppendorf

Informationsschreiben für Eltern und Sorgeberechtigte zur Teilnahme an einem klinischen Forschungsprojekt

Brustwanddeformitäten im Kindesalter - Epidemiologie

Liebe Eltern,
Liebe Sorgeberechtigte,

Sie haben sich mit Ihrem Kind in der Poliklinik und Klinik für Kinderchirurgie auf Grund einer Deformität der Brustwand vorgestellt. Solche Veränderungen an der Brust sind nicht selten und man geht davon aus, dass etwa eins von 300 bis eins von 400 Kindern betroffen sind. Neben angeborenen genetischen Erkrankungen sind die Ursachen bisher unklar.
Um diesen unklaren Ursachen genauer auf den Grund zu gehen bitten wir Sie und Ihr Kind an unserer Studie teilzunehmen.

Die Aufklärung dazu erfolgt in einem ärztlichen Gespräch. Die wichtigsten Punkte sind hier festgehalten, damit Sie diese jederzeit nachlesen können. Diese Untersuchung wurde von der Ethikkommission der zuständigen Ärztekammer ethisch und fachrechtlich beraten.

Die Teilnahme an dieser Untersuchung ist freiwillig und kann jederzeit ohne Angabe von Gründen durch Sie beendet werden, ohne dass dadurch Nachteile in der medizinischen Betreuung entstehen.

1. Was ist Ziel dieser Untersuchung?
Die häufigste Brustwanddeformität ist mit einer Häufigkeit zwischen 1:300 und 1:400 die sog. Trichterbrust (Pectus ecxavatum). Jungen sind dreimal so häufig betroffen wie Mädchen. Die Ursache einer Trichterbrust ist, abgesehen von Ursachen, die als Folge (z.B. nach Eröffnung des Brustkorbes im Rahmen von Herzoperationen) auftreten, weitgehend unklar. Durch Veränderungen in der Knorpelverbindung zwischen Brustbein (Sternum) und Rippen sinkt der vordere Teil der Thoraxwand trichterförmig ein. Kinder mit Marfan- oder Ehlers-Danlos-Syndrom sind überdurchschnittlich häufig von einer Trichterbrustdeformität betroffen. Schon ebenfalls in frühem Alter zeigt sich die Kielbrust (Pectus carinatum). Dabei wölbt sich das Brustbein nach außen vor. Die Vorwölbung kann symmetrisch oder asymmetrisch sein. Auch hier sind Jungen dreimal häufiger betroffen als Mädchen. Die Ursachen sind noch weitgehend unklar. Eine genetische, also vererbbare Ursache, wird stark vermutet, da sich das Auftreten einer Kielbrust in vielen Familien häuft, aber man konnte noch kein dafür verantwortliches Gen nachweisen. Die genetischen Ursachen der Thoraxwanddeformitäten als Teil von Syndromen (z.B. Marfan, Noonan), Anomalien (z.B. Poland, Moebius) oder Assoziationen (z.B. Cantrell Pentalogy, PHACE) sind zu großen Teilen hinreichend bekannt. Dem gegenüber gibt es Patienten, die nicht an den vorher genannten Erkrankungen, Anomalien oder Assoziationen erkrankt sind. Viele Erkrankte haben Verwandte mit einer ähnlichen Veränderung in möglicherweise geringerer oder ausgeprägterer Form, die bislang jedoch nicht untersucht oder behandelt wurden und damit niemals erfasst wurden. Es ist nur wenig bekannt über das familiäre Auftreten von solchen Veränderungen und wenige Veröffentlichungen in der Wissenschaft befassen sich mit diesem Thema.

2. Wie läuft die Untersuchung ab?
Sie wurden angeschrieben, da Sie sich mit Ihrem Kind in unserer Sprechstunde der Brustwandwanddeformitäten vorgestellt haben. Sollten Sie und Ihr Kind damit einverstanden sein an dieser Studie teilzunehmen, erhalten Sie im nächsten Schritt einen Aufklärungsbogen und einen Bogen zur Terminvereinbarung für ein Aufklärungsgespräch. Nach Erhalt dieser beiden Unterlagen werden wir uns telefonisch für ein Aufklärungsgespräch mit Ihnen in Verbindung setzen. Sollten Sie es wünschen, stehen wir auch jederzeit gerne persönlich für ein Aufklärungsgespräch bereit. Hier haben Sie nochmal die Gelegenheit alle Fragen zu dieser Studie zu stellen und Unklarheiten zu beseitigen. Nach diesem Gespräch erhalten Sie noch einmal mindestens 24 Stunden Bedenkzeit, um Ihre Entscheidung zu treffen.
Sollten Sie im Anschluss weiterhin an dieser Untersuchung teilnehmen wollen, freuen wir uns sehr, wenn Sie den beigelegten Fragebogen ausfüllen. Dieser umfasst drei Seiten. Die Beantwortung wird ca. 15 min Zeit in Anspruch nehmen. Wir bitten Sie, diesen gemeinsam mit Ihrem Kind auszufüllen und mit dem beigelegten frankierten Rückumschlag an uns zurückzusenden. Die Daten werden nach Eingang in unsere Klinik digitalisiert und pseudonymisiert[1]. Die Papierunterlagen werden vertraulich über eine Datenmüllentsorgung umgehend vernichtet. Nach Beendigung des Erfassungszeitraumes werden die Daten vollständig anonymisiert[2].

Fig. 16 Sheet of information

Die Studie wird aus dem Universitätsklinikum Hamburg Eppendorf betreut. Alle Korrespondenz sowohl schriftlich als auch telefonisch erfolgt aus der Universitätskinderklinik.

3. Was ist der Nutzen einer Teilnahme?
Die Untersuchung wird möglicherweise helfen die Erkrankung in Zukunft besser zu verstehen und das Krankheitsbild besser zu behandeln.

4. Welche Risiken beinhaltet eine Teilnahme?
Es treten keine Risiken für Ihr Kind dabei auf.
Sollte auf Grund der erhobenen Daten der Verdacht auf eine syndromale Erkrankung bestehen, werden wir uns mit Ihnen in Verbindung setzen um eine Empfehlung auszusprechen. Jedoch nur, wenn Sie dies nicht im Aufklärungsgespräch ausdrücklich abgelehnt haben.

5. Beeinflusst die Teilnahme den Behandlungsablauf?
Eine Teilnahme an unserer Studie wird den Behandlungsablauf in keiner Weise beeinflussen.

6. Datenschutz:
Auf welcher Rechtsgrundlage verarbeiten wir Ihre Patientendaten?
Die Verarbeitung von Patientendaten im Krankenhaus darf nur aufgrund eines Gesetzes oder einer Einwilligung von Ihnen erfolgen. Es gibt unterschiedliche Gesetze und Verordnungen, die dem Krankenhausträger eine Verarbeitung der Daten erlauben. Genannt seien hier insbesondere die Datenschutz-Grundverordnung (DSGVO), z.B. Art. 6, 9 DSGVO, das Hamburgische Krankenhausgesetzt (HmbKHG) oder das fünfte Buch Sozialgesetzbuch (SGB V).

Als Rechtsgrundlagen für die Verarbeitung seien hier beispielhaft genannt:

- Verarbeitung zu Zwecken der Forschung (art. 5 Abs. 1 lit. b DSGVO sowie Art. 6 Abs. 1 lit. f) DSGVO, § 12 HmbKHG, § 27 BDSK)

Werden die im Rahmen der Untersuchung gesammelten Daten verwendet?
Zugang zu dem Schlüssel, der eine persönliche Zuordnung der Daten des Studienteilnehmers ermöglicht, haben ausschließlich die Studienleiter Herr Dr. Trah und Herr Dr. Klohs.
Die Studienteilnehmer haben das Recht über die von ihnen erhobenen personenbezogenen Daten Auskunft zu verlangen und über möglicherweise anfallende personenbezogene Ergebnisse der Studie ggf. informiert oder nicht informiert zu werden.
Diese Studie ist durch die zuständige Ethik-Kommission ethisch und fachrechtlich beraten worden. Der zuständigen Landesbehörde kann ggf. Einsichtnahme in die Studienunterlagen gewährt werden. Sobald der Forschungszweck es zulässt, wird der Schlüssel gelöscht und die Daten damit anonymisiert[2].

Wie lange und in welcher Form werden die Daten Ihres Kindes gespeichert?
Die im Rahmen der Studie nach Einwilligungserklärung des Studienteilnehmers erhobenen persönlichen Daten unterliegen der Schweigepflicht und den datenschutzgesetzlichen Bestimmungen.
Die Daten werden aufgezeichnet und pseudonymisiert (verschlüsselt) für die Dauer von 10 Jahren gespeichert. Bei der Verschlüsselung werden der Name und andere Identifikationsmerkmale durch z.B. eine mehrstellige Buchstaben- oder Zahlenkombination, auch Code genannt, ersetzt, um die Identifizierung des Studienteilnehmers auszuschließen oder wesentlich zu erschweren.
Die Auswertung und Nutzung der Daten durch den Studienleiter und seine Mitarbeiter erfolgt in verschlüsselter Form. Eine Weitergabe der erhobenen Daten im Rahmen der Studie erfolgt nur in anonymisierter[2] Form. Gleiches gilt für die Veröffentlichung der Studienergebnisse.
Im Fall des Widerrufs der Einwilligungserklärung werden die bereits erhobenen Daten gelöscht. Der Widerruf bereits anonymisierter[2] Daten ist nicht möglich da eine Rückverfolgung ausgeschlossen ist.

Welche Rechte stehen Ihnen gegenüber dem UKE wegen der Datenverarbeitung zu?
Ihnen stehen sog. Betroffenenrechte zu, d.h. Rechte, die Sie als im Einzelfall betroffenen Person ausüben können. Diese Rechte können Sie gegenüber dem UKE geltend machen.

Fig. 17 Sheet of information

Sie haben das Recht auf Auskunft über die Sie betreffenden, gespeicherten personenbezogenen Daten nach Art. 15 DSGVO. Wenn Sie feststellen, dass unrichtige Daten zu Ihrer Person verarbeitet werden, können Sie unter bestimmten Voraussetzungen Berichtigung nach Art. 16 DSGVO verlangen. Unvollständige Daten müssen unter Berücksichtigung des Zwecks der Verarbeitung vervollständigt werden soweit die Voraussetzungen des Art. 17 DSGVO erfüllt sind. Sie können insbesondere von Daten, die nicht mehr für den ursprünglichen Zweck erforderlich und deren Aufbewahrungsfristen abgelaufen sind, die Löschung verlangen. Nach Art. 18 DSGVO können Sie unter Umständen von uns verlangen, dass wir die weitere Verarbeitung der Daten einschränken. Dies bedeutet, dass Ihre Daten zwar nicht gelöscht, aber gekennzeichnet werden, um sie für eine weitere Verarbeitung zu sperren. Soweit sich die Verarbeitung Ihrer Patientendaten auf ein öffentliches oder berechtigtes Interesse im Sinne von Art. 6 Abs. 1 lit. e), f) DSGVO stützt, können Sie Widerspruch nach Art 21 DSGVO gegen die Verarbeitung wegen Ihrer besonderen persönlichen Situation erheben.

Wo können Sie sich wegen Datenschutzverstößen beschweren?
Unabhängig von der Inanspruchnahme gerichtlicher Hilfe, haben Sie das Recht auf Beschwerde bei einer Aufsichtsbehörde, wenn Sie der Ansicht sind, dass die Verarbeitung Ihrer Daten datenschutzrechtlich nicht zulässig ist. Dies ergibt sich aus Art. 77 DSGVO. Die Beschwerde bei der Aufsichtsbehörde kann formlos z.B. bei der Datenschutzbehörde in Hamburg erfolgen:

Der Hamburgische Beauftragte für Datenschutz und Informationsfreiheit,
Kurt-Schumacher-Allee 4, 20097 Hamburg, 040/42854-4040,
mailbox@datenschutz-hamburg.de

Wie erreichen Sie den Datenschutzbeauftragten des Krankenhauses?
Der Krankenhausträger hat einen Datenschutzbeauftragten bestellt. Seine Kontaktdaten lauten wie folgt:

Matthias Jaster
Martinistrasse 52
20246 Hamburg
Tel. 040/7410-56890
E-Mail: m.jaster@uke.de

Den Eltern/Sorgeberechtigten wurden Kopien dieses Dokumentes ausgehändigt/zugesandt

Hamburg, den XX.XX.XXXX

Prof. Dr. med K. Reinshagen	Dr. med. Julian Trah	Jasmin Bhullar
Leitender Arzt Kinderchirurgie	Studienleiter	Doktorandin

Bei allfälligen Problemen oder Fragen sind die Studienverantwortlichen jederzeit zu erreichen.

Dr. med. Julian Trah, Facharzt für Kinder- und Jugendmedizin, Klinik und Poliklinik für Kinderchirurgie, Universitätsklinik Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg. Telefon: 01522/2816858. Email: jtrah@uke.de

Dr. med. Stefan Klohs, Facharzt für Kinderchirurgie, Klinik und Poliklinik für Kinderchirurgie, Universitätsklinik Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Email: s.klohs@uke.de

[1] Pseudonymisieren ist das Ersetzen des Namens und anderer Identifikationsmerkmale durch ein Kennzeichen zu dem Zweck, die Identifizierung des Betroffenen auszuschließen oder wesentlich zu erschweren (§ 3 Abs. 6a Bundesdatenschutzgesetz).

[2] Anonymisieren ist das Verändern personenbezogener Daten derart, dass die Einzelangaben über persönliche oder sachliche Verhältnisse nicht mehr oder nur mit einem unverhältnismäßig großen Aufwand an Zeit, Kosten und Arbeitskraft einer bestimmten oder bestimmbaren natürlichen Person zugeordnet werden können (§ 3 Abs. 6 Bundesdatenschutzgesetz).

Fig. 18 Sheet of information

Universitätsklinikum Hamburg-Eppendorf

Universitätsklinikum Hamburg-Eppendorf
Klinik und Poliklinik für Kinderchirurgie
Martinistraße 52
20246 Hamburg
Leiter: Prof. Dr. med. K. Reinshagen

Martinistraße 52
20246 Hamburg
Telefon: 0152 2/28168 58
trah@uke.de; g.kloha@uke.de
Ansprechpartner:
Dr. med. Julian Trah
Dr. med. Stefan Kloha

Studieninformationen

für minderjährigen Patienten im Alter von 12 – 17 Jahren

Brustwanddeformitäten im Kindesalter - Epidemiologie

Liebe Patientin, lieber Patient,

Du hast eine Brust, die Auf Grund Ihrer Form anders aussieht als bei anderen Kindern und hast dich deshalb gemeinsam mit deinen Eltern in unserer Sprechstunde im Krankenhaus vorgestellt. Solche Veränderungen an der Brust sind nicht selten und man geht davon aus, dass etwa eins von 300 bis eins von 400 Kindern das gleiche haben. Wir kennen einige Krankheiten, die eine solche Veränderung der Brust verursachen, das sind zum Glück aber ganz seltene Krankheiten und bei den meisten wissen wir den eigentlichen Grund nicht.
Um vielleicht den wahren Grund zu erfahren würden wir uns freuen, wenn Du an unserer Studie teilnimmst.
Wenn Du Lust hast mitzumachen, rufen wir Dich und Deine Eltern an und erklären Dir alles am Telefon. Die wichtigsten Punkte haben wir hier nochmal aufgeschrieben, damit Du diese jederzeit nachlesen kannst.

Warum wird diese Studie gemacht?
Die häufigste Veränderung der Brustwand ist die Trichterbrust. Dabei sinkt der Brustkorb nach „innen" ein (Pectus excavatum). Man glaubt, dass eins von 300 oder nur eins von 400 Kindern eine solche Veränderung hat. Jungen haben eine solche Veränderung häufiger als Mädchen. Wir wissen, dass man so etwas nach Operationen bekommen kann, bei denen man zum Beispiel am Herzen operiert wird. Eine Trichterbrust kann aber auch spontan auftauchen oder angeboren sein. Man glaubt, das passiert durch Veränderungen in den Knorpeln zwischen Brustbein (Sternum) und Rippen, dabei sinkt der vordere Teil der Brust wie ein Trichter ein. Wir glauben, dass fast jedes dritte Kind, das eine solche Veränderung hat, auch Verwandte hat, die das gleiche Problem haben, es uns aber nicht erzählen. Eine andere häufige Veränderung der Brustwand ist die Kielbrust. Dabei wölbt sicher der Brustkorb nach "außen" vor (Pectus carinatum). Jungen haben diese Veränderung häufiger als Mädchen. Auch hier glauben wir, dass diese Veränderung sich oftmals in Familien häuft.
Wenn diese Veränderung alleine, ohne dass Du eine andere Krankheit hast, auftaucht, dann wissen wir noch nicht genau woher die Krankheit kommt, glauben aber, wenn Deine Eltern, Großeltern oder Geschwister das gleiche haben, dass es damit vererbt wird. Deshalb wollen wir Dich mit einem Fragebogen dazu befragen.

Muss ich an dieser Studie teilnehmen?
Nein – Du musst natürlich überhaupt nichts, eine Teilnahme ist zu 100% freiwillig. Wenn Du zunächst zustimmst, kannst Du auch später noch jederzeit „Nein" sagen, falls Du es Dir dann doch anders überlegen solltest. Du musst dann auch keinen Grund für Deine Entscheidung nennen und kannst aus freien Stücken entscheiden. Das versteht jeder von uns, niemand wird Dir deshalb böse sein. Versprochen!

Fig. 19 Sheet of information

Universitätsklinikum Hamburg-Eppendorf

Was passiert, wenn ich an der Studie teilnehme?
An Deiner Krankenhaus-Behandlung oder Therapie ändert sich überhaupt nichts. Wir werden Dir und deinen Eltern einen Fragebogen zusenden, den Ihr gemeinsam beantworten sollt. Wenn Ihr das gemacht habt, schickt Ihr den Fragebogen an uns zurück. Deinen Namen und Deinen Geburtstag löschen wir dabei aus den Daten, so dass später niemand wissen wird, dass Du der Patient warst, von dem die Informationen stammen. Wenn man eine Person auf diese Weise unkenntlich macht, so nennt man so etwas „anonymisieren" oder „pseudonymisieren".

Weiß dann jeder, der die Daten anschaut, was ich für Beschwerden und Probleme hatte?
Nein. Wir achten ganz besonders darauf, dass alle Informationen, die Dich identifizieren könnten (wie zum Beispiel Deinen Namen, Dein Geburtstag, Deinen Wohnort und so weiter), sofort unkenntlich gemacht werden. So kann niemand herausfinden, welche Daten von Dir stammen. Stattdessen werden Dein Name und alle sonstigen persönlichen Details durch einen Code ersetzt, den nur Deine Dich behandelnden Ärzte kennen. Und die halten dicht und verraten nichts weiter.

Müssen für die Studie Blut abgenommen oder Zusatz-Untersuchungen durchgeführt werden?
Nein. Wir erfassen lediglich Daten. Der Unterschied liegt nur darin, dass wir diese Daten gezielt sammeln und dich danach fragen.

Was habe ich eigentlich von einer Teilnahme an dieser Studie?
Zunächst einmal gar nichts. Wir werden an Deiner jetzigen Behandlung nichts verändern. Wir denken, dass in jedem Fall andere Kinder davon profitieren, die nach Dir wegen einer vergleichbaren Erkrankung behandelt werden.
Eine Belohnung in Form von Geld oder sonstigen Geschenken gibt es leider nicht.
Sollte auf Grund der erhobenen Daten der Verdacht auf eine syndromale Erkrankung bestehen, werden wir uns bei Dir melden um eine Empfehlung auszusprechen. Jedoch nur, wenn Du dies nicht im Aufklärungsgespräch ausdrücklich abgelehnt haben.

Kann ich die Studienergebnisse einsehen?
Deine persönlichen Einzelergebnisse können wir Dir leider nicht präsentieren. Solltest Du aber an den Gesamtergebnissen der Studie interessiert sein, können wir Dir auf Wunsch später gerne die Informationen zuschicken.

Für weitere Fragen stehen wir Dir gerne zur Verfügung. Schreib' einfach eine Mail an jtrah@uke.de oder an s.klohs@uke.de

Den Eltern wurden Kopien dieses Dokumentes ausgehändigt/zugesandt

Hamburg, den 25.2.2019

Prof. Dr. med K. Reinshagen	Dr. med. Julian Trah	Jasmin Bhullar
Leitender Arzt Kinderchirurgie	Studienleiter	Doktorandin

Fig. 20 Sheet of information

10.7 Questionnaire

Liebe Studienteilnehmerin,
Lieber Studienteilnehmer,

wir freuen uns, dass Du an unserer Studie teilnimmst.

Wir möchten Dich bitten den untenstehenden Fragebogen leserlich nach bestem Wissen für uns auszufüllen.
Sollte der Platz nicht ausreichend sein, schreibe gerne auf der Rückseite weiter.
Sollten Fragen nicht verständlich sein schreibe uns gerne eine E-Mail damit wir uns kontinuierlich verbessern können.
Wir stehen gerne mit Rat und Tat zur Seite und beantworten Fragen per Mail so schnell wir können.
Sollten trotz allem Fragen offen bleiben so schreibe uns am Ende des Fragebogens einen kurzen Hinweis oder Kommentar, wir versuchen allen Vorschlägen und Anmerkungen gerecht zu werden.
Bei Interesse können Sie gerne **ab Januar 2020** eine Email an den Kinderchirurgen Dr. Julian Trah schreiben und Auskunft über die Ergebnisse verlangen: **j.trah@uke.de**

Besten Dank für Deine Zeit und Mühe die Du da reininvestierst!
Wir freuen uns auf Deine Antworten

Prof. Dr. K. Reinshagen	Dr. med. Julian Trah	Jasmin Bhullar
Ärztlicher Direktor Kinderchirurgie	Studienleiter	Doktorandin

Fig. 21 Questionnaire

Fragen zur Person:

Persönliche Daten

Erste zwei Buchstaben des Vornamens: _____

Erste zwei Buchstaben des Nachnamens: _____

Geburtsdatum: _____/_____/_____ (dd/mm/jjjj) männlich □ weiblich □

Klinische Daten

Körpermaße

Körpergröße: _____ in cm; Körpergewicht: _____ kg

Brustdeformität

□ Trichterbrust

□ Hühnerbrust (Kielbrust)

□ Sternal Cleft

Seit wann bekannt (z.B. seit Geburt/seit Pubertät/anderer Zeitpunkt; wenn bekannt seit welchem Lebensjahr)

_____

Gliedmaßen und Gelenke

□ "Spinnenfingrigkeit" (Die Finger sind aufgrund vergrößerter Hand- und Fingerknochen- ungewöhnlich lang und dünn, meist zusammen mit langen, schmalen Armen und Beinen)

□ Hohlfuß (Pes cavus)

□ X-Beine

□ O-Beine

□ Skoliose (Wirbelsäulenverkrümmung)

□ Kyphose (Buckel)

□ Arthrose der Gelenke (welche Gelenke sind betroffen): _____

□ andere Fehlbildungen: _____

□ **keine Auffälligkeiten**

Haut

□ extreme Dehnbarkeit der Haut

□ andere Fehlbildungen der Haut (z.B. Neurofibrome, chronische Hautveränderungen wie z.B. Psoriasis): _____

□ **keine Auffälligkeiten**

Fig. 22 Questionnaire

Gelenkmobilität

☐ Kleiner Finger zum Handrücken hin streckbar bis 90 Grad

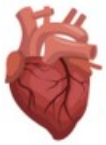
☐ Daumen streckbar bis zum Unterarm (Daumen kann den Unterarm berühren)

☐ Boden kann beim Beugen nach vorne mit der Handfläche berührt werden (ohne dies trainiert zu haben)

☐ **keine überstreckbaren Gelenke**

Erkrankungen von Herz und Lunge

Erkrankungen des Herzens



☐ Erkrankungen der Herzklappen: _____

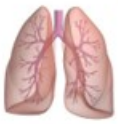
☐ Aortenaneurysmen (Herz-, Gefäßveränderungen): _____

☐ andere Herzfehler: _____

☐ **Herzfunktion getestet (Echokardiographie):**

☐ normal ☐ nicht normal: _____

Erkrankungen der Lunge:



☐ chronische Erkrankung der Lunge (COPD/Asthma/andere): _____

☐ **Lungenfunktionstest erfolgt**:

☐ normal ☐ nicht normal: _____

☐ Andere Erkrankungen der Lunge: _____

Andere Erkrankungen/Fehlbildungen

☐ Leistenbruch

☐ Zahnmissbildungen (z.B. Zahnspange, inkorrekter Kieferschluss,)

☐ Kurzsichtigkeit ☐ Netzhautablösung

☐ Andere Augenprobleme: _____

☐ Andere Erkrankungen: _____

_____

_____

Medikamenteneinnahme

Nehmen Sie Medikamente ein?

☐ Ja ☐ Nein

Falls **Ja**, welche: _____

_____

Fig. 23 Questionnaire

Erhebung der Daten

Wurden die zuvor genannten Untersuchungen und Diagnosen durch einen Arzt erhoben?

Ja □ Nein □

Falls Ja, was für ein Arzt (Facharzt für …/Krankenhaus Abteilung für …/etc.):

_____

Welche Daten, Untersuchungen und Diagnosen wurden durch diesen erhoben:

_____

_____

_____

Wurden bei Ihnen jemals genetische Untersuchungen durchgeführt?

□ Ja □ Nein Falls **Ja**, welche: _____

Familienanamnese

Brustdeformität in der Familie: zutreffendes bitte markieren; **bekannt seit?** (grobe Zeitangaben genügen, z.B. seit Geburt/seit Pubertät/etc.)

Trichterbrust (1)/ Hühnerbrust (2)/ Sternal Cleft (3)/ Wirbelsäulenverkrümmung (4)/

Bindegewebsschwäche (5) in der Familie?

(a) Großmutter (Vater): (1) □, (2) □, (3) □, (4) □, (5) □; _____

(b) Großvater (Vater): (1) □, (2) □, (3) □, (4) □, (5) □; _____

(c) Großmutter (Mutter): (1) □, (2) □, (3) □, (4) □, (5) □; _____

(d) Großvater (Mutter): (1) □, (2) □, (3) □, (4) □,(5) □; _____

(e) Leiblicher Vater: (1) □, (2) □, (3) □, (4) □, (5) □; _____

(f) Leibliche Mutter: (1) □, (2) □, (3) □, (4) □, (5) □; _____

(g) Bruder/Schwester/Halbschwester/Halbbruder: (1) □, (2) □, (3) □, (4) □ , (5) □ **(Alter angeben)**

_____

(h) Onkel/Tante (**Angabe mit z.B. mütterlicherseits**): (1) □, (2) □, (3) □, (4) □, (5) □

_____

(i) weitere Angehörige: _____

Genetische Analyse erfolgt bei (a) □, (b) □, (c) □, (d) □, (e) □, (f) □, (g) □, (h) □ (i) □? (zutreffendes bitte ankreuzen, Mehrfachantworten sind möglich)

Liebe Patientin, Lieber Patient, Du hast das Ende des Fragebogens erreicht.

Wir danken Dir für Deine Zeit und Mühe. Wir hoffen, dass wir mit Deiner Hilfe zukünftigen Patienten helfen können

Fig. 24 Questionnaire

10.8 Declaration of consent

Universitätsklinikum Hamburg-Eppendorf

KiNDER UKE

Einverständniserklärung für Patienten zur Teilnahme an der Studie

Brustwanddeformitäten im Kindesalter - Epidemiologie

Die/Der unterzeichnende Patient/in:

Patient/-in:	
_____	_____
Vorname und Name in Druckbuchstaben	Unterschrift
Ort und Datum: _____, den ____.____._____:	

stimmt hiermit einer Teilnahme an der Befragung zum Thema Brustwanddeformitäten zu.

Federführende Studienleiter sind Dr. Julian Trah und Dr. Stefan Klohs (Universitätsklinikum Hamburg Eppendorf, Klinik und Poliklinik für Kinderchirurgie)

- Mit ihrer Unterschrift bestätige ich, dass ich ausreichend über den Inhalt der Studie und das Ziel des Forschungsprojektes informiert wurde. Mit dem Informationsblatt wurden mir die Ziele, Methoden und Dauer der Studie erklärt.
- Ich und meine Sorgeberechtigten/ Eltern/ gesetzliche Vertreter haben keine weiteren Fragen und bin damit einverstanden freiwillig an der Studie teilzunehmen. Mir wurde erklärt das ich mich jederzeit wieder gegen die Studie entscheiden kann. Mir wurde erklärt, dass wenn ich mich doch gegen eine Teilnahme entscheide keinerlei schlechte Folgen für mich entstehen oder ich etwas zahlen muss.
- Mir wurden alle Fragen so beantwortet das ich sie verstehe. Ich habe alles verstanden was mir erklärt wurde. Ich und alle anderen wissen, dass wenn noch Fragen bestehen sich jeder an den Studienarzt Herrn Dr. Trah oder Herrn Dr. Klohs ansprechen können.
- Ich weiß, dass alles was über mich aufgeschrieben wird nicht weitererzählt wird und werden darf. Nur Ärzte, die mit der Studie arbeiten, können Informationen über mich sehen.
- Ich und mein Sorgeberechtigte/ gesetzliche Vertreter/ meine Eltern sind damit einverstanden, dass alles was über mich aufgeschrieben wird an Herrn Dr. Trah und Herrn Dr. Klohs weitergegeben wird und Sie die Informationen sehen und auswerten dürfen. Sollte ich doch nicht einverstanden sein werden alle Daten über mich, wie mein Name und mein Geburtsdatum gelöscht.
- Sollte es wichtig sein dürfen andere Menschen von Gesundheits- und medizinische Ämtern jederzeit sehen was über mich aufgeschrieben wurde. Alles was zur Sicherheit meiner Daten notwendig ist zählt trotzdem weiterhin.
- Ich und mein/e Sorgeberechtigte/ gesetzliche Vertreter/ Eltern dürfen sich jederzeit bei der Hamburger Datenschutz-Aufsichtsbehörde beschweren (www.datenschutz-hamburg.de). Diese Behörde passt auf das kein Fremder zum Beispiel mein Name oder mein Gebursdatum erfährt oder bekommt.
- Ich und mein/e Sorgeberechtigte/ gesetzliche Vertreter/ Eltern dürfen immer danach Fragen was über mich bekannt ist und dürfen verlangen das alles was über mich bekannt ist, wie zum Beispiel mein Name oder mein Geburtsdatum, gelöscht wird.
- Ich habe lange genug Zeit gehabt, darüber nachzudenken ob ich an dieser Studie mitmachen möchte.

Dem Patienten wurden Kopien dieses Dokumentes ausgehändigt/zugesandt

Fig. 25 Declaration of consent

Universitätsklinikum Hamburg-Eppendorf

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Nur minderjährigen Patienten bis zum 17. Lebensjahr zusätzlich notwendig: Einverständniserklärung

Sorgeberechtigte stimmen hiermit einer Teilnahme an der Befragung zum Thema Brustwanddeformität zu.

Mutter/gesetzliche Vertreterin/ Sorgeberechtige:	
Vorname und Name in Druckbuchstaben	Unterschrift

Vater, gesetzlicher Vertreter/ Sorgeberechtigter:	
Vorname und Name in Druckbuchstaben	Unterschrift

- Mit ihrer Unterschrift bezeugen die Unterzeichnenden, sich ausreichend über den Inhalt der Studie und das Ziel des Forschungsprojektes informiert zu fühlen. Anhand einer Patienten- bzw. Elterninformation wurden Ziele, Methoden und Dauer des Projektes erklärt.
- Die/der kindliche Patient/-in sowie die Sorgeberechtigten/ Eltern/ gesetzliche Vertreter haben keine weiteren Fragen und stimmen einer Teilnahme an der Studie aus freier Entscheidung zu. Die Möglichkeit einer späteren Rücknahme dieses Einverständnisses wurde ausdrücklich erklärt und darauf hingewiesen, dass aus der Ablehnung einer Studienteilnahme keinerlei negative Folgen und/ oder Kosten resultieren.
- Etwaige Fragen wurden verständlich beantwortet, so dass bei Unterzeichnung keinerlei Unklarheiten bestehen. Die Erklärungen waren so verständlich, dass die Unterzeichnenden in der Lage waren sich ein eigenes Urteil über den Sachverhalt zu bilden. Den Kindern/ Sorgeberechtigten/ gesetzlichen Vertretern/ Eltern ist bekannt, dass sie sich bei eventuell noch auftretenden Fragen jederzeit an die Studienleitung wenden können.
- Sämtliche Daten und Informationen werden vertraulich behandelt und unterliegen den Bestimmungen des deutschen und europäischen Datenschutzes unter Gewährleistung der ärztlichen Schweigepflicht. Nur Ärzte, die mir der Studie befasst sind, haben Zugriff auf diese Daten.
- Patient/in und Sorgeberechtigte/ gesetzliche Vertreter/ Eltern erklären sich damit einverstanden, dass die im Rahmen der Studie erhobenen Daten der Studienleitung übermittelt und weiterverarbeitet werden dürfen. Im Falle eines nachträglichen Widerspruchs vom Einverständnis werden alle persönlichen Daten gelöscht.
- Wenn ein wichtiger Grund vorliegt, können Gesundheits- und medizinische Aufsichtsbehörden jederzeit Akten- und Dateneinsicht einfordern, wobei auch im Falle einer Einsicht strengste Datenschutzbestimmungen zum Tragen kommen und garantiert werden.
- Patient/in und Sorgeberechtigte/ gesetzliche Vertreter/ Eltern haben das Recht sich jederzeit bei der Hamburger Datenschutz-Aufsichtsbehörde zu beschweren (www.datenschutz-hamburg.de). Der zuständigen Landesbehörde kann Einsichtnahme in die Studienunterlagen gewährt werden.
- Patient/in und Sorgeberechtigte/ gesetzliche Vertreter/ Eltern haben das Recht jederzeit Auskunft (einschließlich unentgeltlicher Überlassung einer Kopie) über die sie betreffenden personenbezogenen Daten zu erhalten sowie ggf. deren Berichtigung oder Löschung zu verlangen.
- Zur Entscheidungsfindung in Bezug auf eine Studienteilnahme wurde ausreichend Zeit zur Verfügung gestellt.

Den Eltern wurden Kopien dieses Dokumentes ausgehändigt/zugesandt

Fig. 26 Declaration of consent

10.9 Family pedigrees

Family pedigrees of PE index patients and PC patients with more than one affected relative:

Pectus excavatum index patient 1

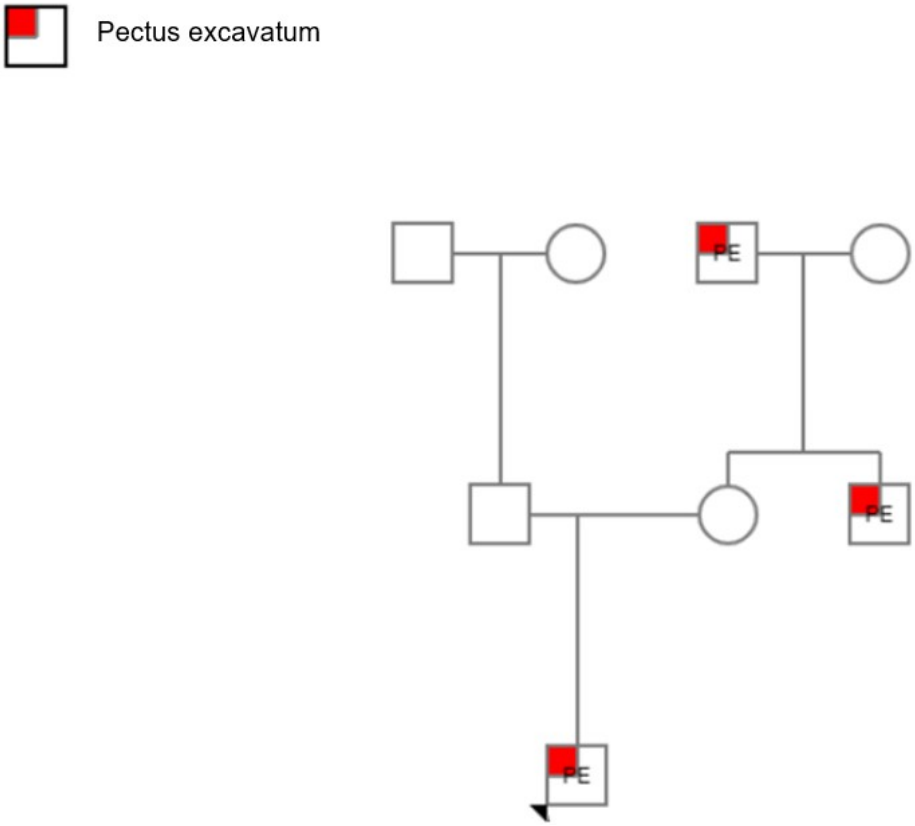

Fig. 27 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 2

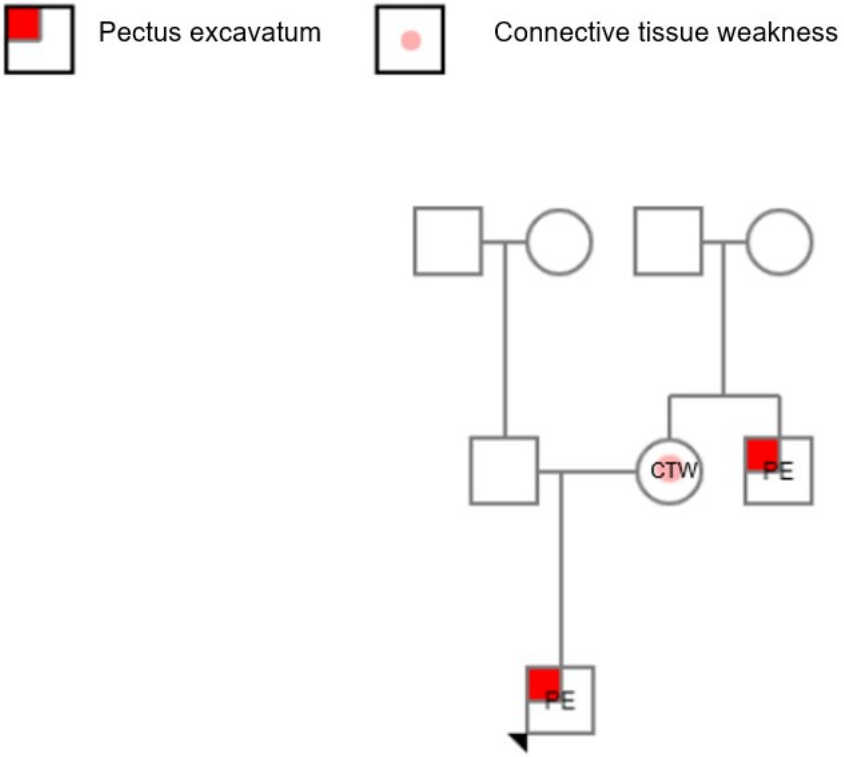

Fig. 28 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 3

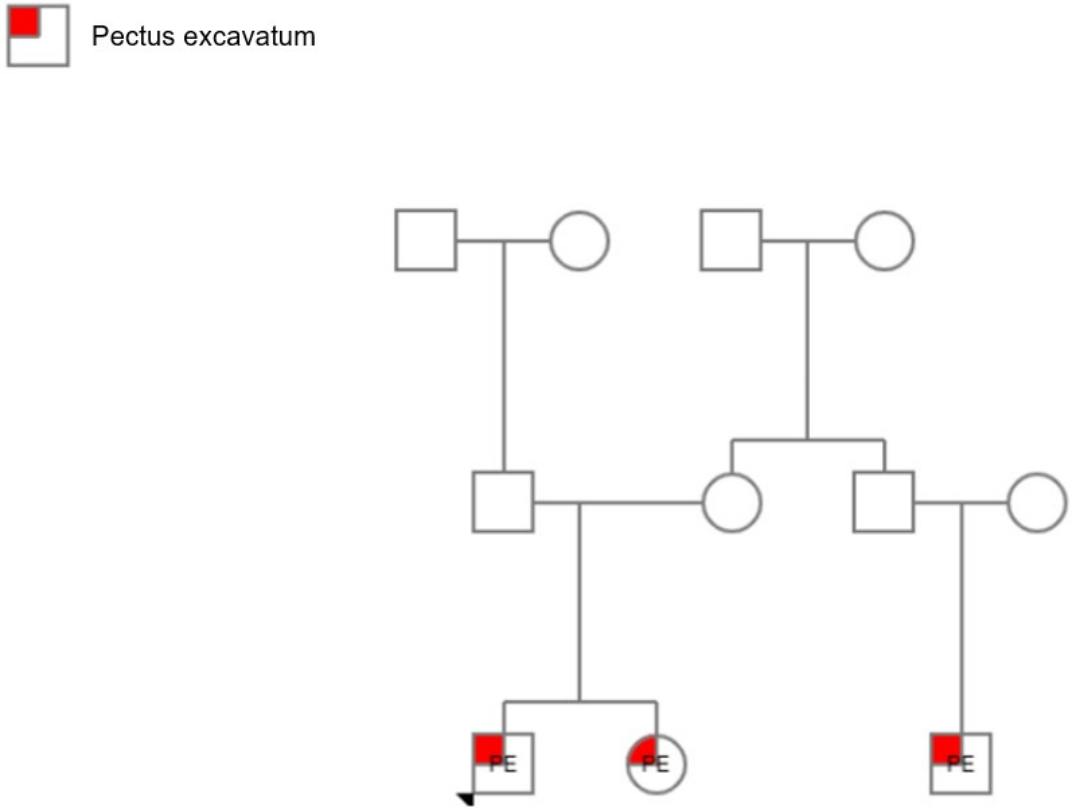

Fig. 29 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 4

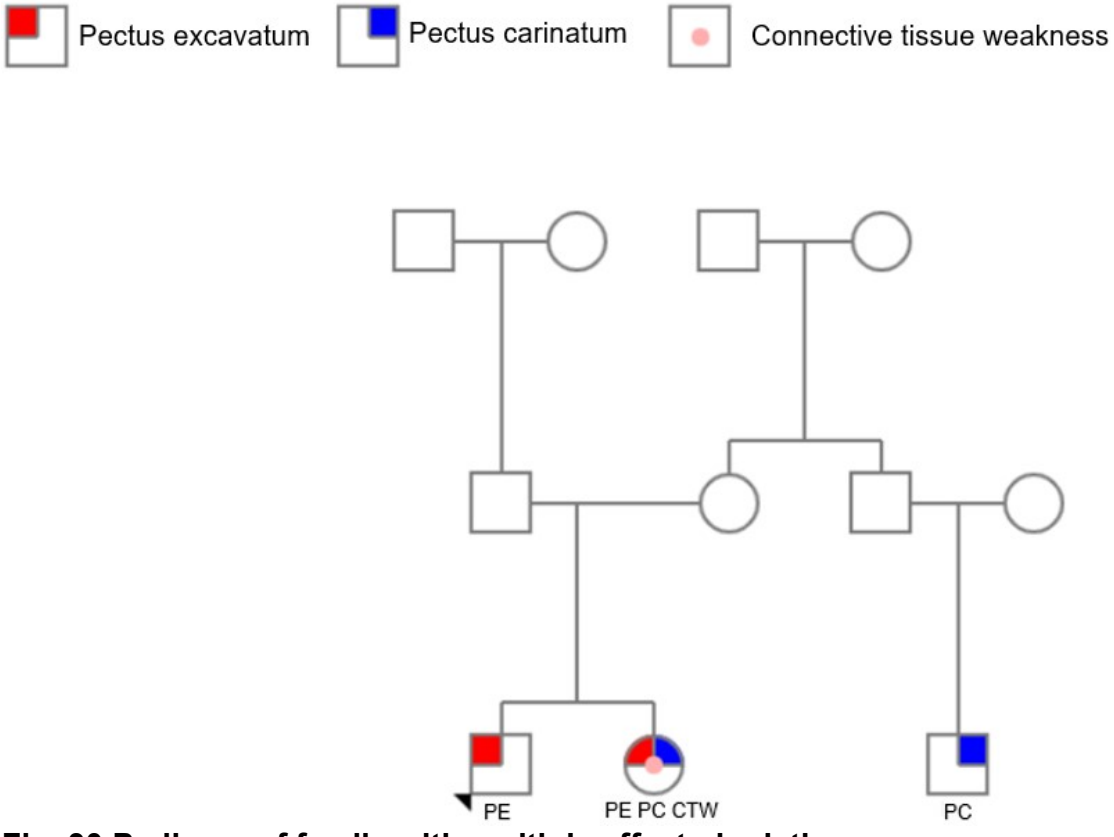

Fig. 30 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 5

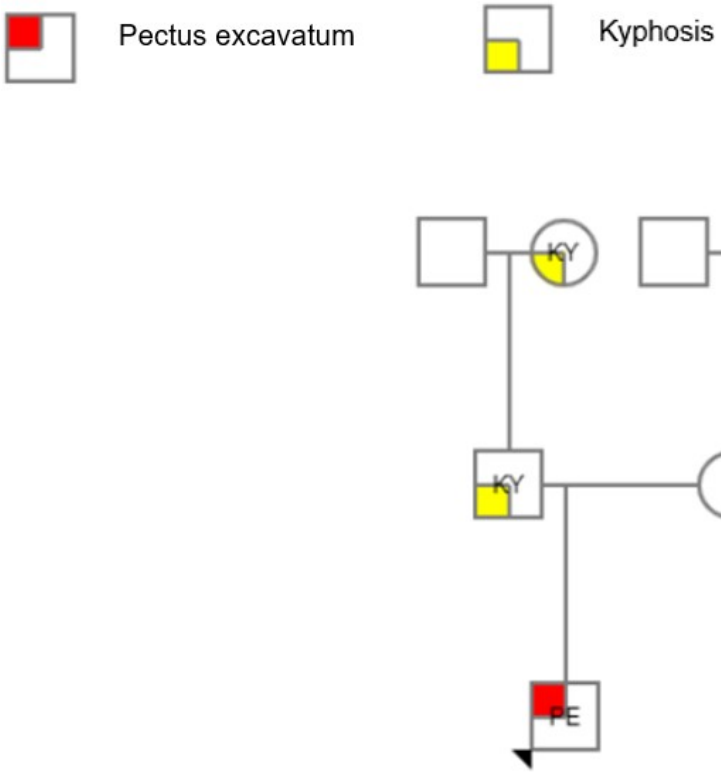

Fig. 31 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 6

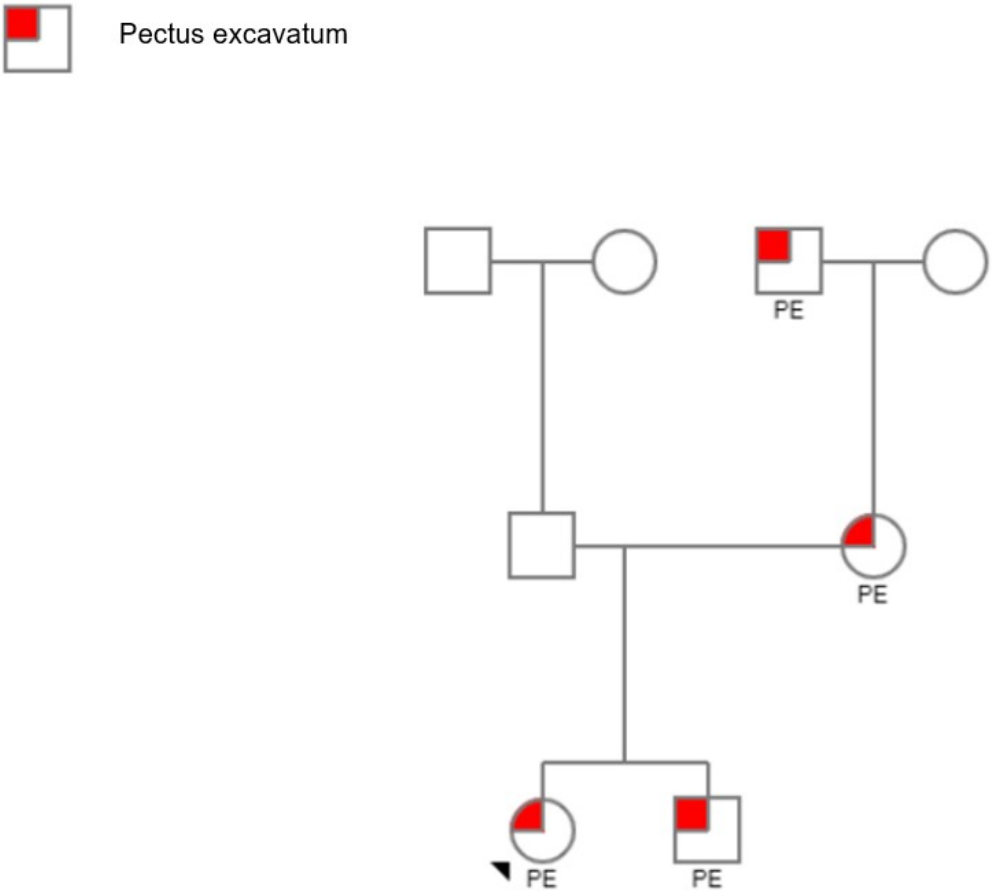

Fig. 32 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 7

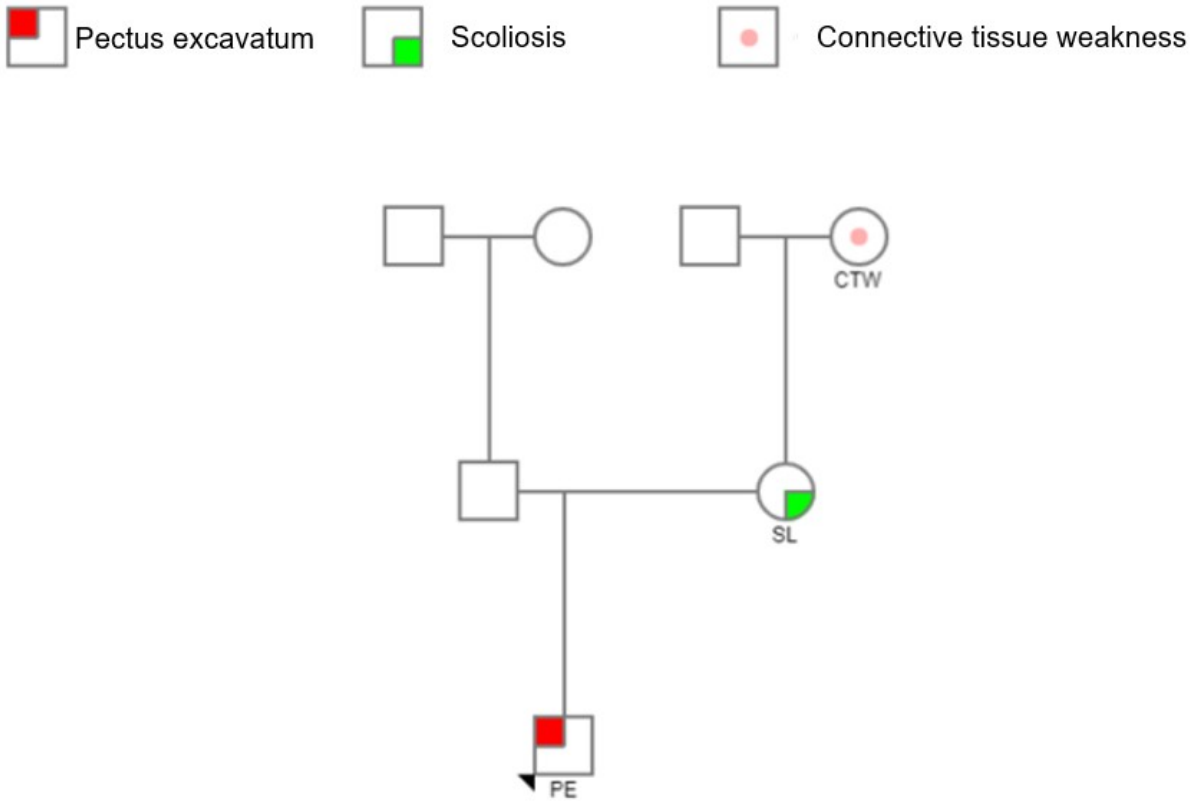

Fig. 33 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 8

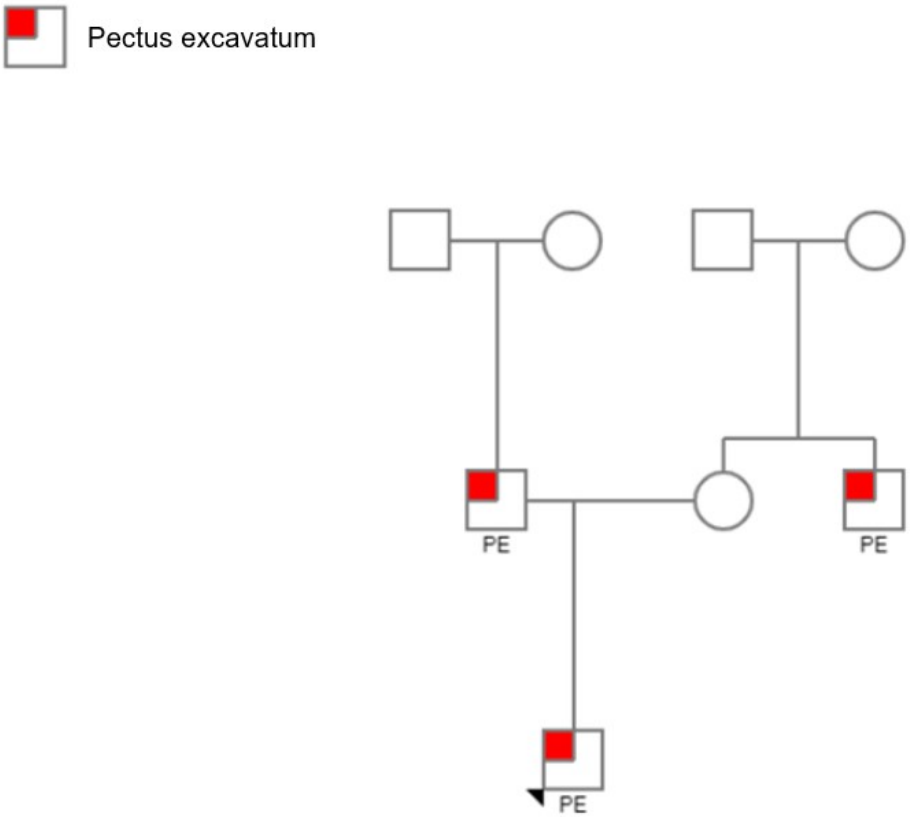

Fig. 34 Pedigree of family with multiple affected relatives

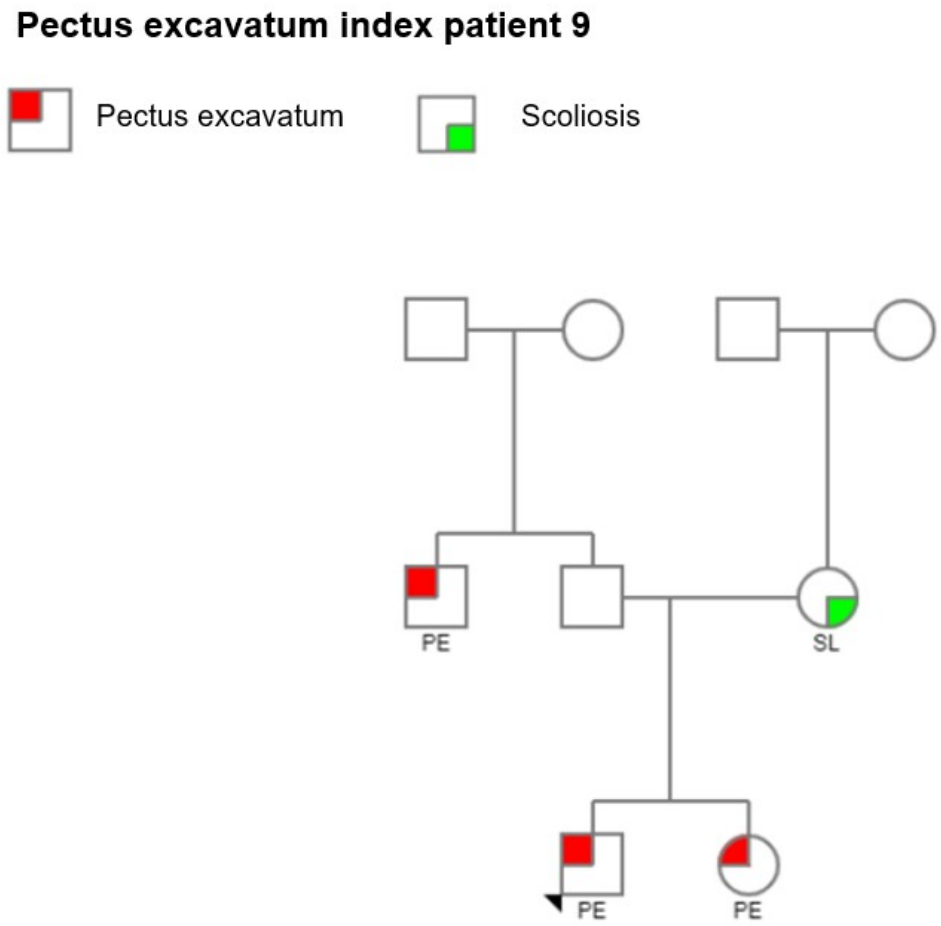

Fig. 35 Pedigree of family with multiple affected relatives

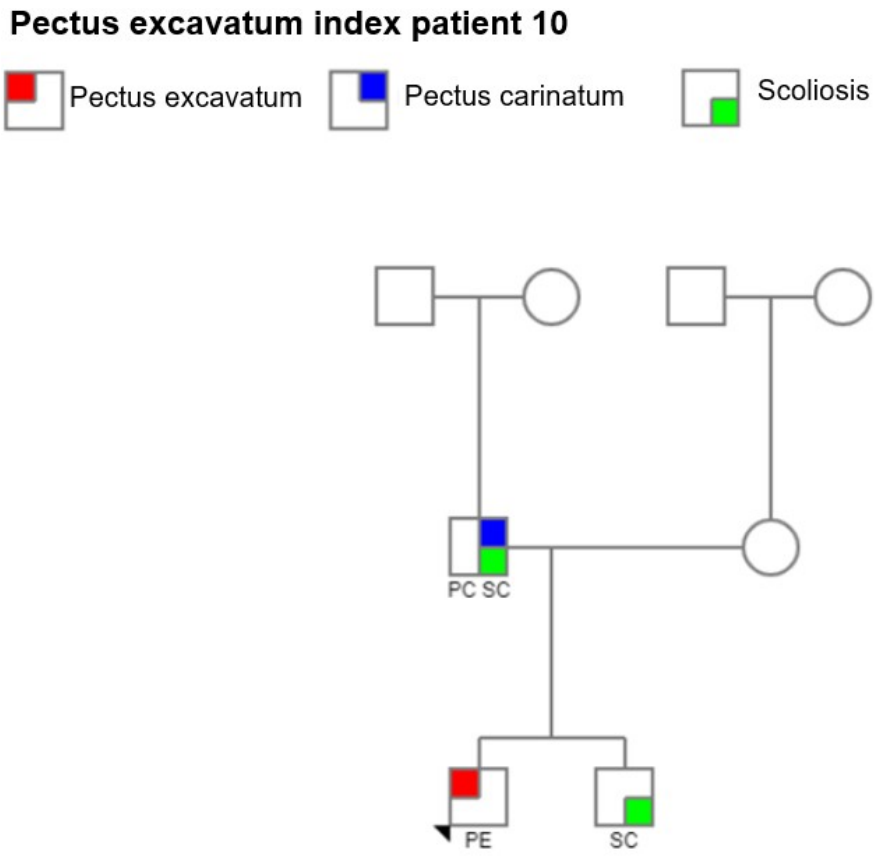

Fig. 36 Pedigree of family with multiple affected relatives

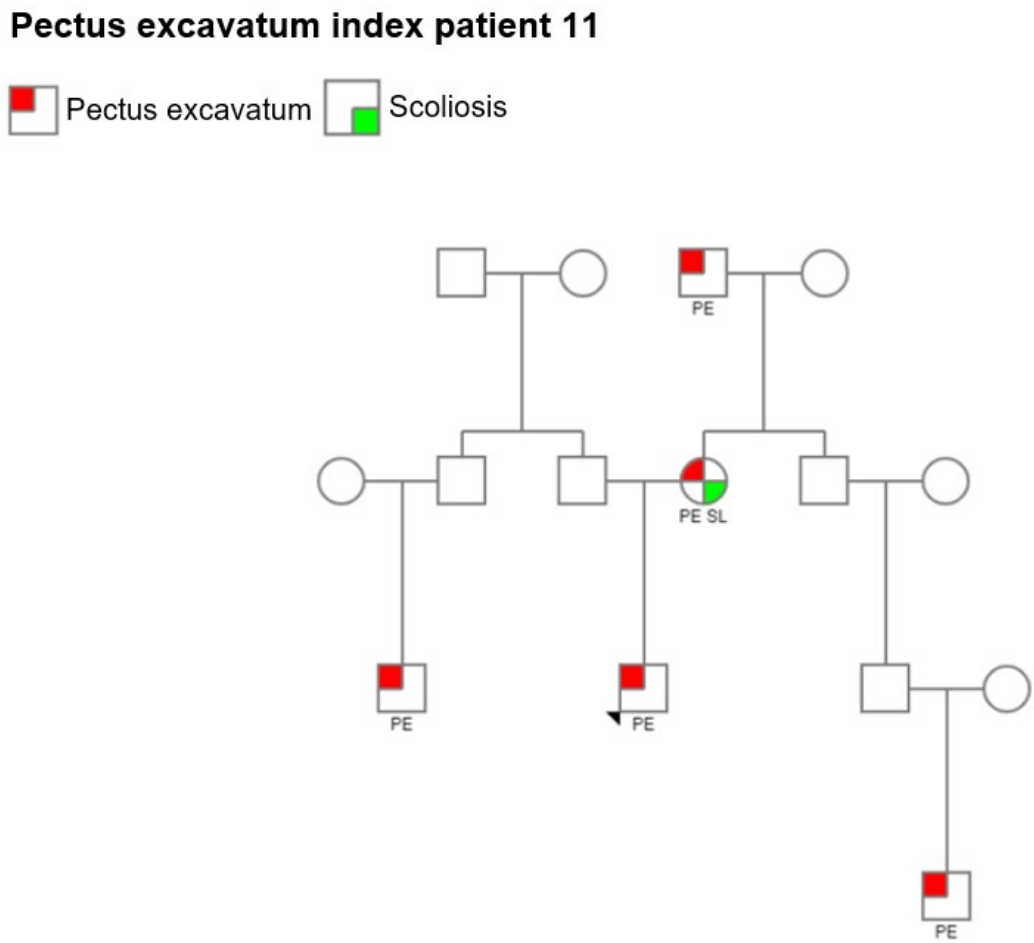

Fig. 37 Pedigree of family with multiple affected relatives

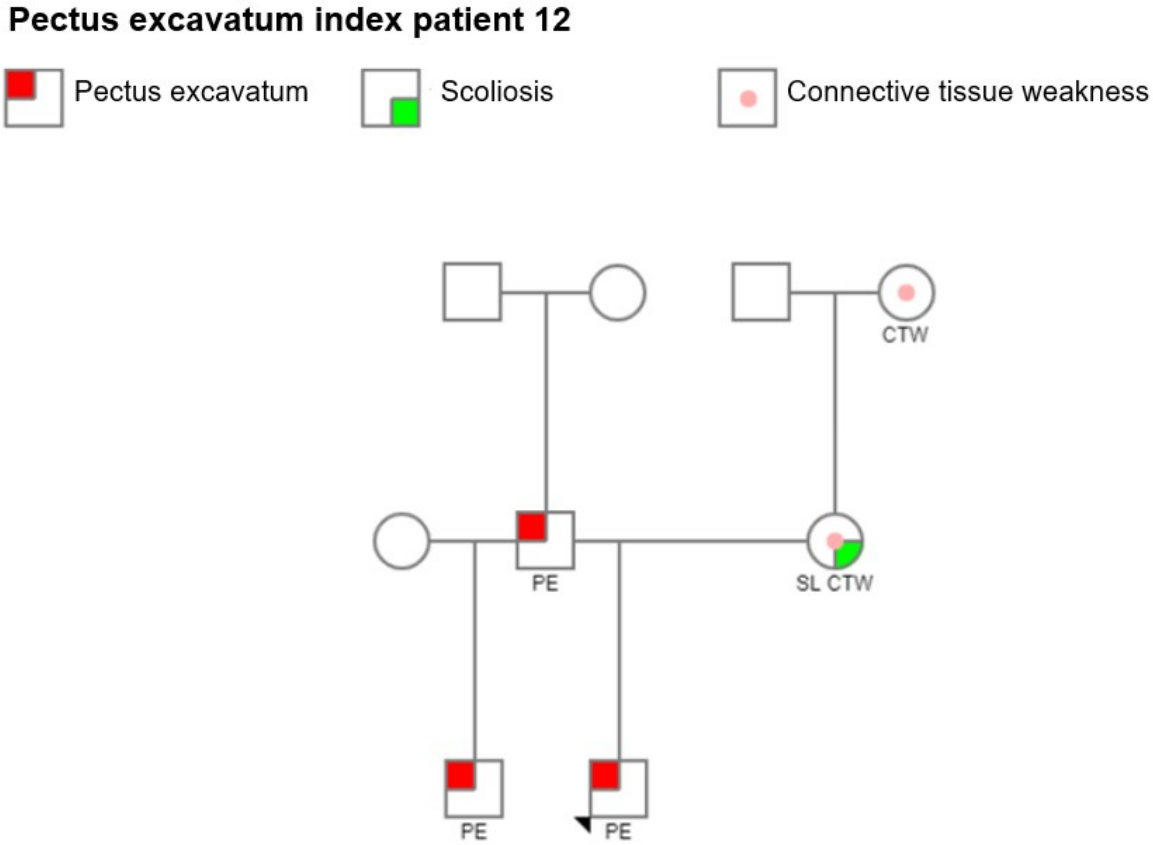

Fig. 38 Pedigree of family with multiple affected relatives

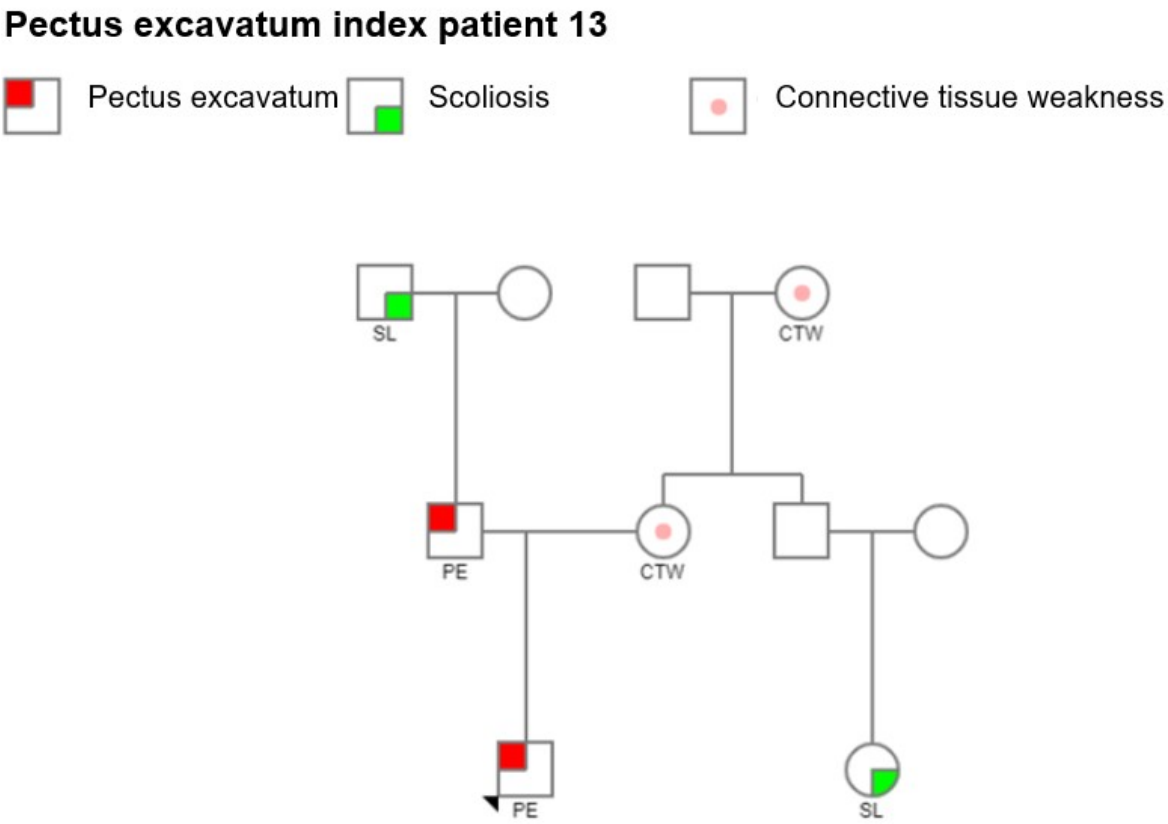

Fig. 39 Pedigree of family with multiple affected relatives

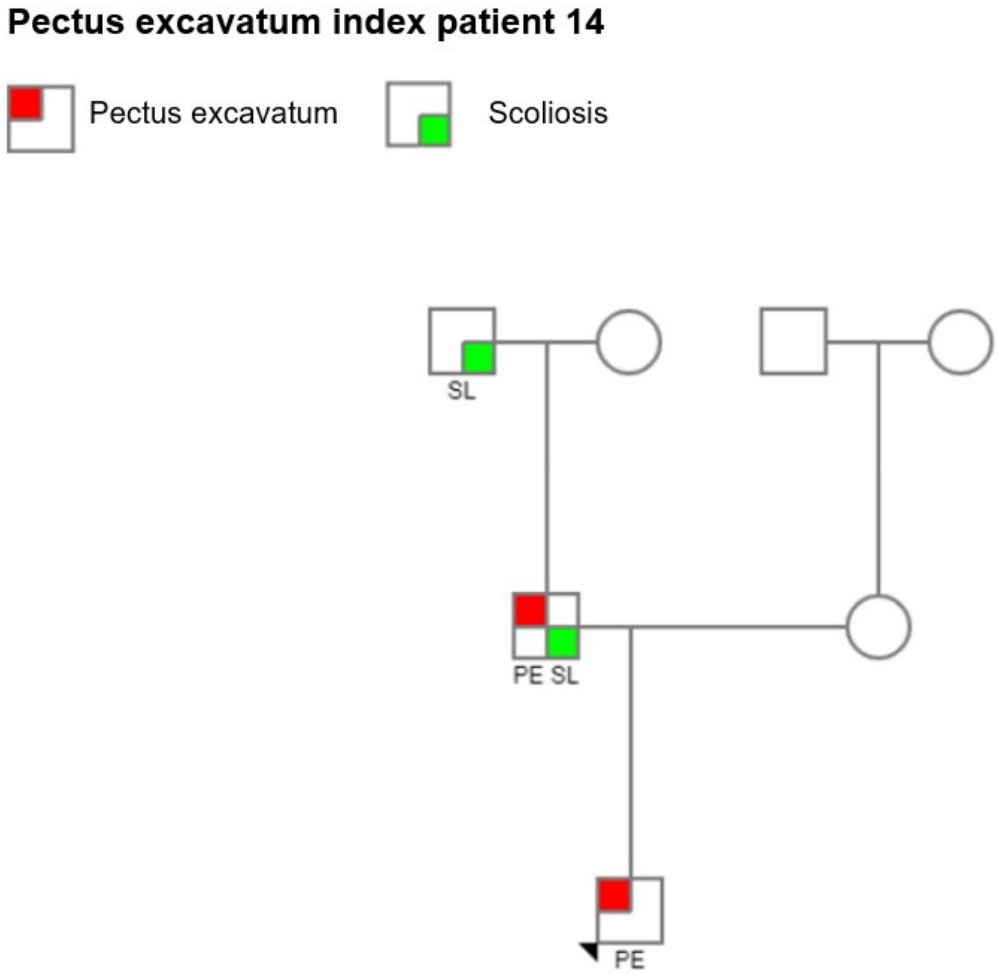

Fig. 40 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 15

Pectus excavatum

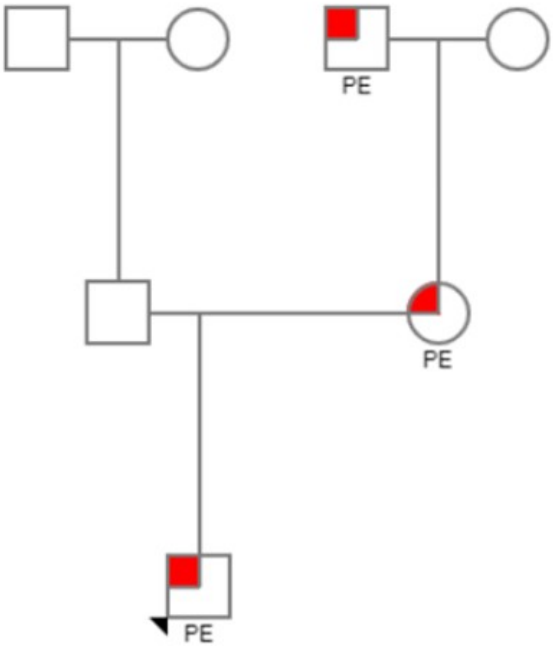

Fig. 41 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 16

Pectus excavatum

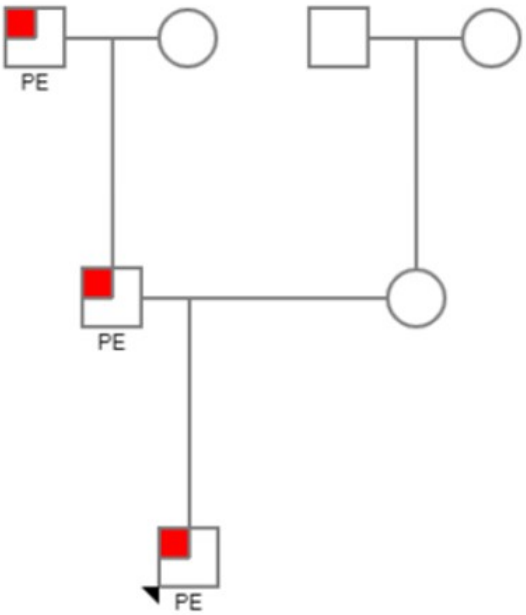

Fig. 42 Pedigree of family with multiple affected relatives

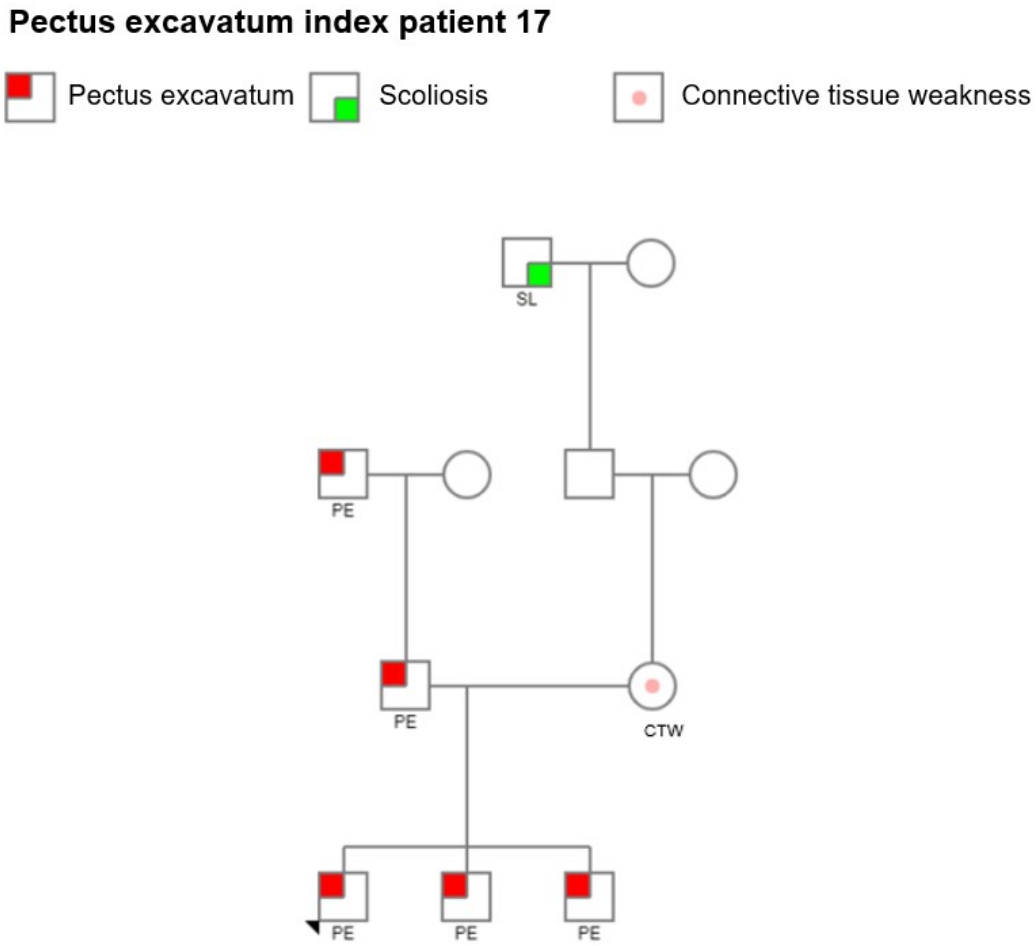

Fig. 43 Pedigree of family with multiple affected relatives

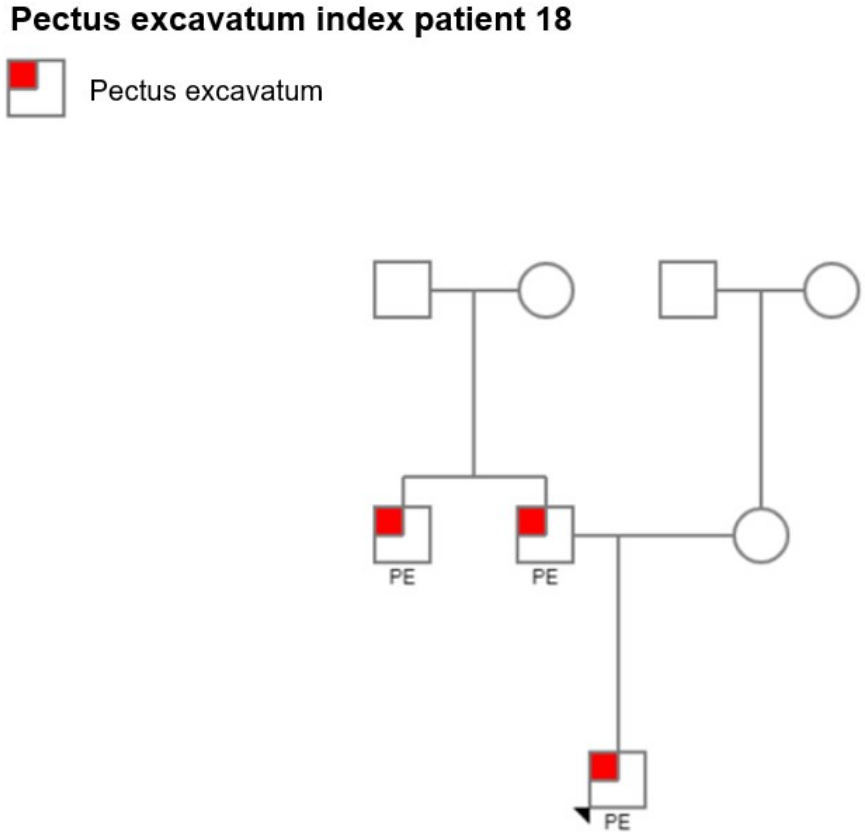

Fig. 44 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 19

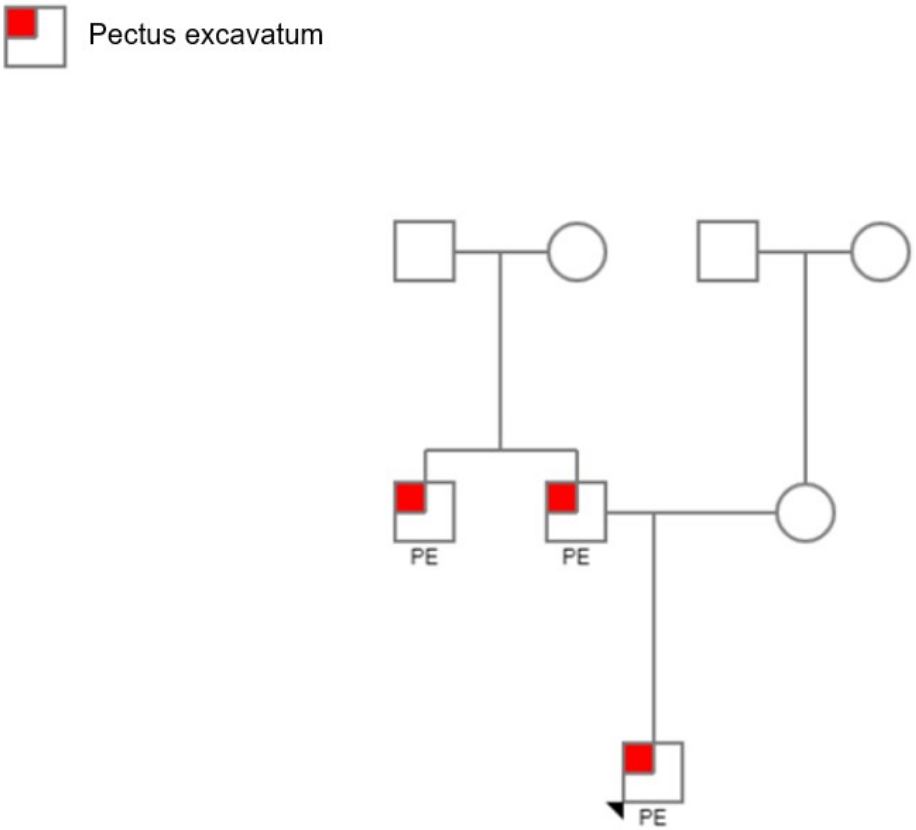

Fig. 45 Pedigree of family with multiple affected relatives

Pectus excavatum index patient 20

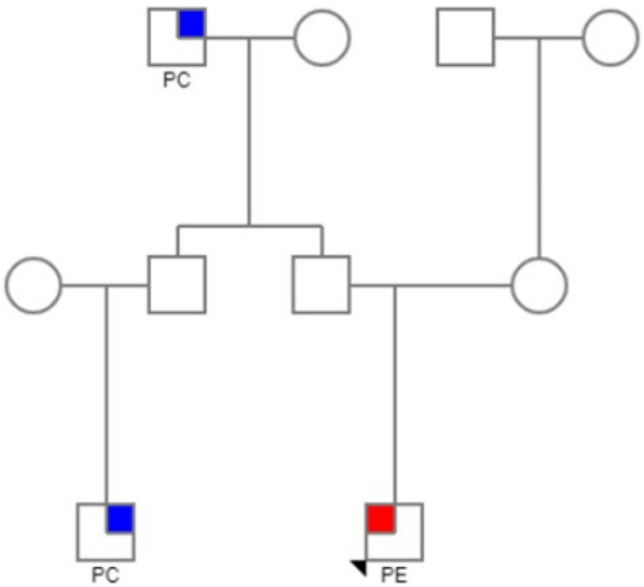

Fig. 46 Pedigree of family with multiple affected relatives

Pectus carinatum and excavatum index patient 21

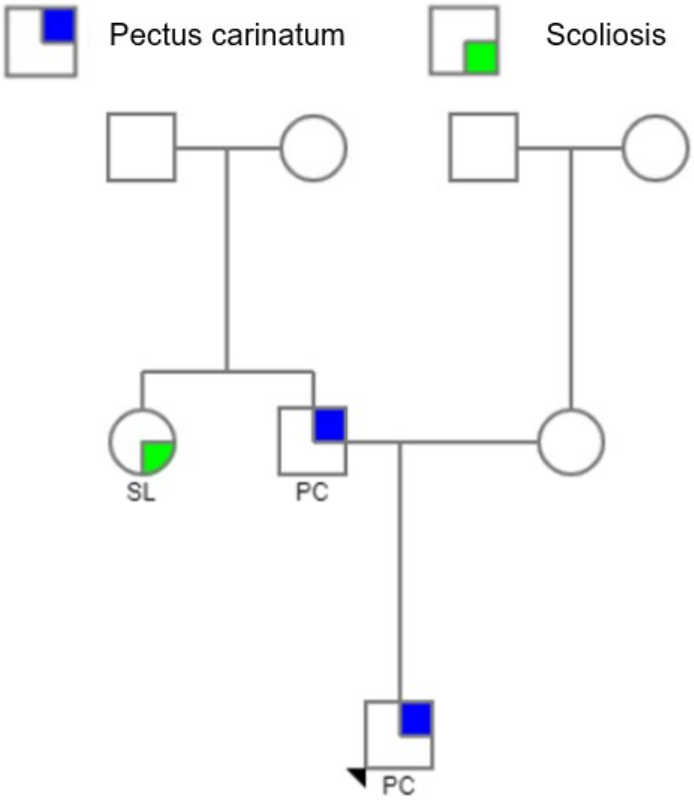

Fig. 47 Pedigree of family with multiple affected relatives

Pectus carinatum index patient 22

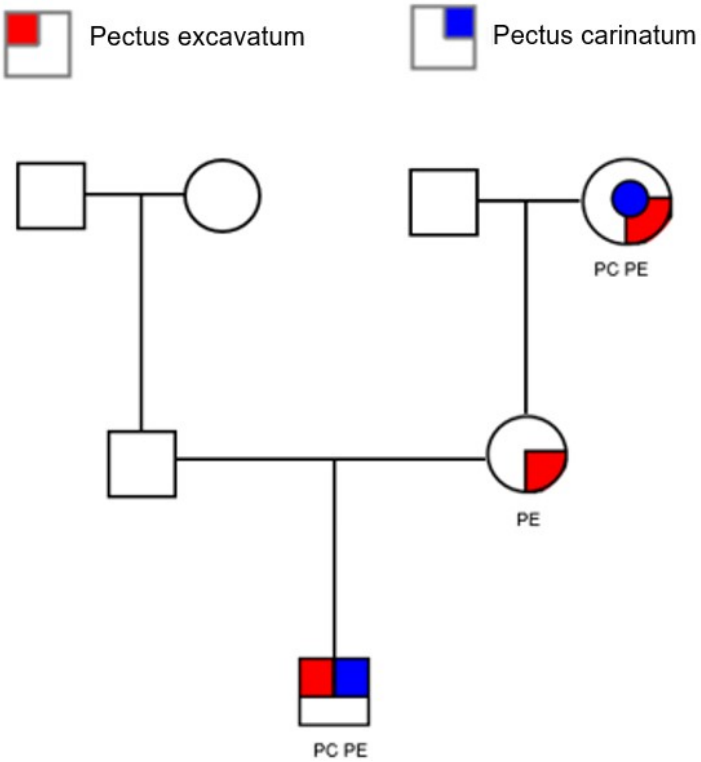

Fig. 48 Pedigree of family with multiple affected relatives

10.10 Associated syndromes according to OMIM, POSSUM, WBDD, Human Phenotype Ontology and MalaCards (selection)

Proven or suspected monogenic syndromes or chromosome aberrations associated with PE in alphabetic order:

Table 12 Common syndromes or chromosome aberrations associated with PE

Name	Inheritance	OMIM	Chromosomal location	Gene
Cantrell Pentalogy	X-linked	**313850**	Xq25-q26.1	*THAS* *TAS*
Cardiofaciocutaneous syndrome	AD	**115150**	12p12.1 7q34	*KRAS* *BRAF*
Coffin-Lowry syndrome	X-linked dominant	**303600**	Xp22.12	*RPS6KA3* *RSK2* *XLID19*
Ehler-Danlos syndrome	AR	**130070** **225400**	5q35.3 1p36.22	*XGPT1* *PLOD1*
Homocystinuria	AR	**236200**	21q22	*CBS*
Loeys	AD	**190182** **609192**	3p22 9q33-q34	*TGFBR2* *TGFBR1* *SMAD3* *TGFB2*
Marfan syndrome	AD	**134797** **154700**	15q21.1	*FBN1*
Moebius syndrome	most sporadically AD	**157900**	13q12.2-q13	*PLXND1* *REV3L*
Multiple endocrine Neoplasia II	AR	**171400**	10q11.21	*RET*
Occipital Horn syndrome	X-linked recessive	**304150**	Xq21.1	*MK* *OHS*
Osteogenesis imperfecta	AD, AR	**166210**	17q22, 7q22.1	*COL1A1* *COL1A2*
Poland syndrome	most sporadically	**173800**	-	-
Ulrich-Noonan syndrome	AD	**163950**	12q24.13	*PTPN11*

Table 13 Syndromes or chromosome aberrations associated with PE

16p11.2p12.2 Microduplication Syndrome	**Lymphangiectasia, Pulmonary, Congenital**
16p13.11 Microdeletion Syndrome	Lymphedema, Hereditary, Iii
16p13.11 Microduplication Syndrome	Malan Overgrowth Syndrome
17q21.31 Microdeletion Syndrome	Mandibuloacral Dysplasia Progeroid Syndrome
19p13.13 Microdeletion Syndrome	Marden-walker Syndrome
20q11.2 Microduplication Syndrome	Marfan Lipodystrophy Syndrome
2p15p16.1 Microdeletion Syndrome	Marfan Syndrome
3-m Syndrome 1	Marfan Syndrome

3q29 Microdeletion Syndrome	Marfanoid Habitus-autosomal Recessive Intellectual Disability Syndrome
45,x/46,xy Mixed Gonadal Dysgenesis	Marfanoid Hypermobility Syndrome
7q11.23 Microduplication Syndrome	Marshall-smith Syndrome
8p Inverted Duplication/deletion Syndrome	Martsolf Syndrome 1
8q24.3 Microdeletion Syndrome	Mcdonough Syndrome
Aarskog-scott Syndrome	Mcdonough Syndrome
Aarskog-scott Syndrome	Melnick-needles Syndrome
Acrocapitofemoral Dysplasia	Menkes Disease
Acrocapitofemoral Dysplasia	Mental Retardation, Autosomal Dominant 36
Acrocraniofacial Dysostosis	Mental Retardation, Autosomal Dominant 7
Acrocraniofacial Dysostosis	Mental Retardation, Buenos Aires Type
Acrofacial Dysostosis, Catania Type	Mental Retardation, X-linked Syndromic, Turner Type
Acrofrontofacionasal Dysostosis 1	Mental Retardation, X-linked, Syndromic 14
Acrootoocular Syndrome	Mental Retardation, X-linked, Syndromic 33
Acropectoral Syndrome	Mental Retardation, X-linked, Syndromic, Claes-jensen Type
Acropectorovertebral Dysplasia	Mental Retardation, X-linked, Syndromic, Snyder-robinson Type
Al-gazali-bakalinova Syndrome	Mgat2-cdg
Allan-herndon-dudley Syndrome	Microbrachycephaly-ptosis-cleft Lip Syndrome
Allan-herndon-dudley Syndrome	Microcephaly, Short Stature, And Impaired Glucose Metabolism 2
Alpha-mannosidosis, Infantile Form	Microcephaly-cervical Spine Fusion Anomalies Syndrome
Amastia, Bilateral, With Ureteral Triplication And Dysmorphism	Microcephaly-corpus Callosum Hypoplasia-intellectual Disability-facial Dysmorphism Syndrome
Anauxetic Dysplasia 3	Micrognathia-recurrent Infections-behavioral Abnormalities-mild Intellectual Disability Syndrome
Aneurysm-osteoarthritis Syndrome	Microphthalmia, Syndromic 1
Anophthalmia-megalocornea-cardiopathy-skeletal Anomalies Syndrome	Microspherophakia And/or Megalocornea, With Ectopia Lentis And With Or Without Secondary Glaucoma
Aortic Aneurysm, Familial Thoracic 10	Mitochondrial Myopathy-cerebellar Ataxia-pigmentary Retinopathy Syndrome
Aortic Aneurysm, Familial Thoracic 9	Mitral Valve Prolapse 1
Arboleda-tham Syndrome	Mohr Syndrome
Arterial Tortuosity Syndrome	Monosomy 18p
Arthrogryposis, Distal, Type 3	Monosomy 18q
Arthrogryposis, Distal, Type 5	Monosomy 9q22.3
Arthrogryposis-oculomotor Limitation-electroretinal Anomalies Syndrome	Monosomy X
Au-kline Syndrome	Mosaic Monosomy X
Auricular Abnormalities-cleft Lip With Or Without Cleft Palate-ocular Abnormalities Syndrome	Mowat-wilson Syndrome
Autoimmune Disease, Multisystem, With Facial Dysmorphism	Mowat-wilson Syndrome
Autosomal Dominant Emery-dreifuss Muscular Dystrophy	Mowat-wilson Syndrome Due To A Zeb2 Point Mutation
Autosomal Dominant Otospondylomegaepiphyseal Dysplasia	Mowat-wilson Syndrome Due To Monosomy 2q22
Autosomal Dominant Robinow Syndrome	Mucopolysaccharidosis-plus Syndrome
Autosomal Recessive Emery-dreifuss Muscular Dystrophy	Multiple Congenital Anomalies-hypotonia-seizures Syndrome 3
Autosomal Recessive Multiple Pterygium Syndrome	Multiple Endocrine Neoplasia, Type Iib
Autosomal Recessive Robinow Syndrome	Multiple Epiphyseal Dysplasia With Robin Phenotype
Ayme-gripp Syndrome	Multiple Epiphyseal Dysplasia, Al-gazali Type
B3galt6-related Spondylodysplastic Ehlers-danlos Syndrome	Multiple Pterygium-malignant Hyperthermia Syndrome
Bannayan-riley-ruvalcaba Syndrome	Multiple Synostoses Syndrome 1
Bannayan-riley-ruvalcaba Syndrome	Muscular Dystrophy, Congenital, Davignon-chauveau Type
Becker Nevus Syndrome	Muscular Dystrophy-dystroglycanopathy (limb-girdle), Type C, 4
Becker Nevus Syndrome	Myopathic Ehlers-danlos Syndrome
Bilateral Perisylvian Polymicrogyria	Myopathy, Areflexia, Respiratory Distress, And Dysphagia, Early-onset
Bohring-opitz Syndrome	Myopathy, Congenital, With Diaphragmatic Defects, Respiratory Insufficiency, And Dysmorphic Facies
Boudin-mortier Syndrome	Myopathy, Mitochondrial, And Ataxia
Brachycephaly, Deafness, Cataract, Microstomia, And Mental Retardation	Myopathy, Myofibrillar, 8
Brachyolmia, Maroteaux Type	Nail-patella Syndrome
Brachyphalangy, Polydactyly, And Tibial Aplasia/hypoplasia	Nail-patella Syndrome
Braddock Syndrome	Nemaline Myopathy 1
Branchioskeletogenital Syndrome	Nemaline Myopathy 11, Autosomal Recessive
Brooks-wisniewski-brown Syndrome	Neurodevelopmental Disorder With Brain Anomalies, Seizures, And Scoliosis
C Syndrome	Neurodevelopmental Disorder With Cataracts, Poor Growth, And Dysmorphic Facies
Camptodactyly Syndrome, Guadalajara Type 1	Neurodevelopmental Disorder With Coarse Facies And Mild Distal Skeletal Abnormalities
Camptodactyly Syndrome, Guadalajara Type 2	Neurodevelopmental Disorder With Dysmorphic Facies And Distal Skeletal Anomalies
Camptodactyly Syndrome, Guadalajara, Type I	Neurodevelopmental Disorder With Hypotonia And Variable Intellectual And Behavioral Abnormalities
Camptodactyly Syndrome, Guadalajara, Type Ii	Neurodevelopmental Disorder With Microcephaly, Impaired Language, Epilepsy, And Gait Abnormalities, Autosomal Dominant
Camptodactyly, Tall Stature, And Hearing Loss Syndrome	Neurofaciodigitorenal Syndrome
Cap Myopathy	Neurofacioskeletal Syndrome With Or Without Renal

	Agenesis
Cardiac-valvular Ehlers-danlos Syndrome	Neurofibromatosis Type 1 Due To Nf1 Mutation Or Intragenic Deletion
Cardiofaciocutaneous Syndrome	Neurofibromatosis, Type I
Cardiofaciocutaneous Syndrome 1	Neurofibromatosis-noonan Syndrome
Cardiofaciocutaneous Syndrome 3	Neuroocular Syndrome
Carpenter Syndrome 2	Non-distal Trisomy 10q
Cataract-hypertrichosis-intellectual Disability Syndrome	Noonan Syndrome
Catel-manzke Syndrome	Noonan Syndrome 1
Catel-manzke Syndrome	Noonan Syndrome 10
Chitayat Syndrome	Noonan Syndrome 11
Christianson Syndrome	Noonan Syndrome 12
Chromosome 15q25 Deletion Syndrome	Noonan Syndrome 2
Chromosome 16p13.3 Duplication Syndrome	Noonan Syndrome 3
Chromosome 17q11.2 Deletion Syndrome, 1.4-mb	Noonan Syndrome 4
Chromosome 17q11.2 Duplication Syndrome, 1.4-mb	Noonan Syndrome 6
Chromosome 2p16.1-p15 Deletion Syndrome	Noonan Syndrome 7
Chromosome 3q29 Deletion Syndrome	Noonan Syndrome With Multiple Lentigines
Chromosome 6pter-p24 Deletion Syndrome	Noonan Syndrome-like Disorder With Loose Anagen Hair
Clapo Syndrome	Noonan Syndrome-like Disorder With Loose Anagen Hair 2
Classic Homocystinuria	Noonan Syndrome-like Disorder With Or Without Juvenile Myelomonocytic Leukemia
Classical-like Ehlers-danlos Syndrome Type 2	Occipital Horn Syndrome
Cleft Palate-large Ears-small Head Syndrome	Occipital Horn Syndrome
Coffin-lowry Syndrome	Ophthalmoplegia, External, With Rib And Vertebral Anomalies
Coffin-lowry Syndrome	Opsismodysplasia
Coffin-siris Syndrome 12	Optic Atrophy, Hearing Loss, And Peripheral Neuropathy, Autosomalrecessive
Coffin-siris Syndrome 6	Orofaciodigital Syndrome Iii
Cohen Syndrome	Orofaciodigital Syndrome Iv
Cole-carpenter Syndrome 2	Orofaciodigital Syndrome Type 3
Congenital Disorder Of Glycosylation, Type Iia	Osteochondrodysplasia, Brachydactyly, And Overlapping Malformed Digits
Congenital Disorder Of Glycosylation, Type Iiw	Osteofibrous Dysplasia, Susceptibility To
Congenital Fiber-type Disproportion Myopathy	Osteogenesis Imperfecta
Congenital Heart Defects And Skeletal Malformations Syndrome	Osteogenesis Imperfecta 21
Congenital Muscular Dystrophy, Fukuyama Type	Osteogenesis Imperfecta Congenita, Microcephaly, And Cataracts
Congenital Muscular Dystrophy-respiratory Failure-skin Abnormalities-joint Hyperlaxity Syndrome	Osteogenesis Imperfecta, Type Ix
Cornelia De Lange Syndrome	Osteogenesis Imperfecta, Type Vii
Corpus Callosum Agenesis-intellectual Disability-coloboma-micrognathia Syndrome	Osteogenesis Imperfecta, Type Xix
Corpus Callosum, Agenesis Of, With Mental Retardation, Ocular Coloboma,and Micrognathia	Osteopathia Striata With Cranial Sclerosis
Cowden Syndrome	Osteopetrosis With Renal Tubular Acidosis
Cowden Syndrome 1	Otofacioosseous-gonadal Syndrome
Cowden Syndrome 5	Otopalatodigital Syndrome, Type I
Cowden Syndrome 6	Otopalatodigital Syndrome, Type Ii
Cranioectodermal Dysplasia	Pectus Excavatum
Cranioectodermal Dysplasia	Pectus Excavatum, Macrocephaly, Short Stature, And Dysplastic Nails
Cranioectodermal Dysplasia 2	Pectus Excavatum-macrocephaly-dysplastic Nails Syndrome
Cranioectodermal Dysplasia 4	Pericardial And Diaphragmatic Defect
Craniofacial Dysostosis With Diaphyseal Hyperplasia	Peters-plus Syndrome
Craniofaciofrontodigital Syndrome	Pierre Robin Sequence With Pectus Excavatum And Rib And Scapular Anomalies
Craniofrontonasal Dysplasia	Polydactyly, Postaxial, With Dental And Vertebral Anomalies
Craniofrontonasal Syndrome	Postaxial Acrofacial Dysostosis
Craniosynostosis-mental Retardation Syndrome Of Lin And Gettig	Primary Microcephaly-mild Intellectual Disability-young-onset Diabetes Syndrome
Cree Mental Retardation Syndrome	Primrose Syndrome
Cutis Laxa, Autosomal Recessive, Type Ia	Proximal Xq28 Duplication Syndrome
Cutis Laxa, Autosomal Recessive, Type Ib	Prune Belly Syndrome
Cutis Laxa, Autosomal Recessive, Type Iiia	Prune Belly Syndrome
D-bifunctional Protein Deficiency	Pseudoaminopterin Syndrome
De Barsy Syndrome	Pseudopapilledema, Ocular Hypotelorism, Blepharophimosis, And Handanomalies
Desbuquois Dysplasia 2	Pterygia, Mental Retardation, And Distinctive Craniofacial Features
Distal Monosomy 10q	Pyruvate Dehydrogenase Deficiency
Distal Monosomy 7q36	Pyruvate Dehydrogenase E3-binding Protein Deficiency
Distal Trisomy 15q	Qazi-markouizos Syndrome
Distal Trisomy 18q	Radioulnar Synostosis-developmental Delay-hypotonia Syndrome
Dubowitz Syndrome	Raine Syndrome
Dyrk1a-related Intellectual Disability Syndrome	Rajab Interstitial Lung Disease With Brain Calcifications
Dyrk1a-related Intellectual Disability Syndrome Due To 21q22.13q22.2 Microdeletion	Recombinant 8 Syndrome
Dysostosis, Stanescu Type	Recombinant Chromosome 8 Syndrome
Early-onset Progressive Diffuse Brain Atrophy-microcephaly-muscle	Renpenning Syndrome

Weakness-optic Atrophy Syndrome	
Ectodermal Dysplasia, Sensorineural Hearing Loss, And Distinctive Facial Features	Renpenning Syndrome
Ectodermal Dysplasia-intellectual Disability-central Nervous System Malformation Syndrome	Richieri-costa/guion-almeida Syndrome
Ehlers-danlos Syndrome, Autosomal Recessive, Cardiac Valvular Form	Ring Chromosome 10 Syndrome
Ehlers-danlos Syndrome, Musculocontractural Type 1	Ring Chromosome 12 Syndrome
Ehlers-danlos Syndrome, Spondylodysplastic Type, 2	Robinow Syndrome, Autosomal Dominant 1
Ehlers-danlos Syndrome, Type I	Robinow Syndrome, Autosomal Recessive
Ehlers-danlos Syndrome, Vascular Type	Rubinstein-taybi Syndrome 1
Elsahy-waters Syndrome	Ruijs-aalfs Syndrome
Emery-dreifuss Muscular Dystrophy	Saul-wilson Syndrome
Emery-dreifuss Muscular Dystrophy 1, X-linked	Schwartz-jampel Syndrome
Eng-strom Syndrome	Short Stature And Facioauriculothoracic Malformations
Epileptic Encephalopathy, Early Infantile, 77	Short Stature, Facial Dysmorphism, And Skeletal Anomalies With Or Without Cardiac Anomalies
Facial Dysmorphism-anorexia-cachexia-eye And Skin Anomalies Syndrome	Short-limb Skeletal Dysplasia With Severe Combined Immunodeficiency
Faciodigitogenital Syndrome, Autosomal Recessive	Shprintzen-goldberg Craniosynostosis Syndrome
Faciothoracogenital Syndrome	Shprintzen-goldberg Syndrome
Fibromuscular Dysplasia, Multifocal	Simpson-golabi-behmel Syndrome
Fibrosis Of Extraocular Muscles, Congenital, 3b	Simpson-golabi-behmel Syndrome, Type 1
Fountain Syndrome	Skeletal Dysplasia, Mild, With Joint Laxity And Advanced Bone Age
Fragile X Mental Retardation Syndrome	Skin Creases, Congenital Symmetric Circumferential, 1
Frank-ter Haar Syndrome	Skin Creases, Congenital Symmetric Circumferential, 2
Frontometaphyseal Dysplasia 2	Sotos Syndrome
Frontoocular Syndrome	Sotos Syndrome 2
Galloway-mowat Syndrome 7	Specc1l-related Hypertelorism Syndrome
Gaucher Disease-ophthalmoplegia-cardiovascular Calcification Syndrome	Spinal Muscular Atrophy, Type I, With Congenital Bone Fractures
Geleophysic Dysplasia 1	Spinocerebellar Ataxia, Autosomal Recessive 31
Global Developmental Delay-neuro-ophthalmological Abnormalities-seizures-intellectual Disability Syndrome	Spondyloepimetaphyseal Dysplasia, Krakow Type
Gordon Syndrome	Spondyloepimetaphyseal Dysplasia, Matrilin-3 Type
Growth Delay Due To Insulin-like Growth Factor I Resistance	Spondyloepiphyseal Dysplasia-brachydactyly And Distinctive Speech
Growth Factors, Combined Defect Of	Spondyloepiphyseal Dysplasia-brachydactyly-speech Disorder Syndrome
Hallermann-streiff Syndrome	Spondylometaepiphyseal Dysplasia, Short Limb-hand Type
Hamamy Syndrome	Stickler Syndrome, Type I
Hennekam Lymphangiectasia-lymphedema Syndrome	Subaortic Ste—sis—short Stature Syndrome
Holt-oram Syndrome	Symptomatic Form Of Coffin-lowry Syndrome In Female Carriers
Holt-oram Syndrome	Tarp Syndrome
Homocystinuria Due To Cystathionine Beta-synthase Deficiency	Tarp Syndrome
Hyperphosphatasia-intellectual Disability Syndrome	Tbck-related Intellectual Disability Syndrome
Hypertelorism And Other Facial Dysmorphism, Brachydactyly, Genital Abnormalities, Mental Retardation, And Recurrent Inflammatory Episodes	Teebi-shaltout Syndrome
Hypertrophic Osteoarthropathy, Primary, Autosomal Recessive 1	Tetrasomy 5p
Hypogonadotropic Hypogonadism 3 With Or Without Anosmia	Thoracic Dysostosis, Isolated
Immunoskeletal Dysplasia With Neurodevelopmental Abnormalities	Trichohepatoneurodevelopmental Syndrome
Insulin-like Growth Factor I, Resistance To	Trisomy X
Intellectual Developmental Disorder, X-linked, Syndromic, Hackman-di Donato Type	Turner Syndrome
Intellectual Disability Syndrome Due To A Dyrk1a Point Mutation	Turner Syndrome Due To Structural X Chromosome Anomalies
Intellectual Disability-cardiac Anomalies-short Stature-joint Laxity Syndrome	Turnpenny-fry Syndrome
Intellectual Disability-cataracts-calcified Pinnae-myopathy Syndrome	Typical Nemaline Myopathy
Intellectual Disability-craniofacial Dysmorphism-cryptorchidism Syndrome	Tyshchenko Syndrome
Intellectual Disability-hypotonia-brachycephaly-pyloric Stenosis-cryptorchidism Syndrome	Usmani-riazuddin Syndrome, Autosomal Recessive
Intellectual Disability-seizures-hypophosphatasia-ophthalmic-skeletal Anomalies Syndrome	Van Den Ende-gupta Syndrome
Jacobsen Syndrome	Vascular Ehlers-danlos Syndrome
Kagami-ogata Syndrome Due To Maternal 14q32.2 Microdeletion	Vater-like Defects With Pulmonary Hypertension, Laryngeal Webs, And Growth Deficiency
Kagami-ogata Syndrome Due To Paternal Uniparental Disomy Of Chromosome 14	Vertebral Hypersegmentation And Orofacial Anomalies
Koolen-de Vries Syndrome	Vertebral, Cardiac, Tracheoesophageal, Renal, And Limb Defects
Koolen-de Vries Syndrome	Viss Syndrome
Koolen-de Vries Syndrome Due To A Point Mutation	Waardenburg Syndrome, Type 2e
Kyphoscoliotic Ehlers-danlos Syndrome	Wiedemann-steiner Syndrome
Kyphoscoliotic Ehlers-danlos Syndrome Due To Lysyl Hydroxylase 1 Deficiency	Williams Syndrome
Larsen Syndrome	Williams-beuren Syndrome
Lateral Meningocele Syndrome	Wrinkly Skin Syndrome
Lateral Meningocele Syndrome	Wrinkly Skin Syndrome
Leopard Syndrome 1	X-linked Emery-dreifuss Muscular Dystrophy
Lichtenstein Syndrome	X-linked Intellectual Disability, Abidi Type

Lipodystrophy Due To Peptidic Growth Factors Deficiency	X-linked Intellectual Disability, Snyder Type
Loeys-dietz Syndrome	X-linked Intellectual Disability-cubitus Valgus-dysmorphism Syndrome
Loeys-dietz Syndrome 2	X-linked Mandibulofacial Dysostosis
Loeys-dietz Syndrome 5	Xp22.13p22.2 Duplication Syndrome
Lujan-fryns Syndrome	Xq12-q13.3 Duplication Syndrome
Lujan-fryns Syndrome	You-hoover-fong Syndrome

Proven or suspected monogenic syndromes or chromosome aberrations associated with PC in alphabetic order:

Table 14 Common syndromes or chromosome aberrations associated with PC

Name	Inheritance	OMIM	Chromosomal location	Gene
Cardiofaciocutaneous syndrome	AD	**115150**	12p12.1 7q34	*KRAS* *BRAF*
Coffin-Lowry syndrome	X-linked dominant	**303600**	Xp22.12	*RPS6KA3* *RSK2* *XLID19*
Ehler-Danlos syndrome	AR	**130070** **225400**	5q35.3 1p36.22	*XGPT1* *PLOD1*
Homocystinuria	AR	**236200**	21q22	*CBS*
Loeys	AD	**190182** **609192**	3p22 9q33-q34	*TGFBR2* *TGFBR1* *SMAD3* *TGFB2*
Marfan syndrome	AD	**134797** **154700**	15q21.1	*FBN1*
Occipital Horn syndrome	X-linked recessive	**304150**	Xq21.1	*MK* *OHS*
Osteogenesis imperfecta	AD, AR	**166210**	17q22, 7q22.1	*COL1A1* *COL1A2*
Poland syndrome	most sporadically	**173800**	-	-
Ulrich-Noonan syndrome	AD	**163950**	12q24.13	*PTPN11*

Table 15 Syndromes or chromosome aberrations associated with PC

17q21.31 Microdeletion Syndrome	Mental Retardation, Buenos Aires Type
20p12.3 Microdeletion Syndrome	Mental Retardation, X-linked Syndromic, Raymond Type
20q11.2 Microduplication Syndrome	Mental Retardation, X-linked, Syndromic 14
3-m Syndrome 2	Mental Retardation, X-linked, Syndromic, Bain Type
3q29 Microdeletion Syndrome	Mental Retardation, X-linked, Syndromic, Snyder-robinson Type
Acro-renal-mandibular Syndrome	Microcephalic Osteodysplastic Primordial Dwarfism, Type Iii
Acrocapitofemoral Dysplasia	Mowat-wilson Syndrome
Acrocapitofemoral Dysplasia	Mowat-wilson Syndrome
Acropectoral Syndrome	Mowat-wilson Syndrome Due To A Zeb2 Point Mutation
Al-gazali-bakalinova Syndrome	Mowat-wilson Syndrome Due To Monosomy 2q22
Alpha-mannosidosis	Mucolipidosis Iii Gamma
Alpha-mannosidosis, Infantile Form	Mucopolysaccharidosis Type 4
Alpha-thalassemia-intellectual Disability Syndrome Linked To Chromosome 16	Mucopolysaccharidosis Vii

Amish Nemaline Myopathy	Mucopolysaccharidosis-like Syndrome With Congenital Heart Defects And Hematopoietic Disorders
Aneurysm-osteoarthritis Syndrome	Mucopolysaccharidosis-plus Syndrome
Aortic Aneurysm, Familial Thoracic 9	Multiple Joint Dislocations, Short Stature, Craniofacial Dysmorphism, With Or Without Congenital Heart Defects
Arterial Tortuosity Syndrome	Myasthenic Syndrome, Congenital, 19
Aspartylglucosaminuria	Myotonia With Skeletal Abnormalities And Mental Retardation
Autosomal Dominant Otospondylomegaepiphyseal Dysplasia	Nemaline Myopathy 5, Amish Type
Autosomal Dominant Robinow Syndrome	Neonatal Marfan Syndrome
Autosomal Recessive Robinow Syndrome	Neurodevelopmental Disorder With Hypotonia, Facial Dysmorphism, And Brain Abnormalities
Autosomal Recessive Spastic Paraplegia Type 53	Neurodevelopmental Disorder With Progressive Microcephaly, Spasticity, And Brain Anomalies
B3galt6-related Spondylodysplastic Ehlers-danlos Syndrome	Neurofibromatosis-noonan Syndrome
Basel-vanagaite-smirin-yosef Syndrome	Neutropenia, Severe Congenital, 4, Autosomal Recessive
Becker Nevus Syndrome	Noonan Syndrome
Brachycephaly, Deafness, Cataract, Microstomia, And Mental Retardation	Noonan Syndrome 1
Brachyolmia Type 1, Hobaek Type	Noonan Syndrome 10
Bruck Syndrome 1	Noonan Syndrome 2
Bruck Syndrome 2	Noonan Syndrome 3
Camptodactyly Syndrome, Guadalajara Type 1	Noonan Syndrome 7
Camptodactyly Syndrome, Guadalajara, Type I	Noonan Syndrome With Multiple Lentigines
Cardiofaciocutaneous Syndrome 1	Noonan Syndrome-like Disorder With Loose Anagen Hair 2
Carpenter Syndrome 2	Occipital Horn Syndrome
Cartilage-hair Hypoplasia	Occipital Horn Syndrome
Catel-manzke Syndrome	Ocular Anomalies-axonal Neuropathy-developmental Delay Syndrome
Childhood-onset Motor And Cognitive Regression Syndrome With Extrapyramidal Movement Disorder	Osteochondrodysplasia
Chromosome 3q29 Deletion Syndrome	Osteogenesis Imperfecta
Classic Homocystinuria	Osteogenesis Imperfecta Congenita, Microcephaly, And Cataracts
Coffin-lowry Syndrome	Osteogenesis Imperfecta, Type Ix
Coffin-lowry Syndrome	Osteogenesis Imperfecta, Type Xii
Combined Oxidative Phosphorylation Deficiency 25	Osteogenesis Imperfecta, Type Xiii
Congenital Disorder Of Glycosylation, Type Iiw	Osteogenesis Imperfecta, Type Xix
90ontractualtural Arachnodactyly, Congenital	Overgrowth-macrocephaly-facial Dysmorphism Syndrome
Contractures, Pterygia, And Spondylocarpostarsal Fusion Syndrome 1a	Pancreatic And Cerebellar Agenesis
Cornelia De Lange Syndrome 4	Parana Hard Skin Syndrome
Costello Syndrome	Penoscrotal Transposition
Craniofaciofrontodigital Syndrome	Plaa-associated Neurodevelopmental Disorder
Craniosynostosis With Ocular Abnormalities And Hallucal Defects	Poland Syndrome
Craniosynostosis-hydrocephalus-arnold-chiari Malformation Type I-radioulnar Synostosis Syndrome	Polydactyly, Postaxial, With Dental And Vertebral Anomalies
Craniosynostosis-mental Retardation Syndrome Of Lin And Gettig	Presynaptic Congenital Myasthenic Syndromes
Cryptorchidism-arachnodactyly-intellectual Disability Syndrome	Prune Belly Syndrome
Desbuquois Dysplasia 2	Pycr2-related Microcephaly-progressive Leukoencephalopathy
Developmental And Speech Delay Due To Sox5 Deficiency	Radioulnar Synostosis-microcephaly-scoliosis Syndrome
Distal Trisomy 17q	Richieri Costa-da Silva Syndrome
Dyggve-melchior-clausen Disease	Ruvalcaba Syndrome
Dyggve-melchior-clausen Disease	Saul-wilson Syndrome
Dysmorphism-pectus Carinatum-joint Laxity Syndrome	Scarf Syndrome
Early-onset Progressive Diffuse Brain Atrophy-microcephaly-muscle Weakness-optic Atrophy Syndrome	Scarf Syndrome
Ehlers-danlos Syndrome, Spondylodysplastic Type, 1	Schwartz-jampel Syndrome
Ellis-van Creveld Syndrome	Schwartz-jampel Syndrome, Type 1
Epidermolysis Bullosa Simplex 2d, Generalized, Intermediate Or Severe, Autosomal Recessive	Short Stature And Facioauriculothoracic Malformations
Geroderma Osteodysplastica	Short-rib Thoracic Dysplasia 6 With Or Without Polydactyly
Glycosylphosphatidylinositol Biosynthesis Defect 18	Shprintzen-goldberg Craniosynostosis Syndrome
Gm1 Gangliosidosis Type 1	Shprintzen-goldberg Syndrome
Hajdu-cheney Syndrome	Sialidosis Type 1
Harel-yoon Syndrome	Sialidosis Type 2
Homocystinuria Due To Cystathionine Beta-synthase Deficiency	Simpson-golabi-behmel Syndrome, Type 1
Hunter-macdonald Syndrome	Smith-mccort Dysplasia 2
Hypertelorism And Other Facial Dysmorphism, Brachydactyly, Genital Abnormalities, Mental Retardation, And Recurrent Inflammatory Episodes	Spastic Paraplegia 53, Autosomal Recessive
Hypospadias, Hypertelorism, Upper Lid Coloboma, And Mixed-type Hearingloss	Spinocerebellar Ataxia 43
Hypotonia, Infantile, With Psychomotor Retardation And Characteristic Facies 1	Spinocerebellar Ataxia Type 43
Immunodeficiency 59 And Hypoglycemia	Spondylocarpotarsal Synostosis Syndrome
Intellectual Developmental Disorder, X-linked, Syndromic, Hackman-di Donato Type	Spondylocostal Dysostosis 5
Intellectual Disability, Buenos-aires Type	Spondylodysplastic Ehlers-danlos Syndrome
Intellectual Disability-coarse Face-macrocephaly-cerebellar Hypotrophy Syndrome	Spondyloenchondrodysplasia
Intellectual Disability-myopathy-short Stature-endocrine Defect Syndrome	Spondyloepimetaphyseal Dysplasia With Joint Laxity
Intellectual Disability-polydactyly-uncombable Hair Syndrome	Spondyloepimetaphyseal Dysplasia, Irapa Type
Joint Laxity, Short Stature, And Myopia	Spondyloepimetaphyseal Dysplasia, Irapa Type
Joubert Syndrome 35	Spondyloepimetaphyseal Dysplasia, Strudwick Type
Joubert Syndrome 36	Spondyloepimetaphyseal Dysplasia, X-linked

Juvenile Paget Disease	Spondyloepiphyseal Dysplasia Congenita
Kilquist Syndrome	Spondyloepiphyseal Dysplasia Tarda, Autosomal Dominant
Kniest-like Dysplasia With Pursed Lips And Ectopia Lentis	Spondyloepiphyseal Dysplasia Tarda, Autosomal Recessive, Leroy-sprangertype
Koolen-de Vries Syndrome Due To A Point Mutation	Spondyloepiphyseal Dysplasia, Kondo-fu Type
Kyphoscoliotic Ehlers-danlos Syndrome	Spondylometaphyseal Dyspla'ia, 'corner Fra'ture' Type
Lamb-shaffer Syndrome	Spondylometaphyseal Dysplasia, Corner Fracture Type
Larsen Syndrome	Spondylometaphyseal Dysplasia, Kozlowski Type
Leopard Syndrome 1	Spondylometaphyseal Dysplasia, Kozlowski Type
Loeys-dietz Syndrome	Spondylometaphyseal Dysplasia, Type A4
Loeys-dietz Syndrome 2	Spondylometaphyseal Dysplasia, X-linked
Loeys-dietz Syndrome 3	Spondyloperipheral Dysplasia
Loeys-dietz Syndrome 5	Stickler Syndrome
Man1b1-cdg	Symptomatic Form Of Coffin-lowry Syndrome In Female Carriers
Marden-walker Syndrome	Teebi-shaltout Syndrome
Marfan Syndrome	Telo2-related Intellectual Disability-neurodevelopmental Disorder
Marfan Syndrome	Trichorhinophalangeal Syndrome Type 1 And 3
Marfanoid Habitus With Situs Inversus	Trichorhinophalangeal Syndrome, Type I
Marfanoid Hypermobility Syndrome	Turnpenny-fry Syndrome
Marinesco-sjögren Syndrome	Ulna And Fibula, Absence Of, With Severe Limb Deficiency
Martsolf Syndrome 1	Ulnar-mammary Syndrome
Mass Syndrome	Usmani-riazuddin Syndrome, Autosomal Dominant
Mcdonough Syndrome	Viss Syndrome
Meier-gorlin Syndrome 1	X-linked Intellectual Disability, Snyder Type

Proven or suspected monogenic syndromes or chromosome aberrations associated with SC in alphabetic order:

Table 16 Common syndromes or chromosome aberrations associated with SC

Name	Inheritance	OMIM	Chromosomal location	Gene
Cantrell Pentalogy	X-linked	**313850**	Xq25-q26.1	*THAS TAS*
Coffin-Lowry syndrome	X-linked dominant	**303600**	Xp22.12	*RPS6KA3 RSK2 XLID19*
Goltz-Gorlin syndrome (focal dermal hypoplasia)	X-linked dominant	**305600**	Xp11.23	*PORCN*
Hemangiomas, cavernous of face and supraumbilical midline raphe		**140850**		
PHACE association	sporadically	**606519**	-	-

Table 17 Associations mentioned in SC

No syndromes mentioned; the following two clinical associations are listed:	Abnormality of vision
Abnormality of the neck, Webbed neck	

10.11 Supplementary figures on percentiles for weight, height, and BMI
Height, weight, and BMI of patients with PE (male and female) are shown in the figures below. The following supplemental figures illustrate the data obtained from this study. They show that body measurements were significantly abnormal.

Percentiles of the above data are shown in the following graphs:

Height percentile curves for boys aged 0 to 18 years

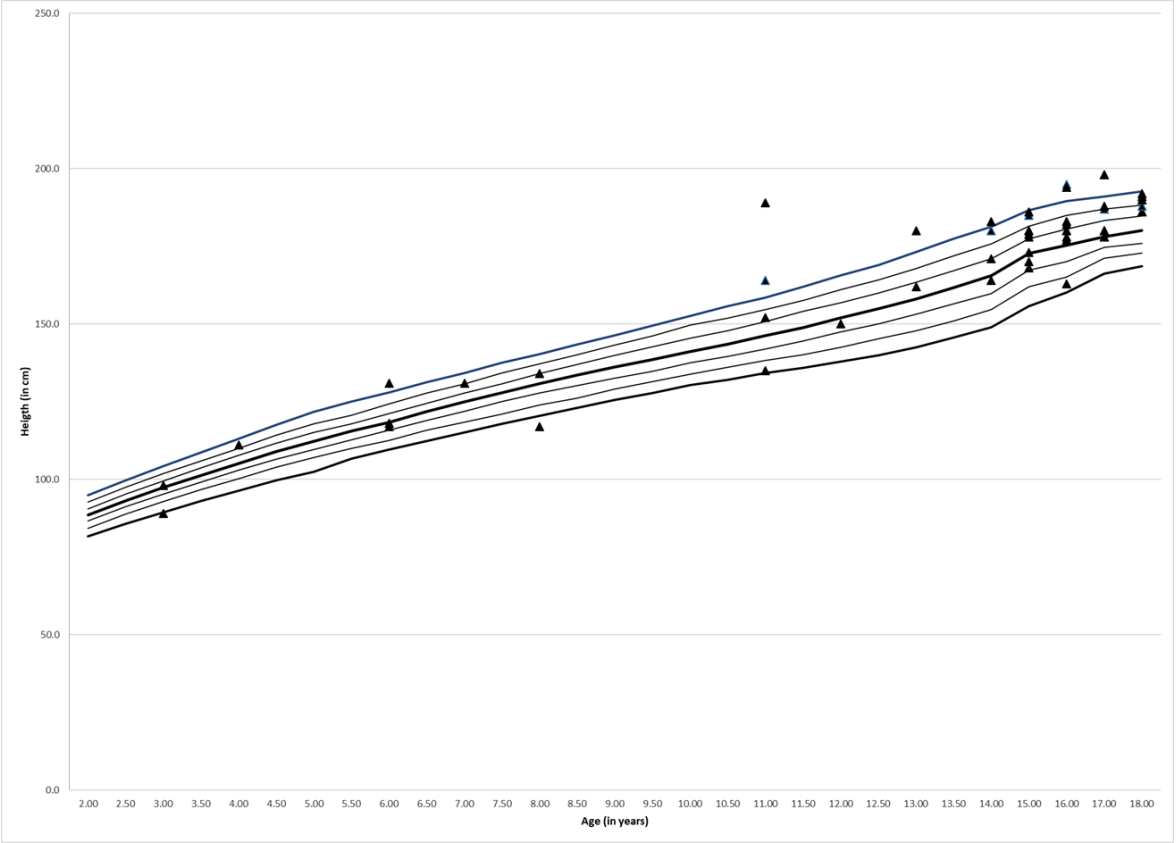

Fig. 49 Height percentile curves for boys aged 0 to 18 years

Weight percentile curves for boys aged 0 to 18 years

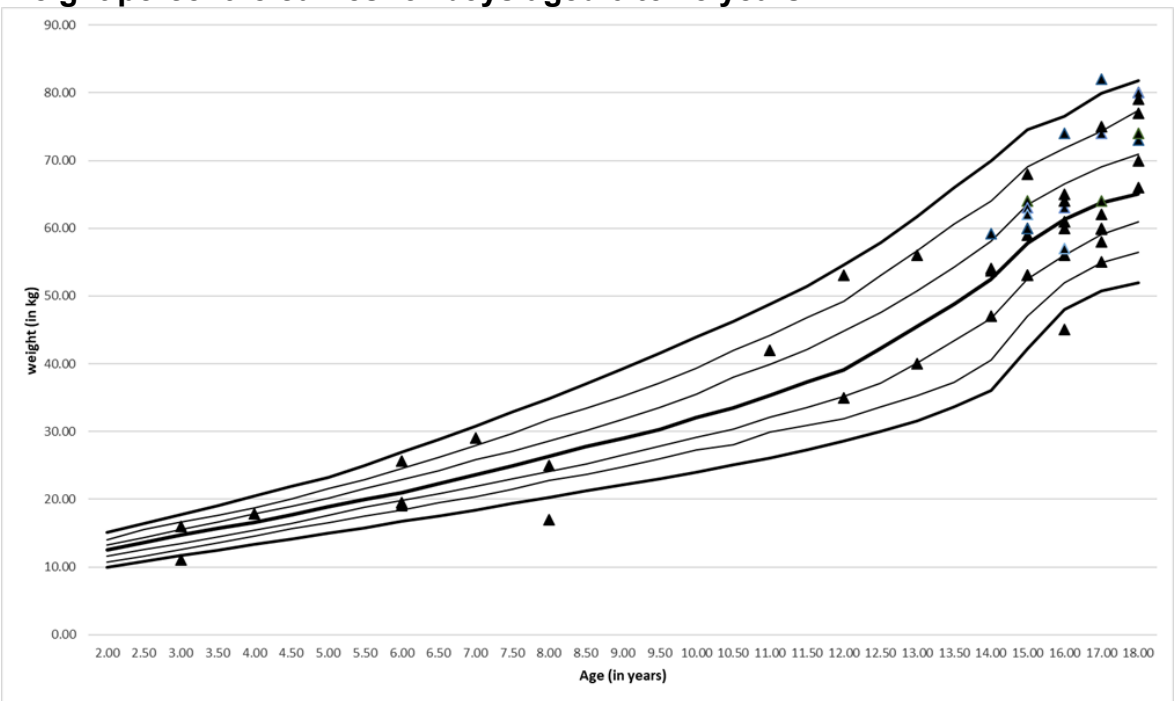

Fig. 50 Weight percentile curves for boys aged 0 to 18 years

Height percentile curves for girls aged 0 to 18 years

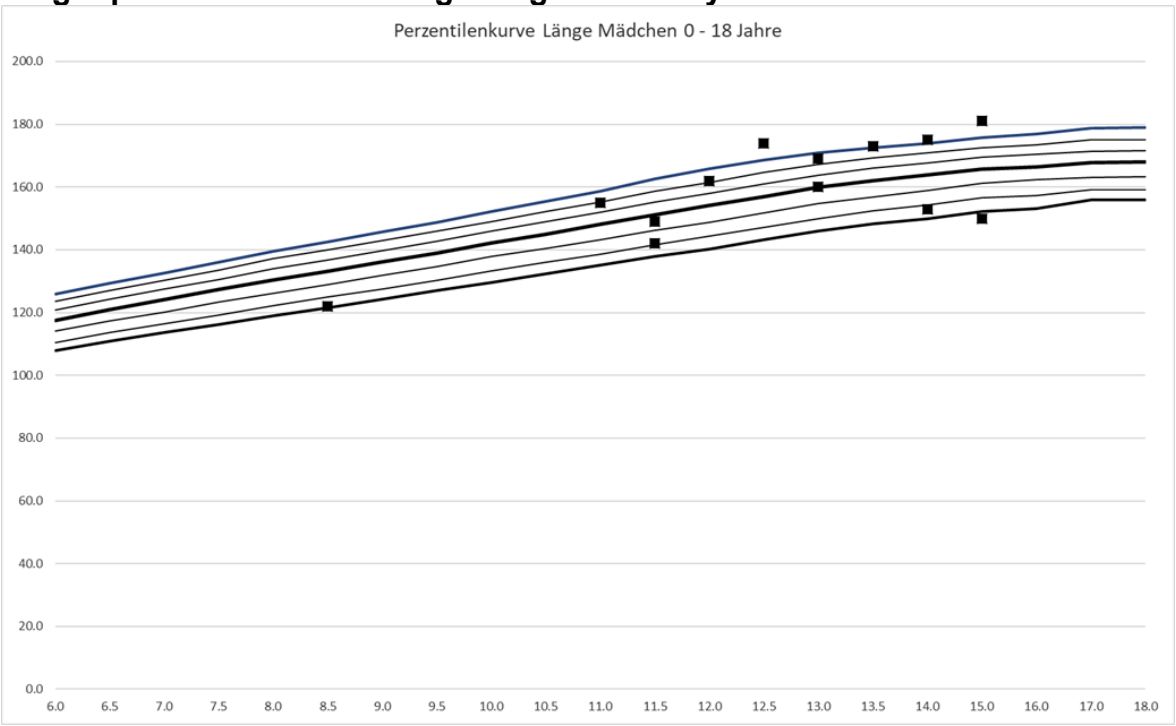

Fig. 51 Height percentile curves for girls aged 0 to 18 years

Weight percentile curves for girls aged 0 to 18 years

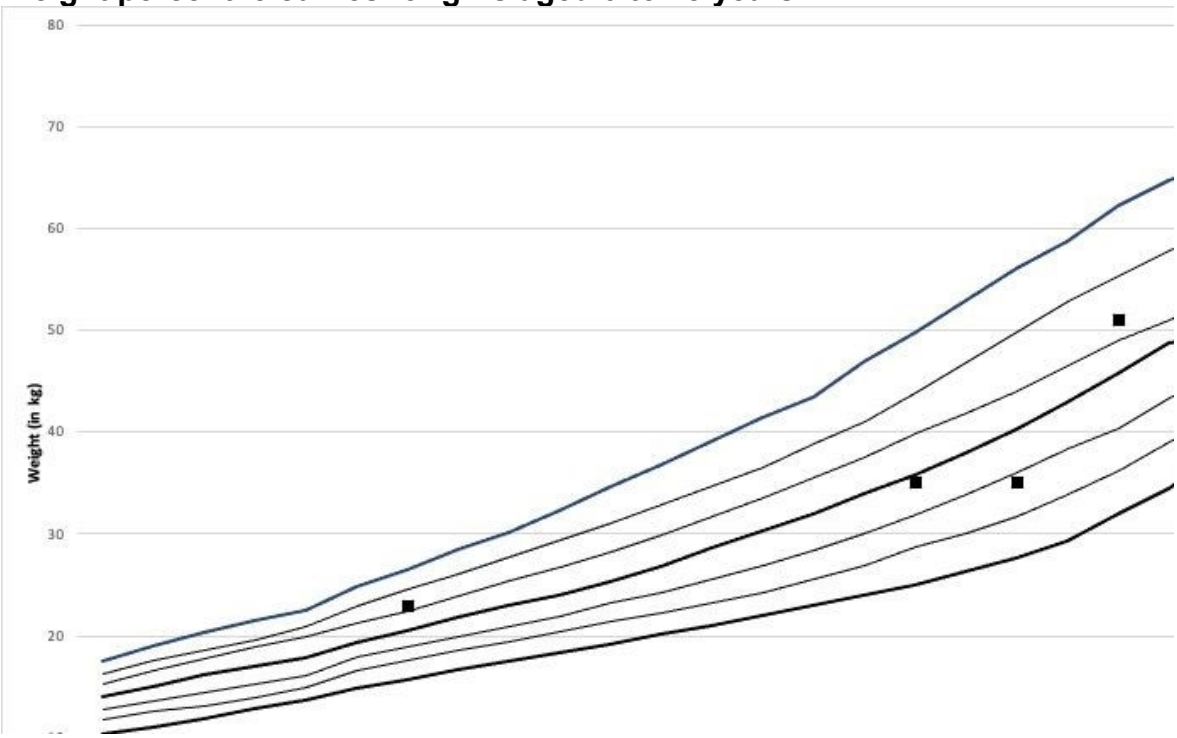

Fig. 52 Weight percentile curves for girls aged 0 to 18 years

Height, weight, and BMI from the above data are shown as age- and gender-adjusted z-scores in the following figure.

Height, weight, and BMI of participants as age- and gender adjusted z-scores

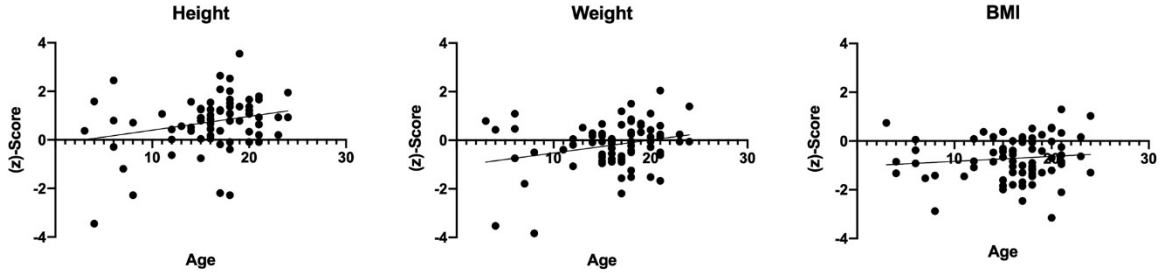

Fig. 53 Height, weight, and BMI of participants as age- and gender adjusted z-scores

The following figure shows the values of student's t tests. These were obtained from the above study data. It shows that significantly more participants were taller than the 50th percentile (p = <0.0001). It also shows that significantly more participants were lighter than the 50th percentile. BMI was significantly more below the age-adjusted 50th percentile (p = <0.0001 for weight and BMI).

T test for height, weight, and BMI z-scores

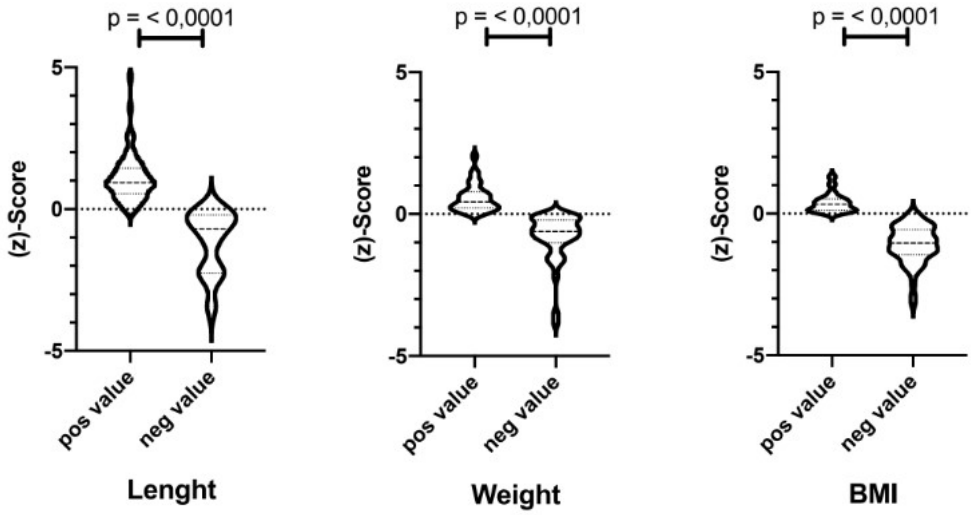

Fig. 54 T test for height, weight, and BMI z-scores

11. Acknowledgement

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12. Curriculum Vitae

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13. Declaration of academic honesty

Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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I expressly assure that I have written the work independently and without outside help. I have not used any sources and aids other than those specified by me. I have marked the passages from the works used that were taken oven verbatim or in terms of content. These were individually identified by edition (edition and year of publication), volume and page of the work used.
Furthermore, I assure that I have not yet submitted the dissertation to a subject representative at another university for review. I assure that I have not applied otherwise for admission to a doctorate.
I agree that my dissertation can be checked by the dean’s office of the medical faculty using standard software for detecting plagiarism.

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