

Atrioventricular canal defect and associated genetic disorders: new insights into polydactyly syndromes

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Abstract

Atrioventricular canal defect (AVCD) is a common congenital heart defect (CHD), representing 7.4% of all cardiac malformations, considered secondary to an extracellular matrix anomaly. The AVCD is associated with extracardiac defects in about 75% of the cases. In this review we analyzed different syndromic AVCDs, in particular those associated with polydactyly disorders, which show remarkable genotype-phenotype correlations. Chromosome imbalances more frequently associated with AVCD include Down syndrome, deletion 8p23 and deletion 3p25, while mendelian disorders include Noonan syndrome and related RASopathies, several polydactyly syndromes, CHARGE and 3C (cranio-cerebello-cardiac) syndrome. The complete form of AVCD is prevalent in patients with chromosomal imbalances. Additional cardiac defects are found in patients affected by chromosomal imbalances different from Down syndrome. Left-sided obstructive lesions are prevalently found in patients with RASopathies. Patients with deletion 8p23 often display AVCD with tetralogy of Fallot or with pulmonary valve stenosis. Tetralogy of Fallot is the only additional cardiac defect found in patients with Down syndrome and AVCD. On the other hand, the association of AVCD and tetralogy of Fallot is also quite characteristic of CHARGE and 3C syndromes. Heterotaxia defects, including common atrium and anomalous pulmonary venous return, occur in patients with AVCD associated with polydactyly syndromes (Ellis-van Creveld, short rib polydactyly, oral-facial-digital, Bardet-Biedl, and Smith-Lemli-Opitz syndromes). The initial clinical evidence of anatomic similarities between AVCD and heterotaxia in polydactyly syndromes was corroborated and explained by experimental studies in transgenic mice. These investigations have suggested the involvement of the Sonic Hedgehog pathway in syndromes with postaxial polydactyly and heterotaxia, and ciliary dysfunction was detected

as pathomechanism for these disorders. Anatomic differences in AVCD in the different groups are probably due to different genetic causes.

Introduction

Atrioventricular canal defect (AVCD) is a common congenital heart defect (CHD), representing 7.4% of all cardiac defects.¹ This malformation is characterized by a spectrum of anomalies of the atrioventricular valves, atrial and ventricular septa. In the complete form a single common atrioventricular valve is found together with an atrial septal defect (ostium primum), and a confluent posterior ventricular septal defect in the inlet portion of the ventricular septum. In the partial form, two separate right and left atrioventricular valves are found with a *cleft* of the mitral valve, an atrial septal defect (ostium primum), and no ventricular septum communication. According to Clark *et al.*,² this malformation is classified in the group of defects of the extracellular matrix.

AVCD is associated with extracardiac malformations in about 75% of the cases.^{3,4} Four major groups can be distinguished, including patients with Down syndrome (45%), or other syndromes (15%), or heterotaxia (15%), or a non-syndromic AVCD (25%).⁴

In this review we analyzed the various forms of AVCD, with particular attention to polydactyly syndromes, which display remarkable genotype-phenotype correlations.

Atrioventricular canal defect and Down syndrome

Down syndrome, due to trisomy 21, is the genetic disorder more frequently associated with AVCD. Clinical manifestations include facial anomalies, mental retardation, CHD, and gastrointestinal malformations (Table 1).⁵ CHD occur in about 40-50% of these patients, and cardiac care can prevent morbidity and mortality due to congestive heart failure and pulmonary vascular disease. The anatomic patterns of AVCD and the associated cardiac malformations are quite distinct in this syndrome. The complete form of AVCD is the most frequent type of CHD associated with trisomy 21, and about 70% of all children with complete AVCD display this aneuploidy. Children with Down syndrome show a *simple* form of AVCD, which is usually complete, and rarely associated with additional cardiac anomalies (with the only notable exception of tetralogy of Fallot) (Table 2). Left-sided obstructive lesions are significantly rare in children with AVCD and Down syndrome compared to patients with AVCD without Down syndrome.^{4,6-10} Accordingly, some types of situs abnormalities such

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as l-loop of the ventricles, atresia of the atrioventricular valves and transposition of the great arteries are virtually absent in subjects with Down syndrome.⁹

It has been shown that surgical correction of AVCD in individuals with Down syndrome results in lower mortality and morbidity rates, compared to the children without trisomy 21.¹¹

The relationship between AVCD and Down syndrome is still unclear. A number of genes located in the CHD critical region on chromosome 21 have been considered pathogenetically related to AVCD, including DSCAM,¹² COL6A1,¹³ and DSCRI.¹⁴

Atrioventricular canal defect and chromosomal anomalies

Deletion 8p23

Terminal deletion of the short arm of chromosome 8 (del8p23) is the second chromosomal anomaly more frequently associated with AVCD.⁴ The number of patients with this anomaly has increased progressively in parallel with the improved ability of molecular and cytogenetic techniques to recognize small imbalances. Clinical characteristics of the syndrome include microcephaly, mental retardation, CHD, hypospadias, and facial anomalies (Table 1).¹⁵⁻¹⁹ Cardiac malformations are present in two third of the patients,¹⁸ and AVCD is found in about 40% of the cases. In general, the AVCD is complete, and often associated with pulmonary valve stenosis (Table 2).^{17,18,20-22} The *GATA4* gene, which maps to the 8p23.1 region, and is often deleted in these patients, is candidate to CHD in del8p23, being expressed in the developing heart.²²⁻²⁴ Other genes within this critical region could contribute to these defects,²⁴ since *GATA4* is not invariably deleted in subjects with CHD and del8p23.1. However,

impaired expression of *GATA4* gene secondary to a positional effect should also be considered.

Dextrocardia, abnormalities of the pulmonary and systemic vein returns, common atrium, pulmonary stenosis, single ventricle, and transposition of the great arteries are found in a number of del8p23 patients,¹⁸ suggesting that monosomy of the short arm of chromosome 8 is responsible for laterality defects in a subset of these subjects.

Deletion 3p25

Deletion 3p25 syndrome can be associated with AVCD.²⁵⁻²⁷ Clinical features of this syndrome include mental retardation, microcephaly, facial anomalies (ptosis, telecanthus and micrognathia) (Table 1). Differences in proximal breakpoints lead to clinical variability, including CHD, postaxial polydactyly, renal anomalies, gastrointestinal malformations, and cleft palate. CHD, including AVCD, is found in about one-third of del3p25 patients.²⁷ Complete AVCD has been reported in at least one individual.²⁸ A cell adhesion molecule, coded by *CRELD1* gene, has been identified as a likely candidate for AVCD, based on its map position on chromosome 3p25 and the expression pattern in the developing heart.²⁹ Analysis of the *CRELD1* gene in patients with non-syndromic partial AVCD has identified heterozygous missense mutations in about 6% of the cases, associated with heterotaxia in at least one of them.³⁰

Atrioventricular canal defect and mendelian disorders

RASopathies (Noonan syndrome and related disorders)

Noonan Syndrome (NS) and related disorders including LEOPARD, Noonan-like with loose anagen hair, Cardio-Facio-Cutaneous and Costello syndromes (the so-called RASopathies) are caused by mutations affecting several genes participating in the RAS-MAP kinase (MAPK) signaling pathway.³¹⁻³³ Clinical features include facial anomalies, CHD, growth retardation, ectodermal and skeletal defects, and variable cognitive deficits (Table 1). CHD is found in about 65-85% of the cases, depending on the mutated genes. AVCD is the third most frequent CHD in Noonan syndrome after pulmonary valve stenosis and hypertrophic cardiomyopathy,^{34,35} and can be also a feature of LEOPARD syndrome.^{36,37} AVCD in RASopathies is usually partial, and may be associated with subaortic stenosis or aortic coarctation (Table 2).^{34,38,39} Structural abnormalities causing congenital subaortic stenosis include accessory fibrous tissue and/or anomalous insertion of the mitral valve and anomalous papillary muscle of the left ventricle. Anomalies of the mitral valve leaflets and of the subvalvular mitral apparatus in patients

with NS and AVCD are similar to those found in patients with hypertrophic cardiomyopathy.^{40,41} This is not surprising, considering that myocardial disarray and cardiac hypertrophy are common features of patients with NS. An abnormal developmental mechanism of the left ventricular myocardium and of the mitral valve

should be considered in the pathogenesis of CHD in patients with NS. Cardiac jelly and extracellular matrix anomalies could account for CHDs in NS, and are likely responsible also for AVCD.^{2,42}

PTPN11 gene mutations have been detected in patients with AVCD associated with

Table 1. Clinical characteristics of genetic disorders associated with atrioventricular canal defect.

Syndrome	Genetic defect	Extracardiac features
Down syndrome	Trisomy 21	Facial anomalies Gastrointestinal malformations Mental retardation
Deletion 8p23	Deletion 8p23	Facial anomalies Microcephaly Hypospadias Mental retardation
Deletion 3p25	Deletion 3p25	Facial anomalies Microcephaly Cleft palate Postaxial polydactyly Gastrointestinal malformations Renal anomalies
Noonan syndrome	<i>PTPN11</i> and other RAS cascade gene mutations	Facial anomalies Growth retardation Skeletal defects Cryptorchidism Cognitive deficit
CHARGE syndrome	<i>CHD7</i> gene mutations	Ocular coloboma Choanal atresia Ear anomalies Deafness Urogenital anomalies Growth retardation
3C syndrome	Unknown	Facial anomalies Macrocephaly Cerebellar malformation Ocular coloboma Mental retardation
Ellis-van Creveld syndrome	<i>EVC</i> gene mutations <i>EVC2</i> gene mutations	Short-limb dwarfism Short ribs Postaxial polydactyly Median cleft lip Oral frenula
Oral-facial digital syndromes	OFD1: <i>CXORF5</i> gene mutations OFD6: <i>TMEM216</i> gene mutations	Hypertelorism Tongue hamartoma Oral frenula Cleft palate Postaxial and central polydactyly
Bardet-Biedl syndrome	<i>BBS1-BBS9</i> genes mutations	Obesity Retinitis pigmentosa Postaxial polydactyly Urogenital malformations Cognitive deficit
Smith-Lemli-Opitz syndrome	<i>DHCR7</i> gene mutations	Facial anomalies Mental retardation Microcephaly Growth retardation Feeding difficulties Cleft palate Postaxial polydactyly Hypospadias 2-3 toe syndactyly

Table 2. Cardiac characteristics of genetic syndromes associated with atrioventricular canal defect.

Syndrome	AVCD (anatomic type)	Associated CHDs Left-sided obstruction	TOF	PVS	Common atrium	APVR
Down syndrome	Complete	-	+	-	-	-
Deletion 8p23	Complete	-	+	+	+	-
Deletion 3p25	Partial/complete	-	-	-	+	-
Noonan syndrome	Partial	+	-	+	-	-
CHARGE syndrome	Complete	-	+	-	-	-
3C syndrome	Complete	-	+	-	-	-
Ellis-van Creveld syndrome	Partial	-	-	-	+	-
Oral-facial digital syndromes	Partial	-	-	-	+	-
Bardet-Biedl syndrome	Partial	-	-	-	-	-
Smith-Lemli-Opitz syndrome	Partial	-	-	-	-	+

AVCD, atrioventricular canal defect; CHD, congenital heart defect; TOF, tetralogy of Fallot; PVS, pulmonary valve stenosis; APVR, abnormal pulmonary venous return. + present, - absent

RASopathies, in particular in patients with Noonan and LEOPARD syndromes.^{35,43} Two adjacent mutations in exon 2 (L43F and T42A) have been found in patients with AVCD, in association with NS⁴³ and with apparently non-syndromic AVCD.⁴⁴

CHARGE and 3C (cranio-cerebello-cardiac) syndromes

CHD occurs in about 84% of patients with CHARGE syndrome.⁴⁵ This disorder is characterized by ocular coloboma, choanal atresia, growth and mental retardation, genital anomalies, and hearing loss (Table 1). Mutations in the *CHD7* gene are detected in the majority of these patients.^{46,47} AVCD is the second most frequent CHD in CHARGE syndrome, often in association with tetralogy of Fallot (Table 2).⁴⁸ AVCD with tetralogy of Fallot is also characteristic of 3C (cranio-cerebello-cardiac) syndrome, a genetic condition of unknown etiology displaying some overlap with CHARGE syndrome. The 3C syndrome is clinically defined by the association of cranial anomalies, cerebellar malformations (prevalently Dandy-Walker anomaly), and CHD.⁴⁹⁻⁵¹

Syndromes with polydactyly

AVCD, particularly in association with common atrium, has been reported in several syndromes with postaxial polydactyly, including Ellis-van Creveld syndrome and other short rib-polydactyly (SRP) disorders, oral-facial-digital syndromes, Bardet-Biedl syndrome, hydrolethalus syndrome, and Smith-Lemli-Opitz syndrome.⁵²⁻⁵⁴

The Ellis-van Creveld syndrome is an autosomal recessive disorder characterized by short-limb dwarfism, short ribs, postaxial polydactyly of hands and feet, ectodermal defects, and CHD (Table 1). This syndrome belongs to the group of SRP syndromes, together with Jeune syndrome and the I and IV subgroups of lethal SRP syndromes.⁵⁵ In the 90's a clinical overlap was established between SRP syn-

dromes and *oral-facial-digital* (OFD) syndromes,^{56,57} prompting the denomination of *oral-facial-skeletal syndromes*.⁵⁷ The OFD syndromes are characterized by anomalies of the oral cavity (hamartoma of the tongue and gingival frenula), hypertelorism, cleft palate, hand and/or feet polydactyly, brachydactyly and clinodactyly (Table 1). At least 12 different types of OFD syndrome have been delineated based on clinical manifestations and inheritance patterns. AVCD is the commonest CHD in OFD syndrome type II.⁵⁸ Examples of transitional phenotypes have been observed.⁵⁹⁻⁶¹ The anatomic types of CHDs occurring in these syndromes also support the clinical overlap between these conditions. Published reports corroborate the association between these syndromes and heterotaxia heart defects.⁵² In particular, the association of AVCD and common atrium found in patients with *oral-facial-skeletal* syndrome is rare in the nonsyndromic patients, while is common in the *oral-facial-skeletal syndromes*, and in heterotaxia syndrome with asplenia⁶² or polysplenia syndromes.⁶³ The heterotaxia syndrome is characterized by an abnormal arrangement of the abdominal and thoracic organs with complex CHDs, including AVCD, common atrium, anomalous systemic and pulmonary venous drainage, persistent left superior vena cava with unroofed coronary sinus, and conotruncal defects.^{62,64} Complete situs inversus has been also found in patients with transitional phenotypes or lethal SRP syndromes.⁶⁵⁻⁷⁰ Interestingly, continuity in severity in the clinical spectrum of SRP syndromes has a counterpart also in the cardiac phenotype showing transition from AVCD and common atrium in Ellis-van Creveld syndrome to complete situs inversus in Jeune and lethal SRP syndromes.

AVCD, dextrocardia without structural cardiac defects and abdominal situs inversus are also found in Bardet-Biedl syndrome (BBS).^{52,54,71,72} This autosomal recessive disorder

is characterized by obesity, retinitis pigmentosa, postaxial polydactyly, genito-urinary malformations, cognitive impairment, and CHD.⁷³ The phenotype of BBS overlaps with that of other disorders with postaxial polydactyly, including Meckel syndrome⁷⁴ and Kaufmann-McKusick syndrome.⁷⁵ BBS is a genetically heterogeneous disorder with at least 15 mutated loci and 9 cloned genes, whose proteins are involved in ciliary function regulation.⁷⁶⁻⁷⁹ The association between BBS and AVCD, which is considered a partial manifestation of heterotaxia, in a subset of these patients is of interest. In fact, while the BBS proteins do affect the ciliary function, the nodal cilium dysfunction is a known cause of left-right axis defects in vertebrates.^{80,81}

Interestingly, failure of the left-axis specification with abnormal cardiac tube retaining a midline position or reversal of the heart loop have been demonstrated also in knock-out male mouse embryos lacking the OFD type I gene (*Ofd1*).⁸² Ultrastructural analysis in these experiments showed a lack of cilia in the embryonic node, and a specific role of the *Ofd1* protein in cilium assembly through basal body dysfunction.

Ciliary anomalies have been demonstrated also in Ellis-van Creveld syndrome,^{83,84} and in some patients with severe forms of SRP syndromes.⁸⁵ Using positional cloning, two genes (*EVC* and *EVC2*) were found to be mutated in most of the patients with Ellis-van Creveld syndrome.⁸⁶ Mutations in the *WRD35* gene have been detected in patients with SRP syndrome.⁸⁵ Experimental studies investigating molecular pathways and developmental processes perturbed in Ellis-van Creveld syndrome have demonstrated that *EVC* gene is an intracellular component of the hedgehog signal transduction pathway that is required for normal transcriptional activation of the Indian hedgehog (*Ihh*) target genes.⁸³ In particular, *EVC* is a positive mediator of the *Ihh*-regulated

bone-growth that localises at the base of chondrocyte cilia.⁸³ Mouse models for the *WDR35* gene mutations resulted in congenital abnormalities usually associated with defects in the Hedgehog signaling pathway.⁸⁵

Following the observations in Smith-Lemli-Opitz (SLO) syndrome, perturbations of the different components of Sonic hedgehog (SHH) pathway have been associated with different developmental errors in patients manifesting partially overlapping features.⁵³ SLO syndrome is an autosomal recessive disorder caused by an inborn error of cholesterol metabolism. Clinical manifestations include mental retardation, microcephaly, growth retardation with feeding difficulties, facial anomalies, cataract, cleft palate, hypospadias, postaxial polydactyly, 2-3 toe syndactyly, and CHD.⁸⁷ Septal defects and AVCD are the most common CHDs in SLO syndrome, and AVCD is often associated with anomalous pulmonary venous return, the latter feature being also a cardiac manifestation of heterotaxia syndrome.⁸⁸ Deficient 7-dehydrocholesterol- Δ -7 reductase (DHCR7) activity results in reduced plasma and tissue cholesterol levels and elevated 7-dehydrocholesterol concentrations.⁸⁹ The human *DHCR7* gene has been found to be responsible for the syndrome.⁹⁰ Cholesterol has a critical role in the formation of normally active hedgehog proteins.⁹¹ Abnormal processing of the Hedgehog proteins secondary to abnormal cholesterol mechanism may have a role in the development of malformations in SLO syndrome. In particular, Sonic Hedgehog proteins are involved in left-right axis development, and the phenotype of Sonic Hedgehog (-/-) mice shows CHDs in the setting of heterotaxia and left pulmonary isomerism.⁹²⁻⁹⁴ Accordingly, the association of AVCD and anomalous pulmonary venous return as partial manifestation of heterotaxia in SLO syndrome is not surprising.

The clinical spectrum of ciliopathies linked to polydactyly and/or cardiac laterality defects has been further expanded, including hydrolethals and acrocallosal syndromes, caused by mutations in *KIF7*, a gene belonging to the Hedgehog pathway through the regulation of Gli targets,⁹⁵ and oculofaciocardiodental syndrome, resulting from mutations in *BCOR*.^{96,97}

Conclusions

AVCD displays a wide anatomic variability, likely reflecting genetic heterogeneity and association with distinct genetic disorders. Chromosome syndromes more frequently associated with AVCD include Down syndrome, deletion 8p23 and deletion 3p25, while mendelian syndromes with AVCD are Noonan syndrome and related RASopathies, syndromes

with polydactyly, CHARGE and 3C (cranio-cerebello-cardiac) syndrome. The complete form of AVCD is prevailing in patients with chromosomal imbalances. Additional cardiac defects are found in patients with syndromes different from Down syndrome. Left-sided obstructive lesions are mainly found in patients with Rasopathies. Patients with deletion 8p23 may be affected by AVCD with tetralogy of Fallot or with pulmonary valve stenosis. Tetralogy of Fallot is the only additional cardiac defect detected in patients with Down syndrome and AVCD. On the other hand, the association of AVCD and tetralogy of Fallot is also characteristic of CHARGE and 3C syndromes. CHDs in the spectrum of heterotaxia syndrome, including common atrium and anomalous pulmonary venous return, are diagnosed in patients with AVCD and polydactyly syndromes (Ellis-van Creveld, short rib polydactyly, oral-facial-digital, Bardet-Biedl, SLO syndromes). The initial clinical observation of phenotypical similarities between the anatomy of AVCD and heterotaxia in syndromes with polydactyly has been supported by experimental studies in transgenic mice, and the suggested involvement of the Sonic Hedgehog pathway in syndromes with postaxial polydactyly and heterotaxia has been confirmed by the detection of ciliary dysfunction in several disorders with polydactyly.

Anatomic differences in AVCD are probably related to distinct genetic causes. The study of peculiar cardiovascular defects associated with extracardiac anomalies occurring in the different syndromes may improve the assessment of prognostic factors and the understanding of genotype-prognostic correlates.⁸⁸

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