Acta Biomed 2019; Vol. 90, Supplement 10: 53-57 DOI: 10.23750/abm.v90i10-S.8760

Review

Atrial septal defects, supravalvular aortic stenosis and syndromes predisposing to aneurysm of large vessels

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Summary. Atrial septal defect is a persistent interatrial communication. It is the second most common congenital heart defect and is detected in 1:1500 live births. Clinical course is variable and depends on the size of the malformation. Clinical diagnosis is based on patient history, physical and instrumental examination. Atrial septal defect is frequently sporadic, but familial cases have been reported. The disease has autosomal dominant inheritance with reduced penetrance, variable expressivity and genetic heterogeneity. Supravalvular aortic stenosis is a congenital narrowing of the lumen of the ascending aorta. It has an incidence of 1:20000 newborns and a prevalence of 1:7500. Clinical diagnosis is based on patient history, physical and instrumental examination. Supravalvular aortic stenosis is either sporadic or familial and has autosomal dominant inheritance with reduced penetrance and variable expressivity. It is associated with mutations in the ELN gene. Syndromes predisposing to aneurysm of large vessels is a group of inherited disorders that may affect different segments of the aorta. They may occur in isolation or associated with other genetic syndromes. Clinical symptoms are highly variable. Familial thoracic aortic aneurysm and dissection accounts for ~20% of all cases of aneurysms. The exact prevalence is unknown. Clinical diagnosis is based on medical history, physical and instrumental examination. Genetic testing is useful for confirming diagnosis of these syndromes and for differential diagnosis, recurrence risk evaluation and prenatal diagnosis in families with a known mutation. Most syndromes predisposing to aneurysm of large vessels have autosomal dominant inheritance with reduced penetrance and variable expressivity. (www.actabiomedica.it)

Key words: atrial septal defect, supravalvular aortic stenosis, aneurysm of large vessels

Atrial septal defect

Atrial septal defect is a persistent interatrial communication (1). It is the second most common congenital heart defect and accounts for approximately 10% of all cardiac malformations. It includes ostium secundum (~75% of cases), ostium primum (15-20%) and sinus venosus (5-10%) (1). It is detected in 1:1500 live births, with a female-to-male ratio of 2-4:1. Its estimated prevalence in the general population is 1:25000 (2). Atrial septal defect is often associated with paradoxical embolism, cerebral abscess, pulmonary hypertension, conduction disturbances, cardiomyopathies, complex congenital heart defect and sudden cardiac death (3).

Clinical course is variable and depends on the size of the malformation. Most very small atrial septal defects (diameter <5 mm) do not have clinical consequences, whereas a defect of 5-10 mm may lead to symptoms in the fourth or fifth decade of life. Larg-

er defects (generally >10 mm) typically present with symptoms in the third decade of life (3).

Clinical diagnosis is based on patient history, physical examination, two-dimensional transthoracic echocardiography and transesophageal echocardiogram, cardiac computed tomography and magnetic resonance imaging (4,5). Differential diagnosis should consider Klippel-Feil syndrome and Eisenmenger syndrome, which features systolic flow murmur in the pulmonary valve region due to increased pulmonary flow (6, 7).

Atrial septal defect is almost always sporadic, but familial cases have been reported. The disease has autosomal dominant inheritance with reduced penetrance, variable expressivity and genetic heterogeneity of familial atrial septal defects (7) (Table 1).

MAGI uses a multi-gene NGS panel to detect nucleotide variations in coding exons and flanking introns of the above genes.

Other authors have reported sensitivities of 90% and 100% in 11 ventricular septal defects and five atrial septal defects, respectively (8) and 80% sensitivity in a combined series of 10 atrial septal defects and ventricular septal defects (9).

Supravalvular aortic stenosis

Supravalvular aortic stenosis (SVAS) is a congenital narrowing of the lumen of the ascending aorta (10). It is often associated with stenosis of other vessels, typically the pulmonary artery, and also with arrhythmia. It may occur as an isolated condition or as a feature of syndromes such as Williams-Beuren (11) or cutis laxa syndrome (12). Its severity varies: some affected patients never experience symptoms and others die in infancy. Although clinical presentation is heterogeneous and severity is variable, surgical treatment is often needed. If not treated, aortic stenosis may lead to dyspnea, chest pain and heart failure. Supravalvular aortic stenosis has an incidence of 1:20000 newborns (13) and a prevalence of 1:7500.

Clinical diagnosis is based on patient history, physical examination, echocardiography, electrocar-

Table 1. Genes associated with various forms of atrial septal defect

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
GATA4	600576	ASD2	607941	AD	Regulation of genes involved in myocardial differentiation and function
TBX20	606061	ASD4	611363	AD	Transcriptional activator and repressor required for heart development, and for functional and structural phenotypes in adult heart
MYH6	160710	ASD3	614089	AD	Alpha heavy chain subunit of cardiac myosin
ACTC1	102540	ASD5	612794	AD	Major constituent of contractile apparatus of muscle tissue
TLL1	606742	ASD6	613087	AD	Essential for interventricular septum formation
NKX2-5	600584	ASD7, with/ without AVCD	108900	AD	Transcription factor necessary for heart formation and development
CITED2	602937	ASD8	614433	AD	Regulatory gene indispensable for prenatal development
GATA6	601656	ASD9	614475	AD	Important in gut, lung and heart development
NKX2-6	611770	ASD	/	AD	Role in embryonic development of heart in conjunction with NKX2-5

ASD=atrial septal defect; AVCD=atrioventricular conduction defects; AD=autosomal dominant.

diography and angiographic evidence of progressive narrowing of the aorta and/or pulmonary artery lumen (14). Differential diagnosis should consider Williams-Beuren syndrome, in which SVAS is identical to the isolated form but associated with behavioral disorders, typical facial features and hypercalcemia (15).

Supravalvular aortic stenosis is either sporadic or familial and has autosomal dominant inheritance with reduced penetrance and variable expressivity. It is associated with more than 60 variations in the ELN gene (OMIM gene 130160; OMIM disease 185500) (16). Pathogenic variants may be missense, nonsense, splicing or small indels. Large deletions/duplications have also been reported in the ELN gene. MAGI uses NGS to detect nucleotide variations in coding exons and flanking introns of the ELN gene and MLPA to detect duplications and deletions.

Worldwide, 6 accredited medical genetic laboratories in the EU and 10 in the US, listed in the Orphanet (17) and GTR (18) databases, respectively, offer genetic testing for SVAS. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (19).

Syndromes predisposing to aneurysm of large vessels

Syndromes predisposing to aneurysm of large vessels are a group of inherited disorders that may affect different segments of the aorta, such as the aortic root, ascending aorta, aortic arch or descending aorta. They manifest as dilation, aneurysm or dissection of these segments. Aneurysms in the abdominal aorta, peripheral artery and cerebral artery are also reported (20).

These syndromes may occur in isolation or associated with other genetic syndromes, including Marfan syndrome, Loeys-Dietz syndrome and Ehlers-Danlos syndrome. Some patients show one or more of the following clinical signs: congenital heart abnormalities, inguinal hernia, scoliosis and livedo reticularis.

Clinical symptoms vary widely. Aortic aneurysm usually has no symptoms, but depending on its growth rate, location and size, it may express as chest, back, jaw or neck pain, upper limb edema, dyspnea and/or dysphagia. Aortic dissections usually cause sudden severe chest or back pain and may be followed by hemorrhagic shock.

Familial thoracic aortic aneurysm and dissection is a frequent disorder. It is estimated to cause about 20% of all cases of thoracic aortic aneurysm and dissection (21). The exact prevalence is not known as most aortic aneurysms do not cause symptoms unless there is dissection.

Clinical diagnosis is based on medical history, physical examination, transthoracic/transesophageal echocardiography, spiral computed tomography and invasive imaging methods such as left ventricular angiography and aortography (22). Genetic testing is useful for confirming diagnosis of these aneurysm predisposition syndromes and for differential diagnosis, recurrence risk evaluation and prenatal diagnosis in families with a known mutation. Differential diagnosis should consider inherited disorders such as Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome and acquired disorders of thoracic aortic aneurysm, such as severe hypertension, atherosclerosis and infectious causes.

Syndromes predisposing to aneurysm of large vessels typically have autosomal dominant inheritance with reduced penetrance and variable expressivity (23) (Table 2).

The mutation detection rate in patients with predisposition for aneurysm of large vessels is about 40% (specifically ACTA2 12-21%, FBN1 3%, FOXE3 1.4%, LOX 1.5%, MAT2A 1%, MFAP5 0.25%, MYH11 1%, MYLK 1%, PRKG1 1%, SMAD3 2%, TGFB2 1%, TGFBR1 3% and TGFBR2 5%) (24). Pathogenic variants may be missense, nonsense, splicing or small indels. Large deletions/duplications have also been reported in COL3A1, ELN, FBN1, MYH11, SLC2A10 and SMAD3.

MAGI uses NGS to detect nucleotide variations in coding exons and flanking introns in the above genes and MLPA to detect duplications and deletions in COL3A1, ELN, FBN1, MYH11, SLC2A10 and SMAD3.

Worldwide, 46 accredited medical genetic laboratories in the EU and 39 in the US, listed in the Orphanet (17) and GTR (18) databases, respectively, offer gene tests for these aneurysm predisposition syndromes. The guidelines for clinical use of genetic testing are described in Genetics Home Reference (19).

Table 2. Genes associated with various forms of aneurysm of large vessels

Gene	OMIM gene	Disease	OMIM disease	Inheritance	Function
ACTA2	102620	AAT6	611788	AD	Smooth muscle actin involved in vascular contractility and blood pressure homeostasis
COL3A1	120180	EDSVASC	130050	AD	Expressed in extensible connective tissues as in the vascular system
ELN	130160	ADCL1	123700	AD	Stabilization of arterial structure
FBN1	134797	Marfan syndrome	154700	AD	Force-bearing structural support in elastic and nonelastic connective tissue as in blood vessels
FLNA	300017	AAT	/	XLR	Role in blood vessels and heart development
FOXE3	601094	AAT11	617349	AD	Aortic development
LOX	153455	AAT10	617168	AD	Crosslinking of collagen and elastin
MFAP5	601103	AAT9	616166	AD	Regulation of growth factors maintaining large vessel integrity
MYH11	160745	AAT4	132900	AD	Major contractile protein
MYLK	600922	AAT7	613780	AD	Facilitation of myosin interaction with actin filaments to produce contraction
PRKG1	176894	AAT8	615436	AD	Regulation of cardiovascular function and relaxation of smooth muscle tone
SKI	164780	SGS	182212	AD	Repressor of TGF-beta signaling, role in muscle differentiation
SLC2A10	606145	ATORS	208050	AD	Required for cardiovascular system development
SMAD3	603109	LDS3	613795	AD	Inhibitor of wound healing
SMAD6	602931	AAT	/	AD	Modulation of endothelial gene expression
TGFB2	190220	LDS4	614816	AD	Regulation of angiogenesis and heart development
TGFB3	190230	LDS5	615582	AD	Involved in embryogenesis and cell differentiation, role in wound healing
TGFBR1	190181	LDS1	609192	AD	Control of mesenchymal cell proliferation and differentiation, wound healing, extracellular matrix production
TGFBR2	190182	LDS2	610168	AD	Control of mesenchymal cell proliferation and differentiation, wound healing, extracellular matrix production
MAT2A	601468	AAT	/	XLR	Development of aortic arches

AAT=Familial aortic aneurysm, thoracic; EDSVASC=Ehlers-Danlos syndrome, vascular type; ADCL=autosomal dominant cutis laxa; SGS=Shprintzen-Goldberg craniosynostosis syndrome; ATORS=arterial tortuosity syndrome; LDS=Loeys-Dietz syndrome; AD=autosomal dominant; XLR=X-linked recessive.

Conclusions

We created a NGS panel to detect nucleotide variations in coding exons and flanking regions of all the genes associated with cardiac disorders. When a suspect of cardiac or aortic structural defects is present, we perform the analysis of all the genes present in this short article.

In order to have a high diagnostic yield, we developed a NGS test that reaches an analytical sensitivity (proportion of true positives) and an analytical specificity (proportion of true negatives) of ≥99% (coverage depth ≥10x).

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Received: 5 August 2019
Accepted: 5 September 2019
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