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Congenital heart defects: from a prenatal perspective

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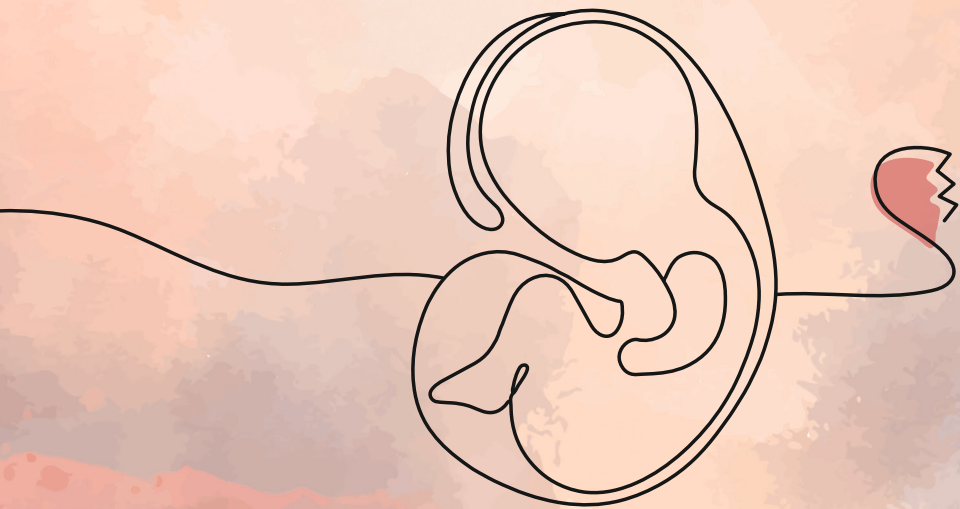
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CHAPTER 4

Response to Thibodeau and Langlois

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LETTER TO THE EDITOR

We thank Thibodeau and Langlois for their interest in our work and the valuable suggestions, which gives us the opportunity to elaborate on our data.¹ The authors particularly acknowledge the fact that genetic counselling for prenatally detected congenital heart defects (CHDs) remains a challenge, as results of genetic studies in these fetuses are highly heterogeneous. The few studies that assess the diagnostic yield of exome sequencing for fetal CHDs thereby often not separately describe their findings in isolated CHD cases nor specify the CHD subtypes included. The authors request additional information on the genetic syndromes associated with each CHD diagnosis, to differentiate between those detectable with chromosome microarray analysis (CMA) and exome sequencing. They suggest that this information would enhance the scientific contribution of our paper to daily clinical practice.²

We completely agree with the authors that this information can aid clinicians to determine when exome sequencing should be offered in a prenatal setting. We have specified the associated genetic syndromes for each CHD diagnosis with the diagnostic modality to detect these genetic variations. To show the potential yield of sequencing in a prenatally detected *isolated* CHD, these cases are separately described (Table 1).

After exclusion of aneuploidy cases, a genetic diagnosis was found in 28.7% of non-isolated and 11.6% of isolated cases with a *severe* CHD in our cohort. A severe CHD was defined as a cases that demised or required surgery before the age of 1. Two-third of these genetic diagnoses involved copy number variations (CNVs), detectable with routine CMA. CNVs appeared particularly associated with aortic valve and arch anomalies, such as interrupted aortic arch, isolated right or hypoplastic aortic arch and an aortic valve stenosis, which was mainly attributable to their association with 22q11.2 deletion syndrome. Other CHDs with a >10% incidence of (likely) pathogenic CNVs involved pulmonary atresia with a ventricular septal defect, Tetralogy of Fallot (ToF), (atrio-)ventricular septal defect and persistent left superior vena cava.

Exome sequencing was however necessary to diagnose the remaining one-third of affected cases, representing 6.3% of all prenatally detected CHD cases, and 4.3% of cases that appeared isolated in the prenatal setting. Interestingly, isolated CHD subtypes that were particularly often accompanied by sequence variants comprised the conotruncal heart defect, such as a critical pulmonary valve stenosis with intact ventricular septum, ToF, double outlet right ventricle (ToF or Taussig Bing) and complex transposition of the great arteries. Tuberosus sclerosis attributed to the high diagnostic

yield in isolated left isomerism and rhabdomyomas, whereas several pathogenic variants were found in cases with cardiomyopathy.

In our cohort we did not encounter genetic diagnoses, but variants of unknown significance (VUS), in cases with Ebstein anomaly (20.0%; 1/5), total anomalous pulmonary vein connection (9.1%, 1/11), aortopulmonary window (25.0%, 1/4), pulmonary atresia with an intact ventricular septum (18.2%, 2/11) and double inlet left ventricle (14.3%, 1/7).

Heart defects that were never accompanied by either a genetic diagnosis or VUS in this cohort were tricuspid valve dysplasia or insufficiency, mitral valve insufficiency, partial anomalous pulmonary vein connection, double aortic arch, congenitally corrected transposition of the great arteries, right isomerism and anomalous left coronary artery from the pulmonary artery.

Exome sequencing for CHD has recently become available in a prenatal setting. Prenatal counseling for fetal CHD however remains a challenge, as limited studies evaluate the diagnostic yield of this modality and full phenotyping with fetal ultrasound is not possible. With this letter we provide additional details on genetic syndromes associated with different CHD diagnoses, and specifically those not detectable with routine CMA. As sequence variants were identified in 4.3% of CHDs that appeared isolated, we believe exome sequencing should be considered in a prenatal setting, especially in those with conotruncal anomalies, left isomerism and rhabdomyomas.

On behalf of all authors,
Amber E.L. van Nesselrooij, Gijs W.E. Santen, Emmelien Aten, Monique C Haak

Table 1. Genetic diagnoses in a retrospective cohort of 708 euploid fetuses with a severe congenital heart defect (2012-2016)

Congenital heart defect	Genetic testing	All cases	Isolated	Genetic syndrome	Other genetic diagnosis
Septal defects					
AVSD, <i>balanced</i>	Microarray	17.9%	15.8%	1q21.1_DS(2)	unbalanced translocation(1;17)(p36.3;q25), unbalanced translocation(15;16)(q26.3;p13.2), unbalanced translocation(12;17)(p13.33p13.32;q12q25.3) - (3)
VSD	Sequencing	10.7%	5.3%	Charge(1/2) and Noonan syndrome(1)	-
	Microarray	10.3%	5.6%	22q11_DS(3), 16p11.2_DS(1/2), Primary microcephaly type 1 (homozygous 8p23.2p23.1 deletion)(1), 13q deletion syndrome(1)	unbalanced translocation(3;6)(p26.3;p22.3)(1), 4q trisomy(1), 2q35-36.2 deletion(1), 8q24.3 deletion(1)
	Sequencing	7.5%	2.8%	Noonan(1), Schaaf-Yang syndrome(1), Jeune(1), CM-AVN(1), Smith-Lemli-Opitz(1)	Variant COL1A1 gene(1), ZMYM2 gene(1), BCOR gene(1)
Valvular anomalies					
AoS	Microarray	12.0%	5.0%	22q11_DS(2), Williams syndrome(1)	-
	Sequencing	8.0%	5.0%	-	Variant in GATA5 gene(1), ELN gene without Williams syndrome(1)
PS	Microarray	6.7%	7.4%	22q11_DS(1)	18p deletion(1)
	Sequencing	0.0%	0.0%	-	-
MS	Microarray	0.0%	-	-	-

Table 1. (Continued)

Congenital heart defect	Genetic testing	All cases	Isolated	Genetic syndrome	Other genetic diagnosis		
	Sequencing	100.0%	1/1	-	0/0	Cornelia de Lange (1)	-
Venous return anomalies							
PLSVC ^a	Microarray	33.3%	2/6	50.0%	1/2	Beckwith-Wiedemann syndrome (1)	7q21.3-31.1 deletion (1)
	Sequencing	0.0%	0/6	0.0%	0/2	-	-
Aortic arch anomalies							
Interrupted AoA	Microarray	64.3%	9/14	66.7%	8/12	22q11_DS(8), 1q21.1_DS (1)	-
	Sequencing	7.1%	1/14	0.0%	0/12	Charge syndrome (1)	-
Right AoA ^b	Microarray	28.6%	2/7	16.7%	1/6	22q11_DS(1)	unbalanced translocation (4;6)(q31.2;q26)(1)
	Sequencing	0.0%	0/7	0.0%	0/6	-	-
Shone syndrome	Microarray	0.0%	0/6	0.0%	0/6	-	-
	Sequencing	16.7%	1/6	16.7%	1/6	-	variant NKX2-6 gene (1)
Hypoplastic AoA	Microarray	12.5%	1/8	16.7%	1/6	22q11_DS(1)	-
	Sequencing	0.0%	0/8	0.0%	0/6	-	-
CoA	Microarray	4.6%	3/65	3.5%	2/57	22q11_DS(1), 15q11-13 duplication syndrome (1)	unbalanced translocation (7;19)(p22.3;q13.4)(1)
	Sequencing	3.1%	2/65	1.8%	1/57	Kabuki syndrome (1/2)	-
Conotruncal anomalies							
PA+VSD	Microarray	33.3%	4/12	16.7%	1/6	22q11_DS (1/2)	unbalanced translocation (2;9)(p15;p22), unbalanced translocation (7;9) - (2)
	Sequencing	8.3%	1/12	0.0%	0/6	Alagille syndrome (1)	-

Table 1. (Continued)

Congenital heart defect	Genetic testing	All cases	Isolated	Genetic syndrome	Other genetic diagnosis		
CAT	Microarray	25.0%	4/16	36.4%	4/11	22q11 DS (4)	-
	Sequencing	0.0%	0/16	0.0%	0/11	-	-
APVS	Microarray	25.0%	1/4	25.0%	1/4	22q11 DS (1)	-
	Sequencing	0.0%	0/4	0.0%	0/4	-	-
ToF	Microarray	15.8%	9/57	10.6%	5/47	22q11 DS (2/5), Cri du chat syndrome (1)	Zp22 deletion (1), homozygous 15q15.3 deletion (1), 17q12 duplication (1)
	Sequencing	5.3%	3/57	6.4%	3/47	Alagille syndrome (1)	variant NKX2-5 gene (1), TBCE + MYH7 gene (1)
DORV-Fallot	Microarray	10.0%	3/30	6.3%	1/16	-	19p13.2 duplication + 19p13.12 deletion (1), mosaic trisomy 9 (1), 9p24.3q21.11 tetrasomy (1)
	Sequencing	6.7%	2/30	6.3%	1/16	Rubinstein-Taybi syndrome (1), Charge syndrome (1)	-
DORV-TGA	Microarray	4.3%	1/23	5.3%	1/19	22q11 DS (1)	-
	Sequencing	8.7%	2/23	5.3%	1/19	Charge syndrome (1)	variant ACVR1 gene (1)
TGA (complex)	Microarray	0.0%	0/20	0.0%	0/17	-	-
	Sequencing	5.0%	1/20	5.9%	1/17	-	variant CDK13 gene (1)
TGA (simple)	Microarray	2.1%	1/47	2.2%	1/46	-	16p11.2 deletion (1)
	Sequencing	2.1%	1/47	2.2%	1/46	-	Hemophilia type A (1)

Table 1. (Continued)

Congenital heart defect	Genetic testing	All cases	Isolated	Genetic syndrome	Other genetic diagnosis	
Univentricular heart defects						
AVSD, unbalanced	Microarray	22.2%	2/9	20.0%	1/5	8p23.1 microdeletion syndrome (1)
	Sequencing	11.1%	1/9	0.0%	0/5	-
HLHS	Microarray	3.8%	2/52	2.2%	1/45	6p25 microdeletion syndrome (1), Waardenburg syndrome (1)
	Sequencing	7.7%	4/52	8.9%	4/45	Kabuki syndrome (1)
HRHS	Microarray	6.7%	1/15	0.0%	0/12	-
	Sequencing	0.0%	0/15	0.0%	0/12	-
TV atresia	Microarray	4.0%	1/25	4.5%	1/22	Charcot-Marie-Tooth syndrome type 1A (1)
	Sequencing	0.0%	0/25	0.0%	0/22	-
Absent left AV-C	Microarray	100.0%	1/1	100.0%	1/1	Ring chromosome 20 syndrome (1)
	Sequencing	0.0%	0/1	0.0%	0/1	-
Atrial isomerism						
Left isomerism	Microarray	8.3%	1/12	0.0%	0/4	18p deletion syndrome (1)
	Sequencing	8.3%	1/12	25.0%	1/4	Tuberous sclerosis complex (1)

Table 1. (Continued)

Congenital heart defect	Genetic testing	All cases	Isolated	Genetic syndrome	Other genetic diagnosis
Miscellaneous					
Rhabdomyomas	Microarray	0.0%	0/3	0/1	-
	Sequencing	100.0%	3/3	1/1	Spondyloepiphyseal dysplasia congenita (1)
Cardiomyopathy	Microarray	0.0%	0/3	0/2	-
	Sequencing	66.7%	2/3	2/2	variant MYBC3 + ACTC1 gene (1), MIPEP gene (1)
DCRV	Microarray	50.0%	1/2	1/2	Phelan-McDermid syndrome (1)
	Sequencing	0.0%	0/2	0/2	-
Left-right discrepancy	Microarray	0.0%	0/6	0/1	-
	Sequencing	16.7%	1/6	0/1	Noonan (1)
Complex CHD ^c	Microarray	20.0%	1/5	0/0	unbalanced translocation (13;17)(q14.13;q25.3) (1)
	Sequencing	0.0%	0/5	0/0	-
Total	Microarray	11.1%	71/639	8.6%	42/487
	Sequencing	6.3%	40/639	4.3%	21/487

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2. Thibodeau ML, Langlois S. Correspondence on “The prevalence of genetic diagnoses in fetuses with severe congenital heart defects”. *Genet Med.* 2020([in press]).