THE GENETIC CAUSES OF CHEST WALL MALFORMATIONS

Adam O[1], Andreea Dobrescu[2], David VL[3], Maria Puiu[4]

Abstract

Introduction. The sternum, a long, narrow flat bonne, has an important structural and functional role in the human body. It has an important role in body structure and function. Sternal malformations are relatively frequent isolated or as part of some genetic syndromes. Pectus excavatum (PE) and pectus carinatum (PC) represent more than 95% of sternum malformations. Objectives. The study aims to highlight the genetic origin of the most common congenital sternum abnormalities (PE and PC) and the role of specific genes in the appearance of those deformities. The etiology of all congenital sternum abnormalities is not clearly identified yet. Material and Methods. We reviewed the online data bases and specific journals archives. The titles and abstracts of studies were evaluated by all the authors independently. For eligible studies, at least one review author extracted the data. We excluded studies who present the management, the treatment or any other different information by the genetic part of the targeted pathology. We also excluded the studies that presented syndromic PE patients. Results. We detected 402 possible eligible studies and after the evaluation according to the inclusion criteria 392 were excluded. Excluded causes were presented in methods section. From the included studies, 8 studies present genes involved in PE appearance, 1 study for PC appearance and 1 study for pectus deformity. Discussions. We included studies that demonstrated the inheritances of PE without emphasize the involved genes and also two studies with syndromic PE but with a new genetic cause. Conclusions. All the described studies sustain the genetic origin of PE and PC. It has large limits that make almost impossible in this moment to estimate a precise contribution of genetic factors in congenital sternum abnormalities. We need more studies with large cohorts to prove the prevalence of genetic factors in PE.

Key words: chest wall malformations, Pectus Excavatum, Pectus Carinatum, genetics

Introduction

The sternum, a long, narrow flat bonne, has an important structural and functional role in the human body. It stabilizes the body skeleton, it is involved in the movement of arms, neck and head and it also protects some vital organs like the heart, the aorta, the timus gland. Sternal malformations (pectus excavatum, pectus carinatum, cleft sternum, pentalogy of Cantrell, asphyxiating thoracic dystrophy, and spondylothoracic dysplasia) are relatively frequent, isolated or as part of some numeric or structural chromosomal disease or monogenic disorder. They affect male and female, with a higher frequency in male. They are present from the first years of life, are progressive and could determine important respiratory and cardiovascular symptoms.

Pectus excavatum (PE) is the most common congenital sternum abnormality (90%); it affects 1 from 300-400 births, predominantly in males (male: female ratio 3:1) [1]. Usually, it is presented at birth and it becomes more pronounced in puberty. The deformity severity and the chest asymmetry varies from a mild to severe form of PE, in some cases the sternum almost touchesd the spine. It is associated with altered pulmonary function on the strength of decrease in intrathoracic volume secondary to the sunken chest [2, 3]. Several studies tried to prove this theory but the results are not clear enough [3, 4]. The malformation can determine heart function disturbances as a result of left ventricle anterior indentation. It could be part of genetic sindromes like Jeune's Syndrome, Marfan Syndrome, Noonan Syndrome.

Pectus carinatum (PC) is an abnormal protrusion of the anterior chest wall. It appears in 5-6% of cases of congenital sternum malformations, male: female ratio 4:1 [5]. It affects 0.06% of the population and about 25% of them have positive family history of sternal abnormalities [6]. There are two types of PC, chondrogladiolar or chondromanubrial, according to the prominence site. Studies showed a higher incidence of cardiac and hemodynamic changes in chondromanubrial abnormalities [7]. PC is associated with respiratory symptoms like dyspnea or tachypnea because of fixed antero-posterior diameter of chest wall that became rigid [8]. However, 22% of patients from one series were asymptomatic [6]. Another significant problem of the malformation is the concern about the body image associated with low self-esteem [9]. Like PE, PC may occur in association with other clinical symptoms as part of genetic syndromes—Trisomy 18, Trisomy 21, Marfan syndrome, Osteogenesis imperfect.

The cleft sternum, a total or partial fissure in the middle of the sternum, is a very rare sternal abnormality. It appears as a result of a disturbance in the embryologic sternum development.

[1] "Louis Turcanu" Children Emergency Hospital, Timisoara
[2] "Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Pediatric Surgery
[3] "Victor Babes" University of Medicine and Pharmacy Timisoara, Department of Genetics
E-mail: adamovidiu29@yahoo.com, dobrescu.andreea.iulia@gmail.com, david.vlad@yahoo.com, maria.puiu@gmail.com

Pentalogy of Cantrell is a very rare congenital malformation; it is represented by 5 major malformations: midline supraumbilical abdominal wall defect, the sternal lower part defect and agenesis of the anterior portion of the diaphragm, an absence of the diaphragmatic part of the pericardium and a malformation of cardia. It affects 1/65,000-1/200,000 live births [10]. The pathology may occur sporadically or in association with other genetic syndromes like Down syndrome, Turner Syndrome, Trisomy 13 or 18.

Asphyxiating thoracic dystrophy is named Jeune syndrome. It consists in small chest, short ribs, and shortened bones in the arms and legs; there also could appear other symptoms like polydactyly, an extremely narrow, bell-shaped chest. It is a rare skeletal pathology; it affects 1 in 100,000 to 130,000 people [11].

Spondylothoracic dysplasia, Jarcho-Levin syndrome, another rare chest wall malformation, is characterized by short and rigid neck, shortened thorax, protuberant abdomen, inguinal and umbilical hernias and moderate to severe scoliosis and kyphosis. The literature describes only 14 cases till now.

The etiology of all congenital sternum abnormalities are not clearly identified yet even if a family tendency was tried to be proved.

Objective. The study aims to highlight the genetic origin of the most common congenital sternum abnormalities (PE and PC) and the role of specific genes in the appearance of those deformities.

Material and Method. We performed a literature review to identify the most relevant studies for our topic. We reviewed data bases like PubMed, Orphanet and The Cochrane Library and online archives of journals like The Lancet, European Journal of Human Genetics, Genetics in Medicine, Human Genetics. The search strategy was based on key words like “gene”, “genetic factors”, “sternum abnormalities”, “congenital sternal malformations”, “pectus excavatum” and “pectus carinatum” used alone and in combination (table 1). We included all published studies that corresponded to our research strategy, with no study design restrictions. We did not filter the studies according to the participants or the published year. Our review targeted infants, children or adults with PC or PE. We excluded studies who present the management, the treatment or any other different information by the genetic part of the targeted pathology. We also excluded the studies that presented syndromic PE patients. The titles and abstracts of studies that were detected by our research strategy were evaluated by all the authors independently for inclusion all the potential studies in our review. For eligible studies, at least one review author extracted the data using the agreed form. We resolved disagreements through discussion between all the authors.

Results. We detected 402 possible eligible studies and after the evaluation according to the inclusion criteria 392 were excluded. Excluded causes were presented in methods section. From the included studies, 8 studies present genes involved in PE appearance, 1 study for PC appearance and 1 study for pectus deformity (PE and PC).

Song Wu et al. analyzed a four-generation Chinese family with congenital PE [12]. DNA samples from the tested persons were whole genome sequenced for four affected members of the family and also for one unaffected. They identified a mutation on chromosome 7, g.chr7: 99764688G>A, in affecting members of the family. The mutation affects the first exon of GAL3ST4 causing a substitution of arginine with tryptophan. The mutation did not appear in healthy tested persons. The first results indicated a specific mutation for PE, but in order to validate them, the research team genotyped a cohort of 378 unrelated healthy individuals and they observed none of the normal tested person had it. They also sequenced the whole exon of GAL3ST4 in another eight individuals with sporadic PE and identified the mutation g.chr7: 99758263C>T in one person [12].

As part of the clinical symptoms in Marfan syndrome, PE was evaluated in a study published by Eliana Disabella and Co in 2005. They identified two new mutations of the TGFBR2 gene in patients non-carriers of FBN1 gene defects. Those patients had major cardio-skeletal signs and no major ocular abnormalities. One of them, a 27 years old male, had an extremely pectus excavatum associated with other skeletal malformations. This case had M425V mutation of TGFBR2; the mutation was absent in healthy tested people. The case of a 4 years old girl had pectus carinatum and she was detected to carry a novo D446N mutation. Another presented case with severe cardio-skeletal malformations associated pectus excavatum with R460H mutation [13]. The authors concluded that the three identified mutations are located in the serine/threonine kinase domain of the TGFBR2 which affecting serine/threonine kinase domains involve signal signaling and transduction mechanisms determining connective tissue disorders and cancer [13].

We identified a study from 2004 by Ghazala Mirza et al. that described two patients with mild PE associated with deletion of BMP6 gene located on chromosome 6[14]. Similar studies on mice revealed sternum malformations associated with the same gene mutation which allowed the authors to suggest that the specific protein has a similar role in humans and mice [15].

A mild form of PC was reported by Ofner et al. as part of clinical manifestations of deletion on paternal chromosome 5, 5q21.1-23.1. The deleted region contains several genes involved in the tissues and bone development [16].

Komatsuzaki et al. analyzed the mutations on SHOC2 gene in patients with Noonan-like syndrome. They analyzed 92 patients and tried to compare the frequency of clinical symptoms between patients with SHOC2 gene mutation associated with Noonan-like syndrome and patients with Noonan syndrome, Costello syndrome and cardio-facio-cutaneous syndrome. They concluded that pectus deformity was 72% more frequent in SHOC2 mutation [17].

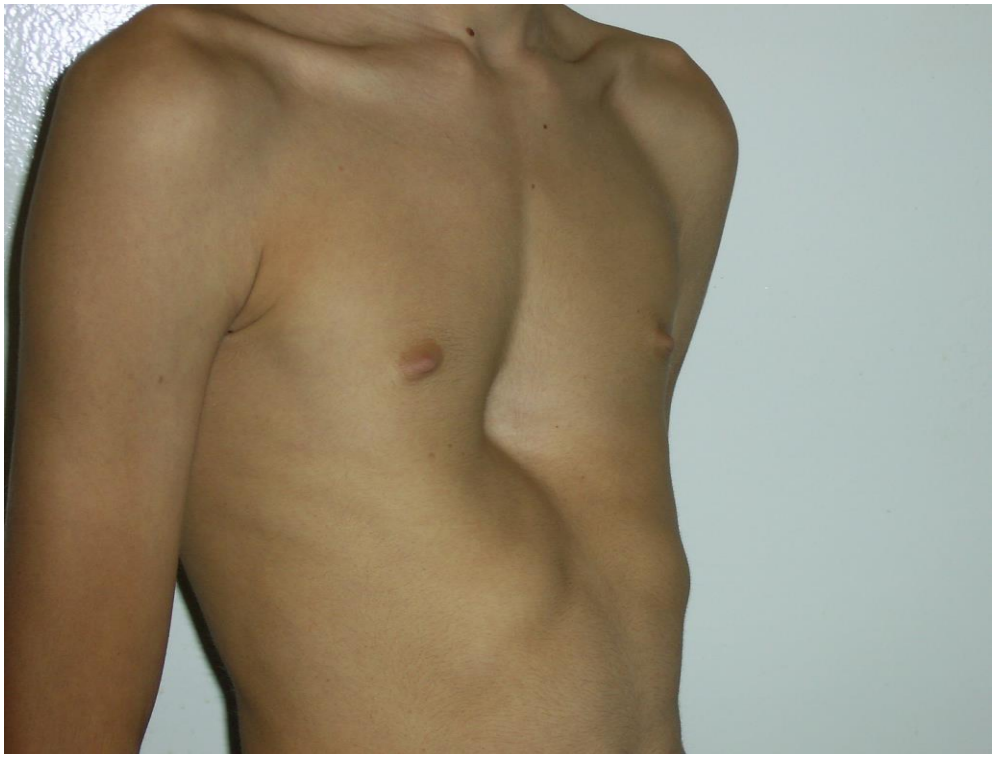

Fig. 1. Pectus excavatum.

#63	Add	Search (((("sternum") AND "pectus carinatum")) AND "genetic factors"	0	06:07:26
#62	Add	Search (((("sternum") AND "pectus excavatum")) AND "genetic factors"	0	06:06:57
#61	Add	Search (((("sternum") AND "pectus carinatum")) AND "gene"	0	06:06:26
#60	Add	Search (((("sternum") AND "pectus excavatum")) AND "gene"	1	06:05:28
#24	Add	Search ("genetic factors") AND "pectus carinatum"	1	06:02:57
#25	Add	Search ("genetic factors") AND "pectus excavatum"	1	05:56:37
#28	Add	Search ("congenital sternal abnormalities") AND "gene"	15	05:27:16
#29	Add	Search ("congenital sternal abnormalities") AND "pectus excavatum"	74	05:20:39
#30	Add	Search ("congenital sternal abnormalities") AND "pectus carinatum"	32	05:08:18
#27	Add	Search "congenital sternal abnormalities"	882	03:25:51
#23	Add	Search "genetic factors"	25044	03:03:27
#22	Add	Search ("sternum") AND "pectus excavatum"	368	02:58:35
#21	Add	Search ("sternum") AND "pectus carinatum"	123	02:58:20
#20	Add	Search ("sternum") AND "gene"	142	02:57:42
#19	Add	Search "sternum"	10763	02:57:25
#18	Add	Search (((bone) AND "chest wall")) AND "gene"	13	02:56:59
#17	Add	Search ("breastbone") AND "gene"	1	02:56:29
#16	Add	Search ("pectus carinatum") AND "gene"	17	02:56:07
#15	Add	Search ("gene") AND "pectus excavatum"	37	02:55:53
#14	Add	Search "gene"	1637992	02:55:46
#13	Add	Search (((bone) AND "chest wall")) AND "pectus excavatum"	117	02:55:31
#12	Add	Search (((bone) AND "chest wall")) AND "pectus carinatum"	53	02:55:20
#11	Add	Search (bone) AND "chest wall"	3241	02:54:58
#10	Add	Search bone	1025454	02:54:51
#9	Add	Search "chest bone"	15	02:54:28
#8	Add	Search "chest wall"	13440	02:54:09
#3	Add	Search "pectus carinatum"	293	02:51:13
#2	Add	Search "breastbone"	25	02:50:57
#1	Add	Search "pectus excavatum"	1514	02:50:46

Table 1. Search strategy on PubMed.

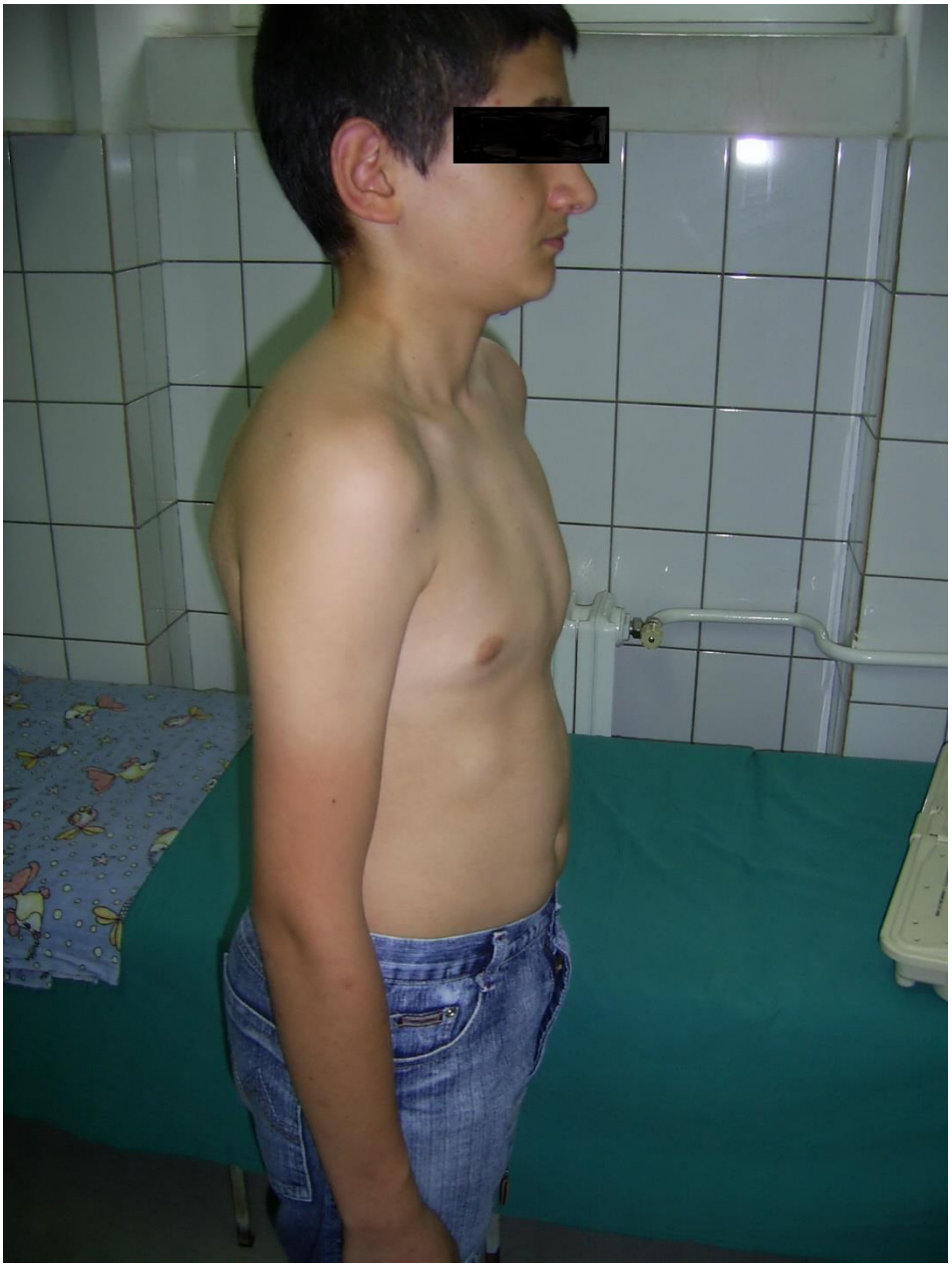

Fig.2. Pectus carinatum.

Gurnette et al tried to map the genes causes adolescent idiopathic scoliosis (AIS) and PE. They evaluated a 5-generation Caucasian family in which segregate. They performed a genome-wide linkage analysis for thirteen affected members of the family, nine female affected by AIS, 3 male and one female affected by PE, and also for ten unaffected members of the same family. The analysis revealed a novel locus for PE and AIS on chromosome 18, 18q12.1–q12.2. In the end, the authors tried to highlight that the genetic conditions of those two bone malformations are likely related [18].

FBN1 gene mutations, the genetic cause of MSS (Mitral valve prolapse, not progressive Aortic enlargement, Skeletal and Skin alterations) is also commonly associated with PE [19].

Several studies tried to demonstrate the genetic condition of PE analyzing the pedigree of families with more than one affected individual. In one study, the authors revealed four families with an autosomal recessive inheritance, six families X-linked recessive inheritance and fourteen autosomal dominant inheritance of the medical condition [20]. Lisa Horth and Co evaluated 48 pedigrees and 56 clinical traits and obtained important evidence of the genetic control of the disorder [21]. They also demonstrated the higher prevalence of PE in male.

Stacey and Co supposed that costal cartilage of patients with PE has modifications of variable number of tandem repeats (VNTRs) of ACAN gene that compromised structural characteristics. They identified an increase

severity of PE in female associated with a decreased number of VNTRs which weakened the cartilages [22].

Discussions. Only 10 studies were eligible to be included in our review. Two studies tried to highlight the inheritance character of PE evaluating the pedigree of families with more than one affected individual. Even if those studies did not present any specific gene for congenital sternal abnormalities, we included them in the review because their outcome was similar with what we needed. Another two studies evaluated the genetic cause of PE or PC like part of two genetic syndromes. We also included them because they presented Marfan and Noonan syndrome determined by new genes which could be associated with severe malformations of sternum.

Conclusions. All the described studies sustain the genetic origin of PE and PC. It has large limits that make almost impossible in this moment to estimate a precise contribution of genetic factors in congenital sternum abnormalities : chromosome 5 or chromosome 18 abnormalities, different gene that can also be the cause of undiagnosed disorders, known syndromes but with a different nonspecific genetic profile. The evaluation of pedigree in families with more than one affected individual is recommended like first step to identify a family predisposition for PE. The genome-wide linkage scan is the most used analysis that can determine gene mutations for PE. We need more studies with large cohorts to prove the prevalence of genetic factors in PE. It is very important to have indicators that predict a high risk of PE appearance because of its cardiovascular and respiratory complications, with a vital impact.

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Correspondence to:
Andreea Dobrescu
Theodor Aman street, 66-68
Timisoara, Romania
E-mail: dobrescu.andreea.iulia@gmail.com