Congenital heart defects: from a prenatal perspective

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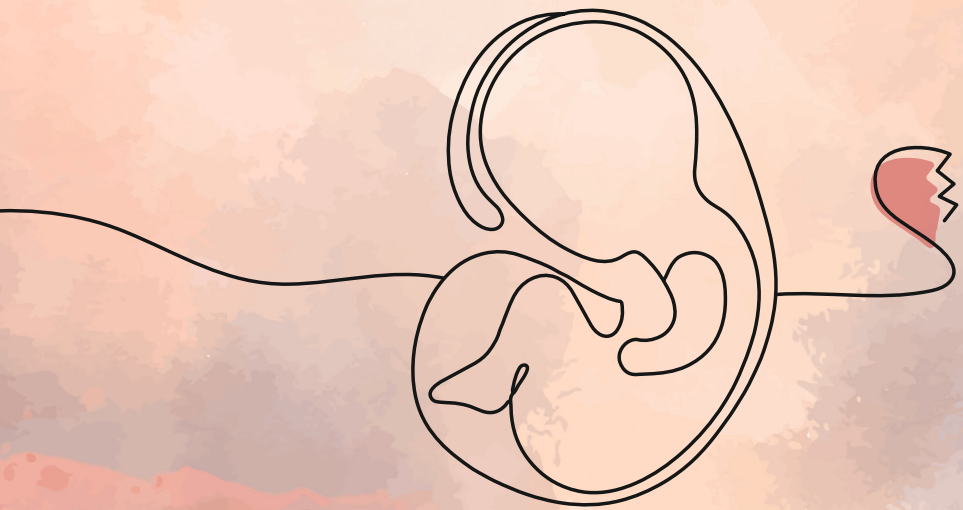

CHAPTER 4

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. Tuberous 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 eiter 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 in 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,
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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, *balanced*	***Microarray***	17.9%	5/28	*15.8%*	*3/19*	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)
	Sequencing	10.7%	3/38	*5.3%*	*1/19*	Charge (1/2) and Noonan syndrome (1)	-
VSD	***Microarray***	10.3%	11/107	*5.6%*	*4/71*	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%	8/107	*2.8%*	*2/71*	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%	3/25	*5.0%*	*1/20*	22q11 DS (2), Williams syndrome (1)	-
	Sequencing	8.0%	2/25	*5.0%*	*1/20*	-	Variant in GATA5 gene (1), ELN gene without Williams syndrome (1)
PS	***Microarray***	6.7%	2/30	*7.4%*	*2/27*	22q11 DS (1)	18p deletion (1)
	Sequencing	0.0%	0/30	*0.0%*	*0/27*	-	-
MS	***Microarray***	0.0%	0/1	-	*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)(q31.23;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;q13.41) (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)	7p22 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)	9p24.3-p11.2 tetrasomy (1)
	Sequencing	11.1%	1/9	*0.0%*	*0/5*	-	variant ZIC3 gene (1)
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)	variant NOTCH 1 gene (1), TKT gene (1), Primary ciliary dyskinesia (1)
HRHS	***Microarray***	6.7%	1/15	*0.0%*	*0/12*	-	10q21q22 deletion (1)
	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*	Ringchromosome 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	*0.0%*	*0/1*	-	-
	Sequencing	100.0%	3/3	*100.0%*	*1/1*	Tuberous sclerosis complex (1/2)	Spondyloepiphyseal dysplasia congenita (1)
Cardiomyopathy	***Microarray***	0.0%	0/3	*0.0%*	*0/2*	-	-
	Sequencing	66.7%	2/3	*100.0%*	*2/2*	-	variant MYBC3 + ACTC1 gene (1), MIPEP gene (1)
DCRV	***Microarray***	50.0%	1/2	*50.0%*	*1/2*	Phelan-McDermid syndrome (1)	-
	Sequencing	0.0%	0/2	*0.0%*	*0/2*	-	-
Left-/right discrepancy	***Microarray***	0.0%	0/6	*0.0%*	*0/1*		-
	Sequencing	16.7%	1/6	*0.0%*	*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*		

REFERENCES

1. van Nisselrooij AEL, Lugthart MA, Clur SA, et al. The prevalence of genetic diagnoses in fetuses with severe congenital heart defects. Genet Med. 2020;22(7):1206-14.
2. Thibodeau ML, Langlois S. Correspondence on "The prevalence of genetic diagnoses in fetuses with severe congenital heart defects". Genet Med. 2020([in press]).