Genetics inMedicine | CORRESPONDENCE

Response to Thibodeau and Langlois

We thank Thibodeau and Langlois for their interest in our work and the valuable suggestions, which give us the opportunity to elaborate on our data.[1] The authors particularly acknowledge the fact that genetic counseling 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 neither 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 (Supplemental Table 1).

After exclusion of aneuploidy cases, a genetic diagnosis was found in 28.7% of nonisolated and 11.6% of isolated cases with a *severe* CHD in our cohort. A severe CHD was defined as a case that died or required surgery before the age of 1. Two-thirds 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 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 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.

SUPPLEMENTARY INFORMATION

The online version of this article (https://doi.org/10.1038/s41436-020-00965-2) contains supplementary material, which is available to authorized users.

DISCLOSURE

The authors declare no conflicts of interest.

Submitted 20 August 2020; revised 2 September 2020; accepted: 2 September 2020
Published online: 27 September 2020

Amber E. L. van Nisselrooij[1], *Emmelien Aten, MD, PhD*[2], *Gijs W. E. Santen, MD, PhD*[2] *and Monique C. Haak, MD, PhD*[1]

[1]Department of Obstetrics and Fetal Medicine, Leiden University Medical Center, Leiden, Netherlands; [2]Department of Clinical Genetics, Leiden University Medical Center, Leiden, Netherlands. Correspondence: Amber E. L.van Nisselrooij (a.e.l.nisselrooij@lumc.nl)

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;22:1206–1214.
2. Thibodeau ML, Langlois S. Correspondence on "The prevalence of genetic diagnoses in fetuses with severe congenital heart defects". Genet Med. (in press).

Advance online publication 27 September 2020. doi:10.1038/s41436-020-00965-2