EXPERIENCE USING NEXT-GENERATION SEQUENCING TECHNOLOGY IN A PATIENT WITH MARFAN SYNDROM

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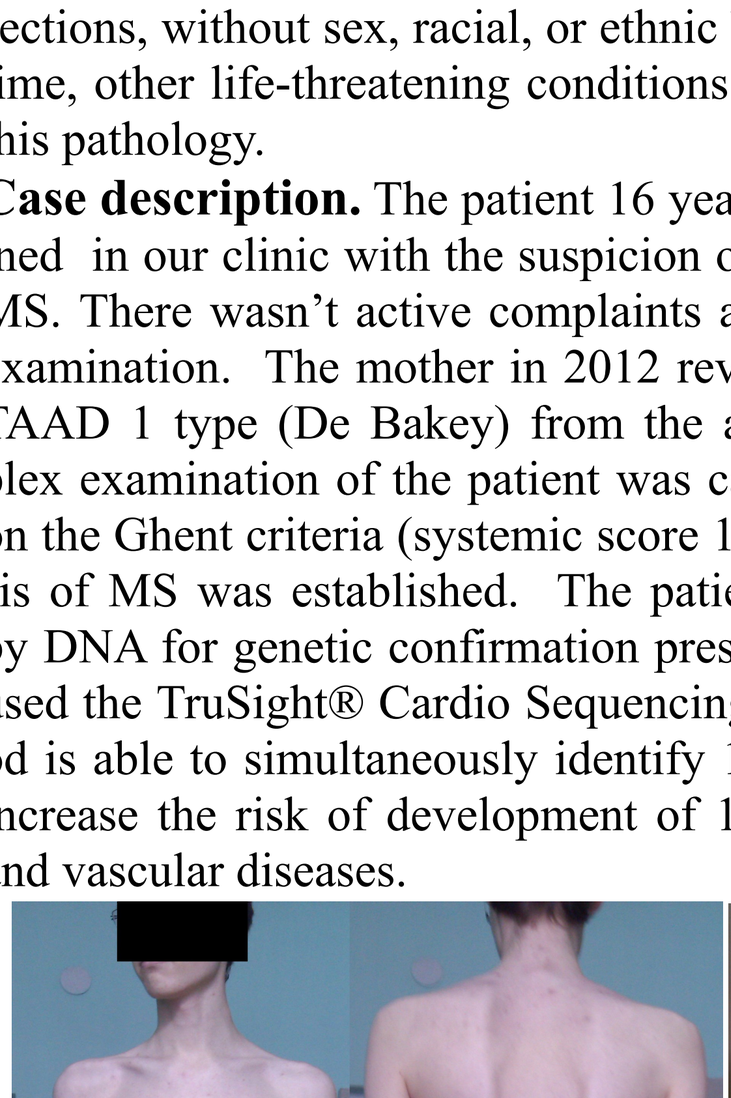
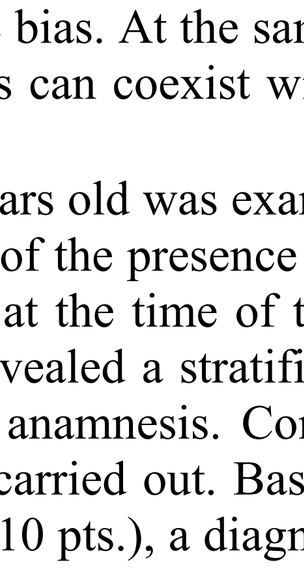
Background. Marfan syndrome (MS) is an autosomal dominant disease characterized by high penetrance and marked phenotypic heterogeneity. The prevalence is estimated at 1:2000-1:5000 and there is no difference between sexes. An international expert panel has established a revised Ghent nosology, which puts more weight on the cardiovascular manifestations and in which aortic root aneurysm (or dilatation/dissection) and ectopia lentis are the cardinal clinical features. In absence of either of these two features, the presence of a bonafide FBN1 mutation (2056 - number of mutation at present time) or a combination of systemic manifestations is required (systemic score ≥7 pts). FBN1 testing, although not mandatory, has greater weight in the diagnostic assessment.

Sanger sequencing is the time-honored gold standard for sequence-based testing of Mendelian disease genes. In current diagnostic scenarios with sequencing of multiple genes in a single patient within a short time span (if there is a mutation in several genes). Sanger sequencing has reached its limits. Conversely, next-generation sequencing (NGS) technologies allow thousands to millions of base pairs of DNA sequence to be examined, where a large set of genes can be tested simultaneously, and this technology has now become feasible for clinical diagnostics. Marfan syndrome is traditionally associated with thoracic aortic aneurysms and dissections (TAAD) accounts for 5% of all aortic dissections, without sex, racial, or ethnic bias. At the same time, other life-threatening conditions can coexist with this pathology.

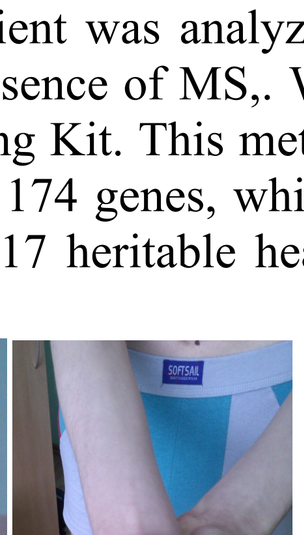
Case description. The patient 16 years old was examined in our clinic with the suspicion of the presence of MS. There wasn't active complaints at the time of the examination. The mother in 2012 revealed a stratified TAAD 1 type (De Bakey) from the anamnesis. Complex examination of the patient was carried out. Based on the Ghent criteria (systemic score 10 pts.), a diagnosis of MS was established. The patient was analyzed by DNA for genetic confirmation presence of MS,. We used the TruSight® Cardio Sequencing Kit. This method is able to simultaneously identify 174 genes, which increase the risk of development of 17 heritable heart and vascular diseases.



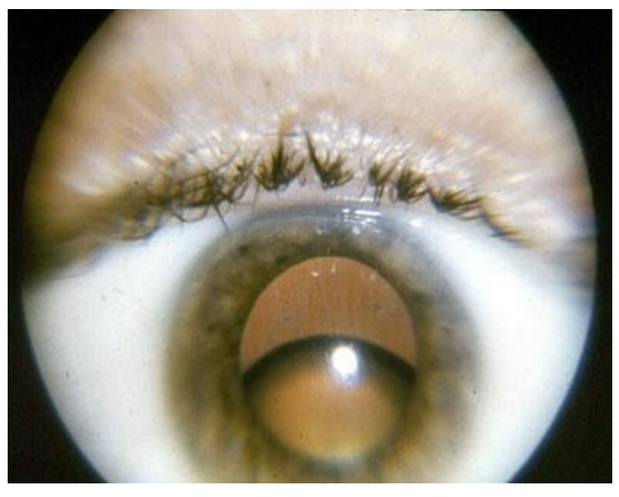
Reduced upper/lower segment ratio



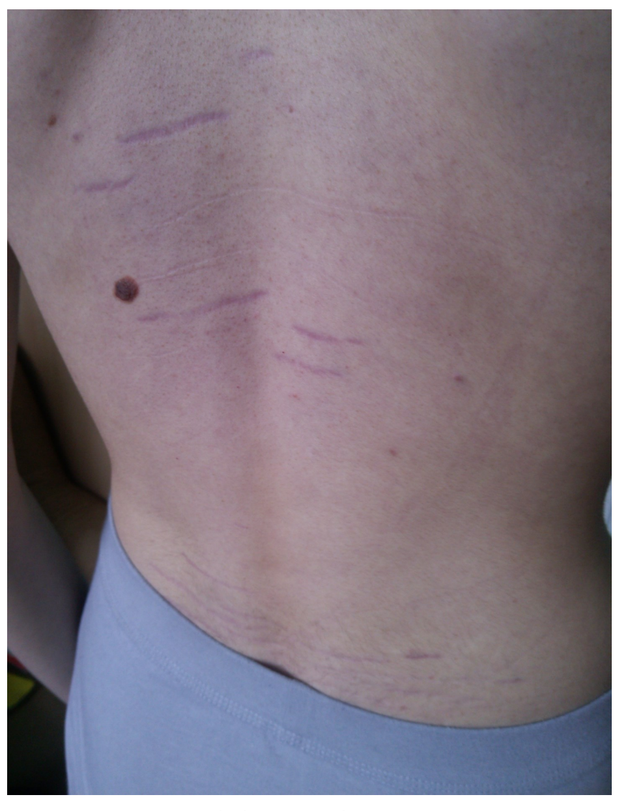
Wrist sign



Thumb sign



Ectopia lentis



Skin striae

Results

Gene	Chromosome (exon)	Mutation	Amino acid change	dbSNP	Population frequency*
FBN1	15 (62)	**c.G7664T**	**p.G2555V**	.	.
ACTN2	4 (38)	**c.G893A**	**p.R298H**	rs142482143	0,0006
CRYAB	11 (1)	**c.C116T**	**p.P39L**	rs149787233	0,0004

.*– project 1000 genomes

Discussion. As widely expected a mutation in FBN1 gene has been identified. New molecular techniques allow the detection of FBN1 mutations in up to 97% of Marfan patients who fulfil the Ghent criteria.

The majority of cases of MS are caused by a mutation in FBN1 gene, witch provides instructions for making protein - fibrillin-1. Fibrillin-1 attach to each other and to other proteins to form threadlike filaments – microfibrils. Microfibrils also provide support to more rigid tissues such as bones and muscles, and lenses of the eyes. At the same time as a mutation in the FBN1 gene, a mutation in the CRYAB gene was detected, which may contribute to the transparency and refractive index of the lens [UniPro]. When examining the ophthalmologist, a complex short-sighted astigmatism of both eyes and ectopia lentis was revealed. To remain undecided, which of the genetic mutations was of decisive importance in the development of the eye pathology.

According results NGS two genetic mutations associated with the development of cardiovascular disease has been exactly identified.

ACTN2 gene mutation is characterized by ventricular hypertrophy, which is usually asymmetric and often involves the interventricular septum [NCBI Gene].

CRYAB gene mutation (previously reviewed) is characterized by ventricular dilation and impaired systolic function, resulting in congestive heart failure and arrhythmia. Patients are at risk of premature death [NCBI Gene].

During the clinical examination of the patient transthoracic echocardiography was performed, which revealed no myocardial pathology. Thus, long before the development of clinical symptoms, we were able to identify the patient's life -threatening conditions, this will radically affect the development and possible outcome of the disease.

Disclosure. The authors report no conflicts of interest in this work.