Genetics inMedicine | CORRESPONDENCE

Correspondence on "The prevalence of genetic diagnoses in fetuses with severe congenital heart defects" by Nisselrooij et al.

To the Editor

In their paper "The prevalence of genetic diagnoses in fetuses with severe congenital heart defects", van Nisselrooij et al. report a cohort of 919 prenatally detected severe congenital heart defects (CHDs).[1] Genetic testing was performed using quantitative fluorescent polymerase chain reaction (QF-PCR), microarray and sequencing either in a targeted fashion or exome-wide. As only 717 cases (542 prenatally, 185 postnatally) underwent genetic investigations, the study provides conservative causative diagnostic yields for QF-PCR (211/919, 23%), microarray (70/919, 8%) and sequencing (41/919, 4%). We wish to congratulate the authors for their excellent research report and contribution to the field of prenatal genetics.

Genetic counseling for prenatally detected isolated CHDs remains challenging. At this time, the published literature is highly heterogeneous in terms of patient selection, genetic testing modalities and outcome data. Most studies group CHDs under a single umbrella of "cardiac defects" and a limited number of studies report the specific CHDs subtypes. Although a large number of scientific reports are available on prenatal CHD chromosomal studies, large discrepancies in diagnostic yields for specific CHDs persist. However, based on the numerous scientific reports of chromosomal studies in prenatal CHDs, it is known that specific CHDs subtypes are associated with higher risks of genetic diagnoses (e.g., conotruncal defects, atrioventricular septal defects).[2–5]

The diagnostic yield of sequencing studies in prenatally detected isolated CHDs remains limited. The PAGE study reported a yield of 11.1% (9/11) on singleton exome in isolated CHDs, but specific CHDs subtypes were not specified.[6] In Petrovski et al., 41 cases of CHDs without extracardiac malformations underwent exome (either singleton or trio) and the diagnostic yield was 1/41 (2%) with one case of rhabdomyoma diagnosed with tuberous sclerosis syndrome.[7] Of note, some published literature suggests that specific CHD subtypes may be more associated with syndromic genes. In their postmortem study of prenatally detected left-sided cardiac lesions, Sun et al. reported a 20% (13/66) diagnostic yield from exome and most disease-causing variants were identified in well-characterized syndromic genes (e.g., 7 in *KMTD2* and 4 in *NOTCH1*).[8]

We believe that the scientific contribution of the van Nisselrooij et al. report would be greatly enhanced by providing the specific CHDs subtypes associated with genetic diagnoses (Table 1) and by separating the diagnostic yields of microarray and sequencing studies (Table 2). Such additional details would be helpful in counseling patients and could inform the clinical decision of whether or not sequencing studies should be offered in specific isolated cardiac defects.

As full phenotyping is not possible in the prenatal setting, a number of isolated CHDs cases will later be identified as syndromic. There is emerging evidence suggesting that more complex single-gene disorders often appear isolated in the prenatal setting and specific Mendelian diagnoses (Kabuki syndrome, Adams–Oliver syndrome, primary ciliary dyskinesia) are recurrent in a number of independent studies.[6–10] Additional data are needed to determine the sequencing yield of specific prenatally detected isolated CHDs.

DISCLOSURE

The authors declare no conflicts of interest.

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