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Review Article

Association between pectus excavatum and congenital genetic disorders: A systematic review and practical guide for the treating physician

Ryan J. Billar[a], Wiem Manoubi[b], Sarina G. Kant[c], René M.H. Wijnen[a], Serwet Demirdas[c,1], Johannes M. Schnater[a,1,*]

[a] Erasmus University Medical Center – Sophia Children's Hospital, department of Paediatric Surgery Rotterdam, Netherlands
[b] Erasmus University Medical Centre, department of Neuroscience, Rotterdam, Netherlands
[c] Erasmus University Medical Centre, department of Clinical Genetics, Rotterdam, Netherlands

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ABSTRACT

Background: Pectus excavatum (PE) could be part of a genetic disorder, which then has implications regarding comorbidity, the surgical correction of PE, and reproductive choices. However, referral of a patient presenting with PE for genetic analysis is often delayed because additional crucial clinical signs may be subtle or even missed in syndromic patients. We reviewed the literature to inventory known genetic disorders associated with PE and create a standardized protocol for clinical evaluation.

Methods: A systematic literature search was performed in electronic databases. Genetic disorders were considered associated with PE if studies reported at least five cases with PE. Characteristics of each genetic disorder were extracted from the literature and the OMIM database in order to create a practical guide for the clinician.

Results: After removal of duplicates from the initial search, 1632 citations remained. Eventually, we included 119 full text articles, representing 20 different genetic disorders. Relevant characteristics and important clinical signs of each genetic disorder were summarized providing a standardized protocol in the form of a scoring list. The most important clinical sign was a positive family history for PE and/or congenital heart defect.

Conclusions: Twenty unique genetic disorders have been found associated with PE. We have created a scoring list for the clinician that systematically evaluates crucial clinical signs, thereby facilitating decision making for referral to a clinical geneticist.

1. Introduction

Pectus excavatum (PE) is the most common congenital chest wall deformity with an estimated prevalence of 1 in 300–1000 live births [1,2]. It is characterized by anomalous growth of several ribs and the sternum, which gives the chest a sunken appearance [1,2]. The etiology of PE is not fully understood and a direct genetic link has yet to be found [3,4]. Current leading hypotheses are focused on a defective collagen metabolism, resulting in biomechanical weakness and an overgrowth of the sternocostal cartilage [5]. Associations of PE with several genetic disorders have been suggested [3,6,7]. The fact that PE could be part of a genetic disorder is of clinical importance and bears significance in regard to comorbidity (such as vascular fragility in Loeys-Dietz syndrome and or increased cancer risk in Noonan syndrome or Gorlin syndrome), the recurrence risk, the timing of the correction, type of surgical technique, stabilization of the sternum, long-term outcomes, and reproductive choices related to the genetic disorder [8,9].

Even with experienced pediatricians-pediatric surgeons primary recognition of an underlying genetic disorder in patients with PE is often difficult, because additional crucial representative signs may be subtle or even missed [10]. Referral for clinical genetic evaluation and genetic analysis could therefore be delayed or not occur at all, resulting in delayed or missed diagnoses of an underlying genetic disorder [10]. A standardized clinical evaluation could assist clinicians treating PE patients in their decision-making for referral.

We performed a systematic review in order to obtain an overview of associated congenital genetic disorders with PE. Based on the findings, we then created a practical clinical guide containing a scoring list that could help the treating clinician to decide whether a patient with PE should be referred for clinical genetic evaluation.

* Corresponding author.
E-mail address: j.schnater@erasmusmc.nl (J.M. Schnater).
[1] both authors contributed equally.

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Abbreviations

Abbreviation	Definition
aCGH	Array comparative genomic hybridization
BAC	Bacterial artificial chromosome
CAP	The College of American Pathologists
CHG	Comparative genomic hybridization
CLIA	Clinical laboratory improvements amendments
DHPLC	Denaturing high performance liquid chromatography
FISH	Fluorescence in situ hybridization
GTG	G-bands after trypsin and giemsa staining
MLPA	Multiplex ligation-dependent probe amplification
NA	Not applicable
NR	Not reported
PCR	Polymerase chain reaction
PE	Pectus excavatum
QFQ	Q-bands fluorescence using quinacrine
RT-PCR	Reverse transcription polymerase chain reaction
RAS/MAPK	Ras mitogen activated protein kinase
TGF-beta	Transforming growth factor beta
U	Unknown

2. Methods

2.1. Study design and search strategy

We performed a systematic review of the literature and reported our strategy according to the PRISMA statement for transparent reporting of systematic reviews [11]. A systematic literature search was performed with assistance of a biomedical specialist (December 27th, 2019). The EMBASE, Medline (ovidSP), Web-Of-Science, Cochrane CENTRAL and Google scholar databases were searched for publications reporting PE in humans with genetic disorders (Appendix A in the supplement and Fig. 1). Keywords used in the literature search were “pectus excavatum”, “gene”, “mutation” and “syndrome”.

2.2. Participants, interventions, comparators

Two reviewers (RB and WM) independently screened for relevance the titles and abstracts of all citations identified from the initial search, and subsequently evaluated the full texts of relevant citations on eligibility for inclusion in this review.

Studies meeting the following criteria were considered for inclusion: 1) available full-text article; 2) performed in humans; 3) investigating and reporting associations between PE and congenital genetic disorders; 4) written in English; and 5) cohort study, case series, and case reports. Phenotypes of rare diseases are hard to capture as publications of large case series are scarce [12,13]. For the purpose of this review congenital genetic disorders, including subtypes, were considered associated with PE when a minimum of 5 cases with PE were reported. Subtypes within a genetic disorder were considered similar if the clinical presentation was alike, and if affected genes causing that certain subtype within a genetic disorder, shared the same signaling pathway. The following exclusion criteria applied: 1) genetic disorders with severe comorbidity and without a spectrum 2) acquired or undefined genetic disorders; 3) cases with multiple genetic disorders; 4) duplicate cases; 5) number of cases with PE not reported. If study populations overlapped between studies, only the most extensively described study was included. Reference lists from relevant reviews were scanned for additional publications that met our inclusion criteria. All disagreements between reviewers were resolved by discussion.

2.3. Data extraction, data analysis & construction of a practical guide

All extracted data were summarized in an Excel spreadsheet (Microsoft Office, 2019). The following study characteristics were collected by two persons (RB and WM) separately: name of the congenital genetic disorder, authors, year of publication, type of study, number of cases with PE, family history, results of genetic analysis (affected gene, mutation, locus), and technique of genetic analysis.

Characteristics and clinical signs of each heritable disorder were extracted according to the Human Phenotype Ontology (https://hpo.jax.org) from all studies and the OMIM database (https://www.omim.org/), an online catalog of human genes and genetic disorders. Identified congenital genetic disorders were categorized based on etiology and pathophysiology in order to facilitate interpretation of similarities and differences between genetic disorders. Subsequently all relevant characteristics and important clinical signs of each genetic disorder were summarized and divided into the following organ systems: craniofacial features, musculoskeletal system, cardiovascular and pulmonary system, neurologic and cognitive system, and other systems. Additionally, the prevalence rates of all relevant clinical signs of each genetic disorder were extracted from the literature. After comparison of clinical signs between genetic disorders, all overlapping clinical signs between genetic disorders as well as the most relevant and pathognomonic clinical signs for each genetic disorder were extracted. Aiming to develop a structural and practical guide for the clinician in the form of a scoring list, we categorized clinical signs into areas within the corresponding organ system. Clinical signs that were more consistently associated with multiple genetic disorders and clinical signs suggestive for the most common genetic diagnosis associated with PE (RASopathy, Turner syndrome and Marfan syndrome [7,14]) were selected and defined as major criteria. Clinical signs suggestive for other/less common genetic diagnosis associated with PE were selected and defined as minor criteria. Not easily recognizable clinical features in a surgical consultation setting were not included in the scoring list. Dysmorphic facial features were standardized following the elements of morphology [15].

2.4. Study quality assessment

Using the tool for evaluating the methodological quality of case reports, case series and uncontrolled cohort studies proposed by Murad et al., (RB and WM) independently evaluated selected articles on study quality until consensus was reached. [16]. Study quality is scored on four domains – selection, ascertainment (exposure and outcome), causality, and reporting – which assess multiple items. With regard to our research question, the “exposure” item was scored based on whether the genetic disorder was properly reported and how the genetic diagnosis was assessed. The “outcome” item was scored as the presence of PE. The causality domain was only assessed on the “follow-up” item, as all other items are relevant mainly in studies investigating adverse drug events [16].

3. Results

The initial search yielded 2563 articles. After removal of duplicates, titles and abstracts of 1632 articles were screened on relevance and 553 articles were assessed full text. Following eligibility assessment, 119 full text articles were included in the systematic review (Fig. 1).

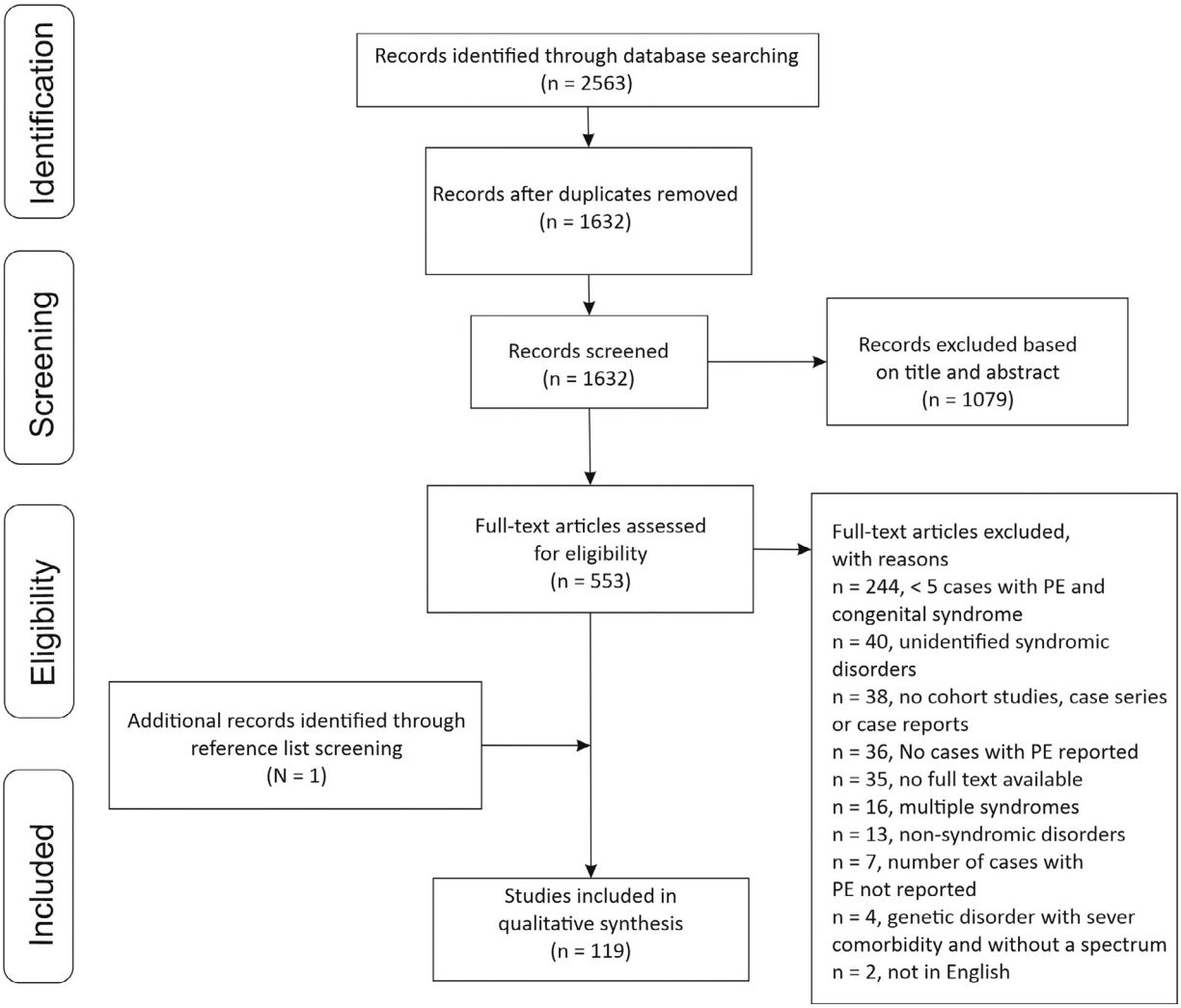

Fig. 1. Flowchart of search strategy describing the number of articles identified, screened, eligible, and included in this review.

3.1. Study characteristics

Study characteristics are presented in Table 1 [17–137] and more detailed study chracteristics are presented in Appendix C. Sixteen uncontrolled cohort studies, 46 case series and 57 case reports have been included, representing 20 different congenital genetic disorders and 487 patients with PE and an underlying genetic disorder. Genetic disorders have been diagnosed through either genetic molecular analysis (n = 51 studies) or clinical features and family history (n = 23 studies). Forty-five studies mentioned neither genetic molecular analysis nor clinical evaluation and thus additional clinical signs. These 45 studies represent 250 patients and 11 congenital genetic disorders.

3.2. Methodological quality

All studies had moderate methodological quality as assessed with the proposed tool for evaluating the methodological quality of case reports and case series by Murad et al. (see Appendix B) [16]. More than half of the studies described the genetic disorder including the subtype, and as well described the diagnostic procedure. In more than half of the studies, cases were described with sufficient details to allow others to replicate their research or to allow practitioners to make inferences related to their own practice.

3.3. Findings

Twenty congenital genetic disorders could be divided into five categories: chromosomal disorders (n = 3), connective tissue diseases (n = 5), neurological disorders (n = 3), syndromic disorders (n = 8), and other disorders (n = 1). These genetic disorders and their most relevant clinical signs are presented in Table 2, ranked from highest prevalence of PE to lowest as reported by the literature [17,26,79,133–178]. A more detailed summary is presented in Appendix D.

The most frequent overlapping clinical signs between genetic disorders within the craniofacial, musculoskeletal, cardiovascular and pulmonary, neurocognitive and other systems are presented in Table 3.

These clinical signs were summarized, divided by organ system and the corresponding area, in a scoring list (Fig. 2).

4. Discussion

In daily practice clinicians treating patients with PE are mostly only aware of a potential underlying connective tissue disease [6]. Genetic analysis is therefore typically performed on genes associated with connective tissue diseases, such as Marfan syndrome [6]. From our systematic review we may conclude that PE can be associated not only with connective tissue disorders, but also with

Table 1
Syndromic and study characteristics in alphabetical order.

Included genetic disorders	Reported subtypes of genetic disorders	Author	Type of study	Total N cases with PE in study	Inheritance	Gene(s)
9q22 deletion		Siggberg et al. (2011)	Case series	6	AD	*PTCH1* and / or *ROR2*
18p deletion Syndrome		Horsley et al. (1998)	Case report	1	AD	NR
		Pachajoa et al. (2010)	Case series	1	AD	NR
		Tekeli et al. (2015)	Case report	1	AD	NR
		Schinzel et al. (1974)	Case series	2	AD	NR
Aarskog-Scott Syndrome		Bawle et al. (1984)	Case report	1	X-linked	NR
		Bottani et al. (2007)	Case report	1	X-linked	*FGD1*
		Al-Semari et al. (2013)	Case series	2	X-linked	*FGD1*
		Berman et al. (1975)	Case series	7	X-linked	NR
ABCA3 mutations		Doan et al. (2008)	Case series	6	AR	ABCA3 genes
Allan-Herndon-Dudley		Bialer et al. (1992)	Case series	6	X-linked	NR
syndrome		Remerand et al. (2019)	Case series	3	X-linked	*MCT8/ SLC16A2*
Autism spectrum		Alkhunaizi et al. (2018)	Case report	1	NR	*ADNP*
disorder		Van Dijck et al. (2019)	Cohort	8	NR	*ADNP*
Cutis Laxa		Duz et al. (2017)	Case report	1	AD	*ELN*
		Hucthagowder et al. (2006)	Case report	1	AR	*FBLN4*
	ARCL2	Morava et al. (2008)	Case series	1	AR	*ATP6V0A2*
		Sawyer et al. (2013)	Case series	1	AR	*FBLN4*
	ARCL2	Tuysuz et al. (2003)	Case report	1	AR	NR
	De Barsy Syndrome	Kivuva et al. (2008)	Case series	8	AR	NR
Ehlers-Danlos Syndrome type VIA		Brady et al. (2017)	Case series	12	AR	*PLOD1* or *LH1*
Holt-Oram Syndrome		Atik et al. (2014)	Case series	1	AD	*TBX5*
		Chryssostomidis et al. (2014)	Case series	1	AD	NR
		Antia et al. (1970)	Case series	3	AD	NR
Gorlin Syndrome		Pirschner et al. (2012)	Case report	1	AD	NR
		Midro et al. (2004)	Case report	1	AD	*PTCH*
		Snoeckx et al. (2008)	Case report	1	AD	*PTCH1*
		Musani et al. (2018)	Case report	1	AD	NR
		Hsu et al. (2018)	Case series	2	AD	*PTCH1*
Loeys-Dietz Syndrome		Byard et al. (2017)	Case report	1	AD	SMAD3
	Type 4	Fontana et al. (2014)	Case report	1	AD	*SMYD2, PTPN14, CENPF, KCNK2,KCTD3, USH2A, ESRRG, SPATA17, RRP15, TGFB2* (1q41); *CHRM3* (1q43);*KANK1* (9p24.3); *RCAN1, CLIC6, RUNX1* (21q22.12).
	Type 4	Ma et al. (2012)	Case report	1	AD	*TGFBR2*
	Type 2	Rahme et al. (2011)	Case report	1	AD	*TGFBR2*
		Suarez et al. (2011)	Case report	1	AD	*TGFBR2*
		Tug et al. (2010)	Case report	1	AD	*TGFBR2*
	Type 1	Vida et al. (2011)	Case report	1	AD	*TGFBR2*
		Yakoviev et al. (2011)	Case report	1	AD	NR
		Zimmermann et al. (2017)	Case report	1	AD	*TGFBR2*
	Type 4	Ritelli et al. (2014)	Case series	1	AD	*TGFBR2*
		Erkuta et al. (2010)	Cohort	35	AD	*TGFBR1* or *TFGBR2*
		Ajmi et al. (2019)	Case report	1	AD	NR
		Hara et al. (2019)	Case report	1	AD	*TGBR1*
Malan (Sotos-like)		Oshima et al. (2017)	Case report	1	AD	*NFIX*
Syndrome		Klaassens et al. (2015)	Case series	4	AD	*NFIX* and / or *CACNA1A*
Marfan Syndrome		Abanador-Kamper et al. (2014)	Case report	1	AD	*FBN1*
		Acherjya et al. (2018)	Case report	1	AD	NR
		Bakalli et al. (2009)	Case report	1	AD	NR
		Barkhudaryan et al. (2015)	Case report	1	AD	NR
		Datta et al. (2009)	Case report	1	AD	NR
		Ellasher et al. (1998)	Case report	1	AD	NR
		Ferrante et al. (2003)	Case report	1	AD	NR
		High et al. (2005)	Case report	1	AD	NR
		Ozyurt et al. (2015)	Case series	1	AD	NR
		Peng et al. (2016)	Case report	1	AD	*FBN1*
		Wang et al. (2016)	Case report	1	AD	*FBN1*
		Zencirci et al. (2010)	Case report	1	AD	*FBN1*
		Aalberts et al. (2010)	Case series	5	AD	*FBN1*
		Ghandi et al. (2013)	Case series	2	AD	NR
		Herzka et al. (2000)	Case series	2	AD	NR
		Reyes-Hernandez et al. (2016)	Case series	2	AD	*FBN1*

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Table 1 (*continued*)

Included genetic disorders	Reported subtypes of genetic disorders	Author	Type of study	Total N cases with PE in study	Inheritance	Gene(s)
		Sureka et al. (2014)	Case series	2	AD	*FBN1*
		Baran et al. (2007)	Cohort	13	AD	NR
		De Maio et al. (2016)	Cohort	49	AD	*FBN1*
		Furtado et al. (2011)	Cohort	4	AD	*FBN1*
		Goliaday et al. (1985)	Cohort	7	AD	NR
		Hawks Arn et al. (1989)	Cohort	28	AD	NR
		Hilhorst-Hofstee et al. (2011)	Cohort	3	AD	*FBN1*
		Roman et al. (1989)	Cohort	29	AD	NR
		Sponseller et al. (2010)	Cohort	75	AD	NR
		Streeten et al. (1987)	Cohort	15	AD	NR
		Aggarwal et al. (2018)	Case report	1	AD	NR
		Löhnhardt et al. (2019)	Case report	1	AD	NR
		Rizvi et al. (2018)	Case series	1	AD	NR
		Wang et al. (2018)	Case series	1	AD	NR
		Zeng et al. (2018)	Case report	1	AD	*FBN1*
		Zakkar et al. (2019)	Case series	2	AD	NR
		Zhang et al. (2015)	Cohort	2	AD	NR
Neurofibromatosis	Type 1	Croonen et al. (2012)	Case report	1	AD	*NF1*
	Type 1	Raja et al. (2012)	Case report	1	AD	NR
	Segmental neurofibromatosis	Sezer et al. (2006)	Case series	1	AD	NR
	Type 1	Rieley et al. (2011)	Case series	1	AD	NR
	Type 1	Koczkowska et al. (2018)	Cohort	4	AD	NR
Noonan Syndrome		Bufalino et al. (2010)	Case report	1	AD	*PTPN11*
		Chevallier et al. (2011)	Case report	1	AD	NR
		Cohen et al. (1991)	Case series	6	AD	NR
		Hanna et al. (2009)	Case series	1	AD	*SOS1*
		Karbach et al. (2012)	Case series	1	AD	*PTPN11*
		Menon et al. (2008)	Case report	1	AD	NR
		Pearl et al. (1977)	Case series	2	AD	NR
		Schon et al. (1992)	Case report	1	AD	NR
		Ucar et al. (1998)	Case report	1	AD	NR
		Sanchez Cascos et al. (1983)	Case series	9	AD	NR
		Slezak et al. (2010)	Case series	2	AD	*SOS1*
		Couser et al. (2018)	Case report	1	AD	*SHOC2*
		McDonald et al. (2018)	Case report	1	AD	*PTPN11*
		Petrin et al. (2019)	Case report	1	AD	NR
		Rodriguez et al. (2019)	Case report	1	AD	*RAF1*
Noonan syndrome with multiple lentigines		Gupta et al. (1998)	Case report	1	AD	NR
		Jozwiak et al. (1998)	Case series	1	AD	NR
	Type 2	Kuburovic et al. (2011)	Case series	1	AD	*RAF1*
		Santoro et al. (2014)	Case report	1	AD	NR
		Sutton et al. (2016)	Case report	1	AD	NR
		Begic et al. (2014)	Case series	3	AD	*PTPN11*
		Kato et al. (2010)	Case series	1	AD	*PTPN11*
		Jurko et al. (2019)	Case series	1	AD	*PTPN11*
Shprintzen-Goldberg Syndrome		Stoll et al. (2002)	Case report	1	AR	NR
		Greally et al. (1998)	Case series	8	AR	NR
Simpson-Golabi-Behmel Syndrome		Yano et al. (2011)	Case series	2	X-linked	NR
		Shawky et al. (2014)	Case report	1	X-linked	NR
		Spencer et al. (2016)	Case series	1	X-linked	*GPC3*
		Thomas et al. (2012)	Case report	1	X-linked	*GPC3*
		Hughes-Benzi et al. (1996)	Case series	8	X-linked	*GPC3*
		Neri et al. (1988)	Case series	2	X-linked	NR
		Fu et al. (2019)	Case report	1	X-linked	GPC3
Turner Syndrome		Saikia et al. (2017)	Case series	3	NA	NA
		Mehta et al. (1993)	Cohort	3	NA	NA
		Miguel-Neto et al. (2016)	Cohort	10	NA	NA
X-Linked myotubular myopathy		Amburgey et al. (2017)	Cohort	8	X-linked	*MTM1*
		Inoue et al. (2018)	Case report	1	X-linked	*MTM1*

NA = Not applicable; NR = Not reported; PE = Pectus excavatum.

several chromosomal disorders, neurologic disorders, syndromic disorders, and pathogenic variants in the *ACAD3* gene. When interpreting these associations, one should be aware that some of these genetic disorders are very rare (estimated prevalence ≥1:1 000 000)[76,169,179–184], while others are more common such as Turner syndrome (estimated prevalence 1:2 500 females)[185], and RASopathies such as Marfan syndrome (estimated prevalence 1:5 000–10 000)[14], Noonan syndrome (estimated prevalence 1:1 000–2 500)[186], and neurofibromatosis type 1 (estimated prevalence 1:3 000)[187]. Furthermore, some of these genetic disorders only occur in women, such as Turner syndrome [185], and others only in men, such as Allan–Herndon–Dudley syndrome [181], and Simpson–Golabi–Behmel syndrome [184]. Lastly, affected genes of associated genetic disorders with PE are involved with multiple signaling pathways. The most observed affected signaling pathways include the TGF-beta pathway [163,188–192] and the RAS/MAPK pathway [193,194]. Knowledge of these genetic disorders and the associated signaling pathways, not only broadens the differential

Table 2
congenital genetic disorders and their most relevant clinical signs divided by organ system.

Genetic disorders	Pectus excavatum (prevalence in%)	Clinical signs (prevalence in%)
ABCA3 mutations	PE (67%)	Musculoskeletal system - Clubbing fingers (67%) Cardiovascular and pulmonary system - Pulmonary symptoms (cough, tachypnoea, dyspnea and exercise intolerance) (100%) Other systems: - Failure to thrive (56%)
Loeys-Dietz Syndrome (1–5) (TGF- β pathway)	PE (54%)	Craniofacial features: - Bifid uvula (25–90%), cleft palate (25–90%), hypertelorism (0–90%), craniosynostosis (0–48%) Musculoskeletal system: - Joint hypermobility (68–100%), cervical congenital malformations (29%), talipes equinovarus (17%), limb joint contractures (5%) Cardiovascular and pulmonary system: - Aortic-arterial aneurysms and arterial tortuosity (52–90%) Other system: - Translucent skin (25%), high bruising susceptibility (25%)
Aarskog-Scott Syndrome	PE (50–75%)	Craniofacial features: - Hypertelorism (>75%), short nose (>75%), widow's peak (50–75%) Musculoskeletal system: - Short stature (>75%), brachydactyly (>75%), joint hypermobility (50–75%) Other systems: - Shawl scrotum (>75), inguinal hernia (50–75%)
Shprintzen-Goldberg Syndrome	PE (47%)	Craniofacial features: - High-arched palate (100%), micrognathia (94%), hypertelorism (88%), down-slanting palpebral fissures (82%), low-set posteriorly rotated ears (76%), craniosynostosis (41%) Musculoskeletal system: - Muscular hypotonia (82%), arachnodactyly (71%), camptodactyly (59%), joint hypermobility (53%), scoliosis (41%), disproportionate tall stature (U), increased length of extremities (U) Neurologic and cognitive system: - Intellectual disability (82%) Other systems: - Inguinal or umbilical hernia (41–59%)
Marfan Syndrome (Fibrilin/TGF- β pathway)	PE (41%)	Craniofacial features: - Enophthalmos (71%), retrognathia (63%), dolichocephaly (60%), down-slanting palpebral fissures (58%), malar hypoplasia (36–78%) Musculoskeletal system: - Joint hypermobility (63%), increased length of extremities (62–92%), disproportionate tall stature (60–88%), scoliosis (53%), thoracolumbar kyphosis (40%), pes planus (25 - 34%), limited elbow extension (15%) Cardiovascular and pulmonary system: - Aortic aneurysm (77%), mitral valve prolapse (68%), history of pneumothorax (4–15%) Neurologic and cognitive system: - Dural ectasia (63–92%) Other systems: - Myopia (34–44%), striae distensae (30%)
Malan Syndrome	PE (40%)	Craniofacial features: - High forehead (96%), long narrow face (85%) Musculoskeletal system: - Advanced bone age (76%), slender habitus (59%), scoliosis (32%) Neurologic and cognitive system: - Intellectual disability (100%), macrocephaly (33%) Other systems: - Postnatal overgrowth (33%)
Simpson-Golabi-Behmel Syndrome	PE (25%)	Craniofacial features: - Coarse facies (90%), hypertelorism (53%), cleft palate and/or bifid uvula(13–26%) Cardiovascular and pulmonary system: - Congenital heart defects (36–46%) Other systems: - Kidney anomalies (64–82%), developmental delay (47%), pre- and postnatal overgrowth (43%), diaphragmatic hernia (10%)

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Table 2 (*continued*)

Genetic disorders	Pectus excavatum (prevalence in%)	Clinical signs (prevalence in%)
X-Linked myotubular myopathy (phosphatase, endocytose and membrane trafficking)	PE (24%)	Craniofacial features: - Long face (92%) Musculoskeletal system: - Muscular hypotonia (100%), long slender fingers (17%) Cardiovascular and pulmonary system: - Respiratory problems (due to hypotonia) (96%) Other systems: - Feeding problems (due to hypotonia) (92%)
Noonan Syndrome	PE (23%)	Craniofacial features: - Short or webbed neck (95%), hypertelorism (67%), low-set posteriorly rotated ears (44–90%), down-slanting palpebral fissures (38%), a high-arched palate (34–45%), Broad forehead (U) Musculoskeletal system: - Short stature (40–80%), scoliosis (10–54%) Cardiovascular and pulmonary system: - Pulmonic stenosis (20–50%), hypertrophic cardiomyopathy (10–30%) Neurologic and cognitive system: - Intellectual disability (25%) Other systems: - Cryptorchidism (60–80%), bleeding diathesis (10–89%)
Neurofibromatosis type 1	PE (22%)	Musculoskeletal system: - Kyphoscoliosis (10–60%) Neurologic and cognitive system: - Neurofibromas (27- 56%) Other systems: - Cafe-au-lait spots (100%), Lisch nodules in the eye (95–100%)
9q22 deletion Syndrome	PE (20%)	Craniofacial features: - Epicanthi (57%), short neck (23%), low-set ears (23%), thick ears (17%), thin upper lip vermilion (17%), broad eyebrows (17%), cleft palate (13%), narrow mouth (13%), broad eyebrows (17%), cleft palate (13%), narrow mouth (13%), broad eyebrows (17%) Musculoskeletal system: - Scoliosis (20%), kyphosis (10%) Neurologic and cognitive system: - Intellectual disability (80%), seizures (17%)
Turner Syndrome	PE (20%)	Craniofacial features: - Low hairline (40%), short-webbed neck (25–40%), low-set ears (15%) Musculoskeletal system: - short stature (95–100%) Cardiovascular and pulmonary system: - Hypertension (50%), anomalies of cardiovascular system (3–42%) Neurologic and cognitive system: - Hearing impairments (30%) Other systems: - Only females (100%), amenorrhea (34–91%),%), lymphedema of hands and feet (25%), spoon-shaped nails (10%), anomalies of renal/collecting system (3–15%)
Kyphoscoliotic Ehlers-Danlos Syndrome	PE (16%)	Craniofacial features: - High palate, epicanthi (U), down-slanting palpebral fissures (U), synophrys (U) and low-set ears (U) Musculoskeletal system: - Joint hypermobility (93%), kyphoscoliosis (74%), disproportionate tall stature (26%), increased length of extremities (26%), joint dislocations (24%), pes planus (15%), muscular hypotonia (U) Other systems: - Hyperextensible skin (65%), myopia (22%)
Autism Spectrum Disorder (Based on *ADNP* gene mutation)	PE (15%)	Craniofacial features: - Thin upper lip vermilion (70%), prominent forehead with a high anterior hairline (50–66%), wide and depressed nasal bridge (50%), short nose with full, upturned nasal tip (47–49%), everted lower lip vermilion (46%), long philtrum (39%), small or dysplastic low-set and posteriorly rotated ears (12–49%), pointed chin (U) Musculoskeletal system: - Muscular hypotonia (78%), short stature (29%), Cardiovascular and pulmonary system: - Congenital heart defects (38%) Neurologic and cognitive system: - Mild to severe intellectual disability, autism (100%), severe speech and motor delay (96–99%), epilepsy (16%) Other systems: - Gastrointestinal problems (83%), visual problems (74%), hormonal deficiencies (24%)

(*continued on next page*)

Table 2 (*continued*)

Genetic disorders	Pectus excavatum (prevalence in%)	Clinical signs (prevalence in%)
Gorlin Syndrome	PE (13–20%)	Craniofacial features: - Coarse face (54%), facial milia (50–60%), frontal bossing (27%) Musculoskeletal system: - Bifid ribs (26%), wedge-shaped vertebrae (15%) Cardiovascular and pulmonary system: - Cardiac fibromas (3%) Neurologic and cognitive system: - Macrocephaly (50%) Other systems: - Multiple jaw keratocysts (74%), basal cell carcinomas (74%), ovarian fibromas (17%)
Allan-Herndon-Dudley Syndrome	PE (9–58%)	Musculoskeletal system: - Muscular hypotonia (75–100%) Neurologic and cognitive system: - Spastic paraplegia (71–94%), athetoid movements (50%), dysarthria (25%), severely impaired intellectual development (17–83%)
18p deletion Syndrome	PE (U)	Craniofacial features: - Dental anomalies (29%), wide mouth, (14–57%), round face (U), dysplastic ears (U) Musculoskeletal system: - Muscular hypotonia (86%) Neurologic and cognitive system: - Intellectual disability (100%) Other systems: - Growth retardation (85%)
Cutis Laxa (ELN, FBLN4, De Barsy Syndrome (cutis laxa) and ARCL2)	PE (U)	Craniofacial features (prevalence in%): - Long philtrum (90%), large ears (66%), high forehead (29%), beaked nose (17%) Musculoskeletal system (prevalence in%): - Joint hypermobility (29%) Cardiovascular and pulmonary system (prevalence in%): - Aortic root dilatation (55–66%), bicuspid aortic valves (33%), and emphysema (17%) Other systems (prevalence in%): - Loose redundant skin (neck, axillar regions, trunk, and groin) (52%), progeria-like appearance (U), diaphragmatic hernia (U)
Holt-Oram Syndrome	PE (U)	Musculoskeletal system (prevalence in%): - Thumb anomaly (Absent thumb or triphalangeal, non-opposable, finger-like digit. The thumb metacarpal has both a proximal and a distal epiphyseal ossification center) (3–30%), bilateral asymmetric limb defects (Radial hypoplasia, absence of radius, ulnar hypoplasia. narrow, sloping shoulders) (1–40%) Cardiovascular and pulmonary system (prevalence in%): - Atrial septal defect (75%)
Noonan Syndrome with multiple lentigines	PE (U)	Craniofacial features (prevalence in%): - Hypertelorism (82%) Cardiovascular and pulmonary system (prevalence in%): - Hypertrophic cardiomyopathy (70%), pulmonic stenosis (25%) Neurologic and cognitive system (prevalence in%): - Sensorineural deafness (20%) Other systems (prevalence in%): - Multiple lentigines (100%), growth retardation (50%), cryptorchidism

PE = Pectus excavatum; *U* = unknown.

diagnosis of the suspected underlying genetic disorder in patients with PE, but could also have implications on the genetic panel used for genetic analysis.

Twenty unique genetic disorders were found to be associated with PE. Our results are in line with part of the reviews of Kotzot et al., and Cobben et al., which present comprehensive overviews regarding associations between genetic disorders and multiple chest wall deformities, including pectus excavatum, pectus carinatum, and cleft chest [7,14]. As the chest wall deformities had not been analyzed separately, we have extended on their research in order to identify genetic disorders specifically associated with PE.

Several studies propose that PE might be part of a genetic disorder, such as a chromosomal disorder, RASopathy or Marfan syndrome [7,14]. Nevertheless, the incidence of such syndromes/disorders among patients seen for their PE is still unclear. The authors of these studies state that PE is most often isolated and that genetic causes are rare. This statement is illustrated by Behr et al., who reported that 5.3% of their cohort of 187 PE patients was affected by Marfan syndrome, and by Akcali et al., who reported that 2.7% of their 24 PE patients was affected by neurofibromatosis type 1 [195,196]. It is however of great clinical importance to recognize those patients with an underlying genetic disorder as a cause of PE, primarily, because the comorbidity and prognosis of the genetic disorder could have great consequences for the patient and his or her psychosocial wellbeing, but also for the family members [197,198]. Understanding the options to deal with regarding the risk of recurrence of the genetic disorder in relatives and the corresponding reproductive choices make genetic counseling imperative in these patients [197,198]. Furthermore, the

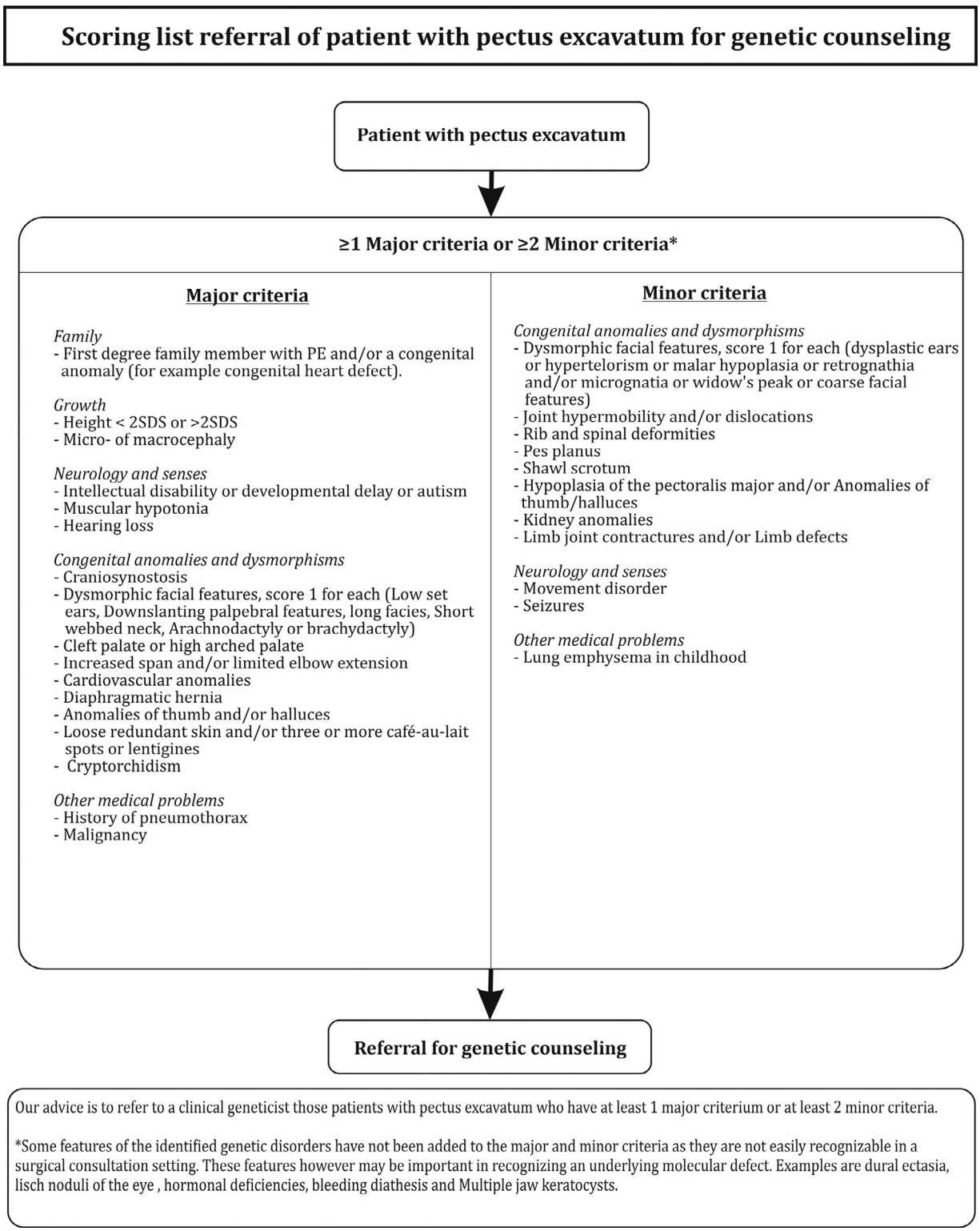

Fig. 2. A structural and practical referral scoring list for the clinician treating patients with a pectus excavatum.

presence of a genetic disorder could influence the choice of anesthesia, the timing of the correction of PE, surgical technique, stabilization of the sternum, and long-term outcome [8]. For example, in patients with Marfan syndrome, the suppleness of the chest wall is increased, resulting in a greater risk of recurrence following any surgical intervention [199]. In case of a minimal invasive approach, a longer duration of the Nuss bar should therefore be considered [199,200]. Open procedures are feasible as well, but the need for cardiac surgery should be evaluated and concomitant procedures should be performed where appropriate [199]. A second important example is Noonan syndrome, as it is associated with an increased risk of bleeding, bruising and a variety of bleeding abnormalities, such as factor XI deficiency and platelet abnormalities [201]. Therefore, patients with Noonan syndrome should be clini-

Table 3
frequency of overlapping clinical signs.

Categories	Areas	Clinical signs	N overlapping clinical signs between genetic disorders
Craniofacial	Head	Prominent forehead	4
		Craniosynostosis	2
		Undersized jaw	3
	Face	Coarse face	2
		Epicanthi	2
		Down-slanting palpebral fissures	4
	Eyes	Hypertelorism	6
		Myopia	2
	Nose	Beaked nose OR short nose	3
	Mouth	Cleft plate	3
		Bifid uvula	2
		High arched palate	3
		Thin upper lip vermilion	2
	Neck	Short (webbed) neck	3
	Ears	Low-set	6
Skeletal	Stature	Short stature	4
		Marfanoid appearance	3
	Spine	Scoliosis	7
		Kyphosis	2
	Extremities	Joint hypermobility AND/OR Joint dislocations	6
		Pes planus	2
	Muscles	Muscular hypotonia	6
Cardiovascular and pulmonary	Cardiac	All congenital cardiac anomalies	9
	Vascular	Aortic-arterial aneurysms	2
Neurologic and cognitive		Intellectual disability	4
		Intellectual disability	3
		Seizures	2
		Hearing impairments	2
Other	Skin	Loose skin OR hyperextensible skin	2
		Lesions (fibromas, cafe-au-lait spots, multiple lentigines, basal cell carcinomas)	3
	Hernias	Diaphragmatic hernia	2
		Inguinal AND/OR umbilical hernia	2
	Urogenital	Cryptorchidism	3
		Anomalies of renal/collecting system	2

cally evaluated prior to any surgical procedure. Even if blood tests are normal, these patients must be carefully monitored as the risk for bleeding events is still present [201].

We created a standardized protocol for clinical evaluation, in the form of a scoring list (Fig. 2), aimed to assess whether a patient with PE should be referred for genetic analysis. Standardizing this clinical evaluation was deemed essential, since associated genetic disorders can differ greatly in severity. For example, patients with Marfan syndrome may have disorders that can range from mild dysmorphic features or an isolated pectoral deformity, to those associated with severe, life-threatening complications such as pneumothorax or aortic aneurysm [202]. Additional crucial representative clinical signs may therefore be subtle or even missed in patients with genetic disorders. Moreover, many representative clinical signs are not likely to be linked to genetic disorders, because of the rarity of genetic disorders associated with PE. These obstacles make the decision to refer a patient presenting with PE for genetic analysis often difficult mandating a standardized approach [9,10].

Added to the scoring list were a positive family history for PE, a congenital cardiac anomaly and/or genetic disorder, as these characteristics increase the probability of the presence of a genetic disorder [9]. Our scoring list includes only family history and relevant clinical signs; additional diagnostic tests are not required, thus making it feasible to use in an outpatient clinic setting. We recommend routine use of our scoring list by clinicians treating PE patients. Its widespread use could potentially result in fewer delayed and missed diagnoses of underlying genetic disorders in patients with PE [9]. Implementation research is recommended to assess whether the scoring list is effectively implemented and has the desired result.

4.1. Limitations

This systematic review faces several limitations. An underestimation of the number of unique genetic disorders associated with PE is likely, as not all patients affected by PE and a genetic disorder are reported in the literature or in genetic databases. Consequently, the data on prevalence of PE within each genetic disorder is incomplete. Furthermore, a few genetic disorders have multiple subtypes. As some studies did not report the affected gene or genes – thus subtype of the reported genetic disorder – for some genetic disorders it is unclear which subtypes are associated with PE. As many genetic disorders are quite rare, this review is limited to mainly case reports and case series with a moderate methodological quality. When interpreting the results of this review, one should be aware of these limitations.

5. Conclusion

Twenty unique genetic disorders were found to be associated with PE. Clinicians treating PE could easily miss representative crucial clinical signs of an underlying disorder. We, therefore, recommend routine use of our scoring list to prevent delayed and missed diagnoses of underlying genetic disorders in patients with PE, as this will facilitate decision making on referral for genetic analysis.

Author contributions

J. Schnater conceived the study idea. R. Billar and W. Manoubi coordinated the systematic review. R. Billar and W. Manoubi screened abstracts and full texts. R. Billar and W. Manoubi wrote the first draft of the manuscript and judged risk of bias in the studies. R. Billar, W. Manoubi, S. Demirdas, S. Kant, and J. Schnater interpreted the data. R. Billar, W. Manoubi, S. Demirdas, S. Kant, R. Wijnen and J. Schnater critically revised the manuscript. R. Billar made all figures and the final drafts of all tables. R. Billar, W. Manoubi, S. Demirdas, S. Kant, R. Wijnen and J. Schnater had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. S. Demirdas and J. Schnater contributed equally. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary materials

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Reference list

[1] Shamberger RC. Congenital chest wall deformities. Curr Probl Surg 1996;33(6):469–542.
[2] Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations. I. Analysis of epidemiologic factors in congenital malformations. Report from the Collaborative Perinatal Project. Birth Defects Orig Artic Ser 1975;11(10):1–22.
[3] Creswick HA, Stacey MW, Kelly RE Jr. Family study of the inheritance of pectus excavatum. J Pediatr Surg 2006;41(10):1699–703.
[4] Jaroszewski D, Notrica D, McMahon L, Steidley DE, Deschamps C. Current management of pectus excavatum: a review and update of therapy and treatment recommendations. J Am Board Fam Med 2010;23(2):230–9.
[5] Brochhausen C, Turial S, Muller FK, et al. Pectus excavatum: history, hypotheses and treatment options. Interact Cardiovasc Thorac Surg 2012;14(6):801–6.
[6] Tocchioni F, Ghionzoli M, Messineo A, Romagnoli P. Pectus excavatum and heritable disorders of the connective tissue. Pediatr Rep 2013;5(3):e15.
[7] Kotzot D, Schwabegger AH. Etiology of chest wall deformities–a genetic review for the treating physician. J Pediatr Surg 2009;44(10):2004–11.
[8] Fokin AA, Steuerwald NM, Ahrens WA, Allen KE. Anatomical, Histologic, and Genetic Characteristics of Congenital Chest Wall Deformities. Semin Thorac Cardiovasc Surg 2009;21(1):44–57.
[9] Solomon BD, Muenke M. When to suspect a genetic syndrome. Am Fam Physician 2012;86(9):826–33.
[10] Delikurt T, Williamson GR, Anastasiadou V, Skirton H. A systematic review of factors that act as barriers to patient referral to genetic services. Eur J Hum Genet 2015;23(6):739–45.
[11] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[12] Taboada M, Rodriguez H, Martinez D, Pardo M, Sobrido MJ. Automated semantic annotation of rare disease cases: a case study. Database (Oxford) 2015:2015.
[13] Hartley T, Balci TB, Rojas SK, et al. The unsolved rare genetic disease atlas? An analysis of the unexplained phenotypic descriptions in OMIM(R). Am J Med Genet C Semin Med Genet 2018;178(4):458–63.
[14] Cobben JM, Oostra RJ, van Dijk FS. Pectus excavatum and carinatum. Eur J Med Genet 2014;57(8):414–17.
[15] Allanson JE, Cunniff C, Hoyme HE, McGaughran J, Muenke M, Neri G. Elements of morphology: standard terminology for the head and face. Am J Med Genet A 2009;149A(1):6–28.
[16] Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23(2):60–3.
[17] Siggberg L, Peippo M, Sipponen M, et al. 9q22 Deletion–first familial case. Orphanet J Rare Dis 2011;6:45.
[18] Horsley SW, Knight SJL, Nixon J, et al. Del(18p) shown to be a cryptic translocation using a multiprobe FISH assay for subtelomeric chromosome rearrangements. J Med Genet 1998;35(9):722–6.
[19] Pachajoa H, Saldarriaga W, Isaza C. 18p-syndrome: presentation of two cases with alobar holoprosencenphaly. Colomb Med 2010;41(4):367–72.
[20] Tekeli H, Kendirli MT, Şenol MG, et al. A case with 18p deletion and dystonia and review of the literature. Neurol Asia 2015;20(3):287–90.
[21] Schinzel A, Schmid W, Luescher U. Structural aberrations of chromosome 18. I. The 18p- syndrome. Arch Genet 1974;47(1):1–15.
[22] Ridler MAC. Clinical atlas of human-chromosomes - grouchy,Jd, Turleau,C.. J Ment Defic Res 1979;23(Jun):153–4.
[23] Saikia U, Sarma D, Yadav Y. Delayed presentation of turner syndrome: challenge to optimal management. J Hum Reprod Sci 2017;10(4):297–301.
[24] Mehta AV, Chidambaram B, Suchedina AA, Garrett AR. Radiologic abnormalities of the sternum in Turner's syndrome. Chest 1993;104(6):1795–9.
[25] Miguel-Neto J, Carvalho AB, Marques-De-Faria AP, Guerra G, Maciel-Guerra AT. New approach to phenotypic variability and karyotype--phenotype correlation in Turner syndrome. J Pediatr Endocrinol Metab 2016;29(4):475–9.
[26] Erkula G, Sponseller PD, Paulsen LC, Oswald GL, Loeys BL, Dietz HC. Musculoskeletal findings of Loeys-Dietz syndrome. J Bone Joint Surg Am 2010;92(9):1876–83.
[27] Byard RW. Manifestations and medicolegal significance of Loeys-Dietz syndrome. J Forensic Sci 2017;62(6):1512–15.
[28] Fontana P, Genesio R, Casertano A, et al. Loeys-Dietz syndrome type 4, caused by chromothripsis, involving the TGFB2 gene. Gene 2014;538(1):69–73.
[29] Ma BO, Song BG, Yang HJ, et al. Annuloaortic ectasia in a 16 year-old boy with Loeys-Dietz syndrome. Heart Lung Circul 2012;21(4):215–17.
[30] Rahme RJ, Adel JG, Bendok BR, Bebawy JF, Gupta DK, Batjer HH. Association of intracranial aneurysm and Loeys-Dietz syndrome: case illustration, management, and literature review. Neurosurgery 2011;69(2):E488–92.
[31] Suarez B, Caldera A, Castillo M. Imaging and clinical features in a child with Loeys-Dietz syndrome. A case report. Interv Neuroradiol 2011;17(1):9–11.
[32] Tug E, Loeys B, De Paepe A, Aydin H, Gideroglu K. A Turkish patient of typical Loeys-Dietz syndrome with a TGFBR2 mutation. Genet Couns 2010;21(2):225–32.
[33] Vida VL, Padalino MA, Motta R, et al. Traumatic aortic dissection in a boy with Loeys-Dietz syndrome. Ann Thorac Surg 2011;92(4):1520–2.
[34] Yakovlev AE, Resch BE, Karasev SA. Treatment of chronic chest wall pain in a patient with Loeys-Dietz syndrome using spinal cord stimulation. Neuromodulation 2011;14(1):27–9.
[35] Zimmermann MT, Urrutia RA, Blackburn PR, et al. Novel pathogenic variant in TGFBR2 confirmed by molecular modeling is a rare cause of Loeys-Dietz syndrome. Case Rep Genet 2017;2017:7263780.
[36] Ritelli M, Chiarelli N, Dordoni C, et al. Further delineation of Loeys-Dietz syndrome type 4 in a family with mild vascular involvement and a TGFB2 splicing mutation. BMC Med Genet 2014;15(1).
[37] Ajmi H, Arifa N, Boughzela E, Ben Mime L. Valve-sparing aortic root and aortic arch replacement in a 5-year-old boy with Loeys-Dietz syndrome. Eur J Cardio-thorac Surg 2019;56(2):409–11.
[38] Hara H, Takeda N, Fujiwara T, et al. Activation of TGF-β signaling in an aortic aneurysm in a patient with Loeys-Dietz syndrome caused by a novel loss-of–function variant of TGFBR1. Hum Genome Var 2019;6(1).
[39] Abanador-Kamper N, Kamper L, Vorpahl M, Tiroch K, Haage P, Seyfarth M. Coronary aneurysm with stent dislocation leading to the diagnosis of Marfan syndrome. Circulation 2014;129(17):1791–2.
[40] Acherjya GK, Tarafder K, Din Ul Islam M, Rahman M, Chowdhury MK. Marfan syndrome with varieties of clinical features. J Med 2018;19(1):58–62.
[41] Bakalli A, Bekteshi T, Basha M, Gashi A, Bakalli A, Ademaj P. Late diagnosis of Marfan syndrome with fatal outcome in a young male patient: a case report. Cases J 2009;2(9).
[42] Barkhudaryan AL. Acute myocardial infarction in a patient with marfan syndrome. New Armenian Med J 2015;9(3):83–8.
[43] Datta S, Datta H. Subluxation of lens in Marfan syndrome. Indian Pediatr 2009;46(5):434.
[44] Ferrante E, Citterio A, Savino A, Santalucia P. Postural headache in a patient with Marfan's syndrome. Cephalalgia 2003;23(7):552–5.
[45] High K, Gleaves AM, Lewis AM. A 27-year-old man with Marfan syndrome and "tearing" nonradiating chest pain. J Emerg Nurs 2005;31(1):26–7.
[46] Ozyurt A, Baykan A, Argun M, et al. Early onset Marfan syndrome: atypical clinical presentation of two cases. Balk J Med Genet 2015;18(1):71–6.
[47] Peng Q, Deng Y, Yang Y, Liu H. A novel fibrillin-1 gene missense mutation associated with neonatal Marfan syndrome: a case report and review of the mutation spectrum. BMC Pediatr 2016;16(1).
[48] Wang J, Yan Y, Chen J, et al. Novel FBN1 mutations are responsible for cardiovascular manifestations of Marfan syndrome. Mol Biol Rep 2016;43(11):1227–32.
[49] Zencirci B. Marfan syndrome with acute abdomen: a case report. Int J Gen Med 2010;3:359–63.
[50] Aalberts JJJ, Schuurman AG, Pals G, et al. Recurrent and founder mutations in the Netherlands: extensive clinical variability in Marfan syndrome patients with a single novel recurrent fibrillin-1 missense mutation. Neth Heart J 2010;18(2):85–9.
[51] Ghandi Y, Sayadpour Zanjani K, Mazhari-Mousavi SE, Parvaneh N. Neonatal marfan syndrome: report of two cases. Iran J Pediatr 2013;23(1):113–17.
[52] Herzka A, Sponseller PD, Pyeritz RE. Atlantoaxial rotatory subluxation in patients with Marfan syndrome: a report of three cases. Spine 2000;25(4):524–6.
[53] Reyes-Hernandez OD, Palacios-Reyes C, Chavez-Ocana S, et al. Skeletal manifestations of Marfan syndrome associated to heterozygous R2726W FBN1 variant: sibling case report and literature review Review. BMC Musculoskelet Disord 2016;17:79.
[54] Sureka D, Stheneur C, Odent S, Arno G, Murphy D, Bernstein JA. A recurrent fibrillin-1 mutation in severe early onset Marfan syndrome. J Pediatr Genet 2014;3(3):157–62.
[55] Baran S, Ignys A, Ignys I. Respiratory dysfunction in patients with Marfan syndrome. J Physiol Pharmacol 2007;58(Suppl 5(Pt 1)):37–41.
[56] De Maio F, Fichera A, De Luna V, Mancini F, Caterini R. Orthopaedic aspects of Marfan syndrome: the experience of a referral center for diagnosis of rare diseases. Adv Orthop 2016:2016.
[57] Furtado LV, Wooderchak-Donahue W, Rope AF, et al. Characterization of large genomic deletions in the FBN1 gene using multiplex ligation-dependent probe amplification. BMC Med Genet 2011:12.
[58] Golladay ES, Char F, Mollitt DL. Children with Marfan's syndrome and pectus excavatum. South Med J 1985;78(11):1319–23.
[59] Hawks Arn P, Scherer LR, Haller Jr JA, Pyeritz RE. Outcome of pectus excavatum in patients with Marfan syndrome and in the general population. J PEDIATR 1989;115(6):954–8.
[60] Hilhorst-Hofstee Y, Hamel BCJ, Verheij JBM, et al. The clinical spectrum of complete FBN1 allele deletions. Eur J Hum Genet 2011;19(3):247–52.
[61] Roman MJ, Devereux RB, Kramer-Fox R, Spitzer MC. Comparison of cardiovascular and skeletal features of primary mitral valve prolapse and Marfan syndrome. Am J Cardiol 1989;63(5):317–21.
[62] Sponseller PD, Erkula G, Skolasky RL, Venuti KD, Dietz IHC, Henze EP. Improving clinical recognition of Marfan syndrome. J Bone Jt Surg Ser A 2010;92(9):1868–75.
[63] Streeten EA, Murphy EA, Pyeritz RE. Pulmonary function in the Marfan syndrome. Chest 1987;91(3):408–12.
[64] Aggarwal P, Mahajan S, Garg S. Left parasternal approach for Bentall proce-

dure in a patient of Marfan syndrome with severe pectus excavatum. Indian J Thoracic Cardiovasc Surg 2018;34(3):413–16.
[65] Löhnhardt M, Hättich A, Andresen A, et al. Rescue Nuss procedure for inferior vena cava compression syndrome following posterior scoliosis surgery in Marfan syndrome. Eur Spine J 2019;28:31–6.
[66] Rizvi SAA, Qureshi Z, Sikandar S, Latif-Jangda MJ, Rehan MA, Reyes RA. Familial marfan syndrome. Consultant 2018;58(7):190–1.
[67] Wang Y, Li X, Li R, Yang Y, Du J. Identification of novel causal FBN1 mutations in pedigrees of Marfan syndrome. Int J Genomics 2018:2018.
[68] Zeng Y, Li J, Li G, et al. Correction of the Marfan syndrome pathogenic FBN1 mutation by base editing in human cells and heterozygous embryos. Mol Ther 2018;26(11):2631–7.
[69] Zakkar M, Lansac E, Wurtz A, Brian E. Concomitant aortic root and pectus deformity repair in Marfan syndrome patients. Perfusion 2019;34(2):164–6.
[70] Zhang D.K., Tang J.M., Ben X.S., Xie L. Surgical correction of 639 pectus excavatum cases via the Nuss procedure: ncbi.nlm.nih.gov; 2015.
[71] Duz MB, Kirat E, Coucke PJ, et al. A novel case of autosomal dominant cutis laxa in a consanguineous family: report and literature review. Clin Dysmorph 2017;26(3):142–7.
[72] Hucthagowder V, Sausgruber N, Kim KH, Angle B, Marmorstein LY, Urban Z. Fibulin-4: a novel gene for an autosomal recessive cutis laxa syndrome. Am J Hum Genet 2006;78(6):1075–80.
[73] Morava E, Lefeber DJ, Urban Z, et al. Defining the phenotype in an autosomal recessive cutis laxa syndrome with a combined congenital defect of glycosylation. Eur J Hum Genet 2008;16(1):28–35.
[74] Sawyer SL, Dicke F, Kirton A, et al. Longer term survival of a child with autosomal recessive cutis laxa due to a mutation in FBLN4. Am J Med Genet Part A 2013;161(5):1148–53.
[75] Tüysüz B, Arapoğlu M, Ilikkan B, Demirkesen C, Perk Y. Congetial cutis laxa syndrome: type II autosomal recessive inheritance. Turk J Pediatr 2003;45(3):265–8.
[76] Kivuva EC, Parker MJ, Cohen MC, Wagner BE, Sobey G. De Barsy syndrome: a review of the phenotype. Clin Dysmorphol 2008;17(2):99–107.
[77] Stoll C. Shprintzen-Goldberg marfanoid syndrome: a case followed up for 24 years. Clin Dysmorphol 2002;11(1):1–7.
[78] Robinson PN, Neumann LM, Demuth S, et al. Shprintzen-Goldberg syndrome: fourteen new patients and a clinical analysis. Am J Med Genet A 2005;135a(3):251–62.
[79] Amburgey K, Tsuchiya E, de Chastonay S, et al. A natural history study of X-linked myotubular myopathy. Neurology 2017;89(13):1355–64.
[80] Inoue K, Kumada T, Hiejima I, Fujii T. Successful use of non-invasive positive pressure ventilation in a patient with the severe form of X-linked myotubular myopathy. Brain Dev 2018;40(5):421–4.
[81] Croonen EA, Yntema HG, Van Minkelen R, Van Den Ouweland AMW, Van Der Burgt I. Patient with a neurofibromatosis type 1 mutation but a clinical diagnosis of Noonan syndrome. Clin Dysmorphol 2012;21(4):212–14.
[82] Raja W, Yousef A, Ahmed MI, Omer ul H, Waheed S. Neurofibromatosis-1 with intraventricular haemorrhage and pectus excavatum. J Coll Phys Surg Pak 2012;22(10):669–70.
[83] Rieley MB, Stevenson DA, Viskochil DH, Tinkle BT, Martin LJ, Schorry EK. Variable expression of neurofibromatosis 1 in monozygotic twins. Am J Med Genet Part A 2011;155(3):478–85.
[84] Koczkowska M, Chen Y, Callens T, et al. Genotype-phenotype correlation in NF1: evidence for a more severe phenotype associated with missense mutations affecting NF1 codons 844–848. Am J Hum Genet 2018;102(1):69–87.
[85] Elefteriou F, Kolanczyk M, Schindeler A, et al. Skeletal abnormalities in neurofibromatosis type 1: approaches to therapeutic options. Am J Med Genet Part A 2009;149(10):2327–38.
[86] Sezer E, Senayli A, Sezer T, Bicakci U. Segmental neurofibromatosis: report of two cases. J Dermatol 2006;33(9):635–8.
[87] Alkhunaizi E, Walkiewicz MA, Chitayat D. Mutation in the ADNP gene associated with Noonan syndrome features. Clin Dysmorphol 2018;27(2):53–7.
[88] Bawle E., Tyrkus M., Lipman S. Aarskog syndrome: full male and female expression associated with an X-autosome translocation. American Journal of …. 1984.
[89] Bottani A, Orrico A, Galli L, et al. Unilateral focal polymicrogyria in a patient with classical Aarskog-Scott syndrome due to a novel missense mutation in an evolutionary conserved RhoGEF domain of the faciogenital dysplasia gene FGD1. Am J Med Genet Part A 2007;143(19):2334–8.
[90] Al-Semari A, Wakil SM, Al-Muhaizea MA, et al. Novel FGD1 mutation underlying Aarskog-Scott syndrome with myopathy and distal arthropathy. Clin Dysmorphol 2013;22(1):13–17.
[91] Berman P, Desjardins C, Fraser FC. The inheritance of the Aarskog facial digital genital syndrome. J Pediatr 1975;86(6):885–91.
[92] Yano S, Baskin B, Bagheri A, et al. Familial Simpson-Golabi-Behmel syndrome: studies of X-chromosome inactivation and clinical phenotypes in two female individuals with GPC3 mutations. Clin Genet 2011;80(5):466–71.
[93] Shawky RM, Abd-Elkhalek HS, Gad S. Intrafamilial variability in Simpson–Golabi-Behmel syndrome with bilateral posterior ear lobule creases. Egypt J Med Hum Genet 2014;15(1):87–90.
[94] Spencer C, Fieggen K, Vorster A, Beighton P. A clinical and molecular investigation of two South African families with simpson-golabi-behmel syndrome. S Afr Med J 2016;106(3):272–5.
[95] Thomas M, Enciso V, Stratton R, et al. Metastatic medulloblastoma in an adolescent with Simpson-Golabi-Behmel syndrome. Am J Med Genet Part A 2012;158 A(10):2534–6.
[96] Hughes-Benzie R.M., Pilia G., Xuan J.Y. Simpson-Golabi-Behmel syndrome: genotype/phenotype analysis of 18 affected males from 7 unrelated families. American journal of …. 1996.
[97] Neri G., Marini R., Cappa M., Borrelli P. Simpson-Golabi-Behmel syndrome: an X-linked encephalo-trophoschisis syndrome. American journal of …. 1988.
[98] Fu Q, Wang H, Qi Z, Zhang Y. Simpson–Golabi–Behmel syndrome with 46,XY disorders of sex development: a case report. Am J Med Genet Part A 2019;179(2):285–9.
[99] Bialer M.G., Lawrence L., Stevenson R.E. Allan-Herndon-Dudley syndrome: clinical and linkage studies on a second family. American Journal of …. 1992.
[100] Remerand G, Boespflug-Tanguy O, Tonduti D, et al. Expanding the phenotypic spectrum of Allan–Herndon–Dudley syndrome in patients with SLC16A2 mutations. Dev Med Child Neurol 2019;61(12):1439–47.
[101] Antia AU. Familial skeletal cardiovascular syndrome (Holt-Oram) in a polygamous African family. Br Heart J 1970;32(2):241–4.
[102] Atik T, Dervisoglu H, Onay H, Ozkinay F, Cogulu O. A new mutation in the TBX5 gene in holt-oram syndrome: two cases in the same family and prenatal diagnosis. J Trop Pediatr 2014;60(3):257–9.
[103] Chryssostomidis G, Kanakis M, Fotiadou V, et al. Diversity of congenital cardiac defects and skeletal deformities associated with the Holt–Oram syndrome. Int J Surg Case Rep 2014;5(7):389–92.
[104] Oshima T, Hara H, Takeda N, et al. A novel mutation of NFIX causes Sotos-like syndrome (Malan syndrome) complicated with thoracic aortic aneurysm and dissection. Hum Genome Var 2017;4.
[105] Bufalino A, Carrera M, Carlos R, Coletta RD. Giant cell lesions in noonan syndrome: case report and review of the literature. Health Neck Pathol 2010;4(2):174–7.
[106] Chevallier S, Cook S, Goy JJ. Heart failure in a patient with Noonan syndrome. Circulation 2011;123(23):e629–30.
[107] Cohen Jr MM, Gorlin RJ. Noonan-like/multiple giant cell lesion syndrome. AM J MED GENET 1991;40(2):159–66.
[108] Hanna N, Parfait B, Talaat IM, Vidaud M, Elsedfy HH. SOS1: a new player in the Noonan-like/multiple giant cell lesion syndrome. Clin Genet 2009;75(6):568–71.
[109] Karbach J, Coerdt W, Wagner W, Bartsch O. Case report: noonan syndrome with multiple giant cell lesions and review of the literature. Am J Med Genet Part A 2012;158 A(9):2283–9.
[110] Menon S, Pierpont ME, Driscoll D. Giant cell aortitis and Noonan syndrome. Congenit Heart Dis 2008;3(4):291–4.
[111] Pearl W. Cardiovascular anomalies in Noonan's syndrome. Chest 1977;71(5):677–9.
[112] Schon F, Bowler J, Baraitser M. Cerebral arteriovenous malformation in Noonan's syndrome. Postgrad Med J 1992;68(795):37–40.
[113] Uçar B, Ökten A, Mocan H, Erçin C. Noonan syndrome associated with central giant cell granuloma. Clin Genet 1998;53(5):411–14.
[114] Sanchez Cascos A. The Noonan syndrome. Eur Heart J 1983;4(4):223–9.
[115] Slezak R, Luczak K, Kalscheuer V, Neumann TE, Sasiadek MM. Noonan–like/multiple giant cell lesion syndrome in two adult patients with SOS1 gene mutations. Clin Dysmorphol 2010;19(3):157–60.
[116] Couser NL, Keelean-Fuller D, Davenport ML, et al. Cleft palate and hypopituitarism in a patient with Noonan-like syndrome with loose anagen hair-1. Am J Med Genet Part A 2018;176(9):2024–7.
[117] McDonald BS, Pigors M, Kelsell DP, et al. Noonan syndrome with multiple lentigines and associated craniosynostosis. Clin Exp Dermatol 2018;43(3):357–9.
[118] Petrin Z, Soffer B, Daniels SJ. Sudden cardiac arrest in the field in an 18-year-old male athlete with Noonan syndrome: case presentation and 5-year follow-up. Cardiol Young 2019;29(9):1214–16.
[119] Rodríguez F, Ponce D, Berward FJ, Lopetegui B, Cassorla F, Aracena M. RAF1 variant in a patient with Noonan syndrome with multiple lentigines and craniosynostosis. Am J Med Genet Part A 2019;179(8):1598–602.
[120] Gupta P, Loiwal V, Rai R, Baruah MC, Mishra K, Krishna A. Leopard syndrome: a tropical rarity. J Dermatol 1998;25(5):341–3.
[121] Jóźwiak S, Schwartz RA, Janniger CK, Zaremba J. Familial occurrence of the LEOPARD syndrome. Int J Dermatol 1998;37(1):48–51.
[122] Kuburović V, Vukomanović V, Carcavilla A, Ezquieta-Zubicaray B, Kuburović N. Two cases of LEOPARD syndrome - RAF1 mutations firstly described in children. Turk J Pediatr 2011;53(6):687–91.
[123] Santoro C, Pacileo G, Limongelli G, et al. LEOPARD syndrome: clinical dilemmas in differential diagnosis of RASopathies. BMC Med Genet 2014;15(1).
[124] Sutton L, Sutton E, Sutton M. Leopard syndrome: progressively increasing pigmented macules in an 8-year-old boy. Consultant 2016;56(6):532–5.
[125] Begić F, Tahirović H, Kardašević M, Kalev I, Muru K. Leopard syndrome: a report of five cases from one family in two generations. Eur J Pediatr 2014;173(6):819–22.
[126] Kato H, Yoshida R, Tsukamoto K, et al. Familial cases of atypical clinical features genetically diagnosed as LEOPARD syndrome (multiple lentigines syndrome). Int J Dermatol 2010;49(10):1146–51.
[127] Jurko T, Jurko A, Krsiakova J, Jurko A, Minarik M, Mestanik M. Importance of cardiovascular examination in patients with multiple lentigines: two cases of LEOPARD syndrome with hypertrophic cardiomyopathy. Acta Clin Belg Int J Clin Lab Med 2019;74(2):82–5.
[128] Pirschner F, Bastos PM, Contarato GL, Bimbato ACBL, Filho AC. Gorlin syndrome and bilateral ovarian fibroma. Int J Surg Case Rep 2012;3(9):477–80.
[129] Snoeckx A, Vanhoenacker FM, Verhaert K, Chappelle K, Parizel PM. Gorlin—

Goltz syndrome in a child: case report and clinical review. J Belge Radiol 2008;91(6):235–9.
[130] Musani V, Ozretić P, Trnski D, et al. Potential hot spot for de novo mutations in PTCH1 gene in Gorlin syndrome patients: a case report of twins from Croatia. Croat Med J 2018;59(1):20–4.
[131] Hsu SW, Lin CY, Wang CW, Chung WH, Yang CH, Chang YY. Novel patched 1 mutations in patients with Gorlin–Goltz syndrome strategic treated by smoothened inhibitor. Ann Dermatol 2018;30(5):597–601.
[132] Eliashar R, Sichel JY, Biron A, Dano I. Multiple gastrointestinal complications in Marfan syndrome. Postgrad Med J 1998;74(874):495–7.
[133] Greally MT, Carey JC, Milewicz DM, et al. Shprintzen–Goldberg syndrome: a clinical analysis. Am J Med Genet 1998;76(3):202–12.
[134] Brady AF, Demirdas S, Fournel-Gigleux S, et al. The Ehlers–Danlos syndromes, rare types. Am J Med Genet C Semin Med Genet 2017;175(1):70–115.
[135] Doan ML, Guillerman RP, Dishop MK, et al. Clinical, radiological and pathological features of ABCA3 mutations in children. Thorax 2008;63(4):366–73.
[136] Klaassens M, Morrogh D, Rosser EM, et al. Malan syndrome: sotos-like overgrowth with de novo NFIX sequence variants and deletions in six new patients and a review of the literature. Eur J Hum Genet 2015;23(5):610–15.
[137] Van Dijck A, Vulto-van Silfhout AT, Cappuyns E, et al. Clinical presentation of a complex neurodevelopmental disorder caused by mutations in ADNP. Biol Psychiatry 2019;85(4):287–97.
[138] Dabrowski E, Jensen R, Johnson EK, Habiby RL, Brickman WJ, Finlayson C. Turner syndrome systematic review: spontaneous thelarche and menarche stratified by karyotype. Horm Res Paediatr 2019;92(3):143–9.
[139] Gravholt CH, Andersen NH, Conway GS, et al. Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol 2017;177(3):G1–G70.
[140] Cayrol J, Nightingale M, Challis J, Campbell M, Sullivan M, Heloury Y. Wilms tumor associated with the 9q22.3 microdeletion syndrome: 2 new case reports and a review of the literature. J Pediatr Hematol Oncol 2019;41(8):e517–20.
[141] Wester U, Bondeson ML, Edeby C, Anneren G. Clinical and molecular characterization of individuals with 18p deletion: a genotype-phenotype correlation. Am J Med Genet A 2006;140(11):1164–71.
[142] Goyal M, Jain M, Singhal S, Nandimath K. 18p deletion syndrome: case report with clinical consideration and management. Contemp Clin Dent 2017;8(4):632–6.
[143] van de Laar IM, Oldenburg RA, Pals G, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nat Genet 2011;43(2):121–6.
[144] Pepe G, Giusti B, Sticchi E, Abbate R, Gensini GF, Nistri S. Marfan syndrome: current perspectives. Appl Clin Genet 2016;9:55–65.
[145] Judge DP, Dietz HC. Marfan's syndrome. Lancet 2005;366(9501):1965–76.
[146] Pyeritz RE, Wappel MA. Mitral valve dysfunction in the Marfan syndrome. Clinical and echocardiographic study of prevalence and natural history. Am J Med 1983;74(5):797–807.
[147] Bollero P, Arcuri L, Miranda M, Ottria L, Franco R, Barlattani A Jr. Marfan Syndrome: oral implication and management. Oral Implantol (Rome) 2017;10(2):87–96.
[148] Ting BL, Mathur D, Loeys BL, Dietz HC 3rd, Sponseller PD. The diagnostic value of the facial features of Marfan syndrome. J Child Orthop 2010;4(6):545–51.
[149] Lindsey JM, Michelson JD, MacWilliams BA, Sponseller PD, Miller NH. The foot in Marfan syndrome: clinical findings and weight-distribution patterns. J Pediatr Orthop 1998;18(6):755–9.
[150] Demetracopoulos CA, Sponseller PD. Spinal deformities in Marfan syndrome. Orthop Clin North Am 2007;38(4):563–72 vii.
[151] Esfandiari H, Ansari S, Mohammad-Rabei H, Mets MB. Management strategies of ocular abnormalities in patients with marfan syndrome: current perspective. J Ophthalmic Vis Res 2019;14(1):71–7.
[152] De Maio F, Fichera A, De Luna V, Mancini F, Caterini R. Orthopaedic aspects of Marfan syndrome: the experience of a referral center for diagnosis of rare diseases. Adv Orthop 2016;2016:8275391.
[153] Stheneur C, Tubach F, Jouneaux M, et al. Study of phenotype evolution during childhood in Marfan syndrome to improve clinical recognition. Genet Med 2014;16(3):246–50.
[154] Mahesh Kappanayil SN, Kannan Rajesh, Renard Marjolijn, Coucke Paul, Malfait Fransiska, Menon Swapna, et al. Anne De Paepe Characterization of a distinct lethal arteriopathy syndrome in twenty-two infants associated with an identical, novel mutation in FBLN4 gene, confirms fibulin-4 as a critical determinant of human vascular elastogenesis. Orphanet J. Rare Dis. Vol. 2012;7:61.
[155] Beyens A, Boel A, Symoens S, Callewaert B. Cutis laxa: a comprehensive overview of clinical characteristics and pathophysiology. Clin Genet 2021;99(1):53–66.
[156] Callewaert B, Renard M, Hucthagowder V, et al. New insights into the pathogenesis of autosomal-dominant cutis laxa with report of five ELN mutations. Hum Mutat 2011;32(4):445–55.
[157] Nunley KS, Gao F, Albers AC, Bayliss SJ, Gutmann DH. Predictive value of cafe au lait macules at initial consultation in the diagnosis of neurofibromatosis type 1. Arch Dermatol 2009;145(8):883–7.
[158] Cimino PJ, Gutmann DH. Neurofibromatosis type 1. Handb Clin Neurol 2018;148:799–811.
[159] Yao Z, Guo D, Li H, et al. Surgical treatment of dystrophic scoliosis in neurofibromatosis type 1: outcomes and complications. Clin Spine Surg 2019;32(1):E50–5.
[160] Fois A, Calistri L, Balestri P, et al. Relationship between cafe-au-lait spots as the only symptom and peripheral neurofibromatosis (NF1): a follow-up study. Eur J Pediatr 1993;152(6):500–4.
[161] Gorlin RJ. Nevoid basal cell carcinoma (Gorlin) syndrome. Genet Med 2004;6(6):530–9.
[162] Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet 1997;69(3):299–308.
[163] Priolo M, Schanze D, Tatton-Brown K, et al. Further delineation of Malan syndrome. Hum Mutat 2018;39(9):1226–37.
[164] Gelb BD, Tartaglia M. Noonan syndrome with multiple lentigines, Seattle (WA): GeneReviews(R); 1993. Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, et al., editors..
[165] Digilio MC, Conti E, Sarkozy A, et al. Grouping of multiple-lentigines/LEOPARD and Noonan syndromes on the PTPN11 gene. Am J Hum Genet 2002;71(2):389–94.
[166] Sarret C, Oliver Petit I, Tonduti D. Allan-Herndon-Dudley syndrome, Seattle (WA): GeneReviews(R); 1993. Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, et al., editors.
[167] Remerand G, Boespflug-Tanguy O, Tonduti D, et al. Expanding the phenotypic spectrum of Allan-Herndon-Dudley syndrome in patients with SLC16A2 mutations. Dev Med Child Neurol 2019;61(12):1439–47.
[168] Cassidy JCCABDVSB. Aarskog syndrome. Cassidy and Allanson's management of genetic syndromes; 2020. Fourth Edition.
[169] Tenorio J, Arias P, Martinez-Glez V, et al. Simpson-Golabi-Behmel syndrome types I and II. Orphanet J Rare Dis 2014;9:138.
[170] Cottereau E, Mortemousque I, Moizard MP, et al. Phenotypic spectrum of Simpson-Golabi-Behmel syndrome in a series of 42 cases with a mutation in GPC3 and review of the literature. Am J Med Genet C Semin Med Genet 2013;163C(2):92–105.
[171] McDermott DA, Fong JC, Basson CT. Holt-Oram Syndrome, Seattle (WA): GeneReviews(R); 1993. Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, et al., editors.
[172] Barisic I, Boban L, Greenlees R, et al. Holt Oram syndrome: a registry-based study in Europe. Orphanet J Rare Dis 2014;9:156.
[173] Allanson JE, Roberts AE. Noonan Syndrome, Seattle (WA): GeneReviews(R); 1993. Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, et al., editors.
[174] Jorge AA, Malaquias AC, Arnhold IJ, Mendonca BB. Noonan syndrome and related disorders: a review of clinical features and mutations in genes of the RAS/MAPK pathway. Horm Res 2009;71(4):185–93.
[175] Lee NB, Kelly L, Sharland M. Ocular manifestations of Noonan syndrome. Eye (Lond) 1992;6(Pt 3):328–34.
[176] Tartaglia M, Zampino G, Gelb BD. Noonan syndrome: clinical aspects and molecular pathogenesis. Mol Syndromol 2010;1(1):2–26.
[177] Smpokou P, Tworog-Dube E, Kucherlapati RS, Roberts AE. Medical complications, clinical findings, and educational outcomes in adults with Noonan syndrome. Am J Med Genet A 2012;158A(12):3106–11.
[178] Tekendo-Ngongang C, Agenbag G, Bope CD, Esterhuizen AI, Wonkam A. Noonan syndrome in South Africa: clinical and molecular profiles. Front Genet 2019;10:333.
[179] E Muller LH. 9q22.3 Microdeletion.. GeneReviews 2014.
[180] Sarkozy A, Digilio MC, Dallapiccola B. Leopard syndrome. Orphanet J Rare Dis 2008;3:13.
[181] C Sarret IP, Tonduti D. Allan-Herndon-Dudley syndrome. GeneReviews 2020.
[182] Morava E, Guillard M, Lefeber DJ, Wevers RA. Autosomal recessive cutis laxa syndrome revisited. Eur J Hum Genet 2009;17(9):1099–110.
[183] Oshima T, Hara H, Takeda N, et al. A novel mutation of NFIX causes Sotos-like syndrome (Malan syndrome) complicated with thoracic aortic aneurysm and dissection. Hum Genome Var 2017;4:17022.
[184] O'Dougherty GR, Fulkerson DH, Kern M, Haldar K, Calhoun B. Complications of insufficient dura and blood loss during surgical intervention in Shprintzen–Goldberg syndrome: a case report. Am J Case Rep 2019;20:1159–69.
[185] M Mazzocco A.Q., M. Murphy, M. McCloskey. Genetic Syndromes as Model Pathways to Mathematical Learning Difficulties: Fragile X, Turner, and 22q Deletion Syndromes. 2016.
[186] van der Burgt I. Noonan syndrome. Orphanet J Rare Dis 2007;2:4.
[187] Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet 1999;89(1):1–6.
[188] Urban Z, Davis EC. Cutis laxa: intersection of elastic fiber biogenesis, TGFbeta signaling, the secretory pathway and metabolism. Matrix Biol 2014;33:16–22.
[189] Qi Y, Xu R. Roles of PLODs in collagen synthesis and cancer progression. Front Cell Dev Biol 2018;6:66.
[190] Pezzini A, Del Zotto E, Giossi A, Volonghi I, Costa P, Padovani A. Transforming growth factor beta signaling perturbation in the Loeys–Dietz syndrome. Curr Med Chem 2012;19(3):454–60.
[191] Matt P, Schoenhoff F, Habashi J, et al. Circulating transforming growth factor–beta in Marfan syndrome. Circulation 2009;120(6):526–32.
[192] Doyle AJ, Doyle JJ, Bessling SL, et al. Mutations in the TGF-beta repressor SKI cause Shprintzen-Goldberg syndrome with aortic aneurysm. Nat Genet 2012;44(11):1249–54.
[193] Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev 2009;19(3):230–6.

[194] Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The pathoetiology of neurofibromatosis 1. Am J Pathol 2011;178(5):1932–9.
[195] Behr CA, Denning NL, Kallis MP, et al. The incidence of Marfan syndrome and cardiac anomalies in patients presenting with pectus deformities. J Pediatr Surg 2019;54(9):1926–8.
[196] Akcali Y, Ceyran H, Hasdiraz L. Chest wall deformities. Acta Chir Hung 1999;38(1):1–3.
[197] Biesecker BB. Goals of genetic counseling. Clin Genet 2001;60(5):323–30.
[198] Rubio-Perez C, Guney E, Aguilar D, et al. Genetic and functional characterization of disease associations explains comorbidity. Sci Rep 2017;7(1):6207.
[199] Fraser S, Child A, Hunt I. Pectus updates and special considerations in Marfan syndrome. Pediatr Rep 2017;9(4):7277.
[200] Arn PH, Scherer LR, Haller JA Jr, Pyeritz RE. Outcome of pectus excavatum in patients with Marfan syndrome and in the general population. J Pediatr 1989;115(6):954–8.
[201] Nugent DJ, Romano AA, Sabharwal S, Cooper DL. Evaluation of bleeding disorders in patients with Noonan syndrome: a systematic review. J Blood Med 2018;9:185–92.
[202] Takeda N, Inuzuka R, Maemura S, et al. Impact of pathogenic FBN1 variant types on the progression of aortic disease in patients with Marfan syndrome. Circ Genom Precis Med 2018;11(6):e002058.