Prenatal Array Comparative Genomic Hybridization in Fetuses With Structural Cardiac Anomalies

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Abstract

Objectives: To examine the diagnostic performance of array comparative genomic hybridization (CGH) for fetal cardiac anomalies in two medium-sized Canadian prenatal genetics clinics.

Methods: We prospectively recruited 22 pregnant women with fetal structural cardiac anomalies, normal rapid aneuploidy detection, and FISH for 22q11.2 testing for array CGH analysis.

Results: One case had an 8p deletion that was also visible on karyotype and included the *GATA4* gene, which has been associated with congenital heart disease. Two cases had inherited pathogenic copy number variants (CNVs) of variable expressivity and penetrance: one was a duplication of 16p11.2 and the other a deletion of 15q11.2. One case had the incidental finding of being a carrier of a recessive disease unrelated to the cardiac anomaly.

Conclusions: Of these prospectively recruited cases of fetal cardiac anomalies, 14% had a pathogenic result on array CGH. Pathogenic CNVs of variable penetrance and expressivity were a significant proportion of the positive results identified. These CNVs are generally associated with neurodevelopmental issues and may or may not have been associated with the fetus' underlying congenital heart disease. Array CGH increases the diagnostic yield in this group of patients; however, certain CNVs remain a challenge for counselling in the prenatal setting.

Résumé

Objectifs : Examiner le rendement diagnostique de l'hybridation génomique comparative (HGC) sur microréseau dans les cas d'anomalies cardiaques fœtales, au sein de deux cliniques de génétique prénatale de taille moyenne établies au Canada.

Méthodes : Nous avons procédé, aux fins de la mise en œuvre d'une analyse par HGC sur microréseau, au recrutement prospectif de 22 femmes enceintes qui présentaient des anomalies cardiaques structurelles fœtales, qui avaient obtenu des résultats normaux au dépistage rapide de l'aneuploïdie et qui avaient fait l'objet d'un test de dépistage de la délétion 22q11.2 par hybridation in situ en fluorescence.

Résultats : Un cas de délétion 8p, qui était également visible à l'établissement du caryotype, renfermait le gène *GATA4*, associé aux cardiopathies congénitales. Deux cas avaient hérité de variations pathogènes du nombre de copies (VNC) d'expressivité et de pénétrance variables : le premier consistait en une duplication 16p11.2 et le second en une délétion 15q11.2. Nous avons également constaté, par découverte fortuite, qu'un cas était porteur d'une maladie récessive non liée à une anomalie cardiaque.

Conclusions : L'HGC sur microréseau a révélé un résultat pathogénique dans 14 % de ces cas d'anomalies cardiaques fœtales recrutés de façon prospective. Des VNC pathogènes de pénétrance et d'expressivité variables constituaient toutefois une proportion significative des résultats positifs obtenus. Ces VNC sont généralement associées à des troubles neurodéveloppementaux et pourraient avoir été associées ou non à la cardiopathie congénitale sous-jacente du fœtus. L'HGC sur microréseau augmente le rendement diagnostique chez ce groupe de patientes; cependant, certaines VNC continuent de poser un défi dans le cadre du counseling génétique prénatal.

Key words: Array comparative genomic hybridization, congenital heart defects, prenatal diagnosis, genetic counselling

Competing interests: None declared.

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INTRODUCTION

Congenital heart disease (CHD), with a prevalence of 9/1000 births, is a significant cause of morbidity and

mortality in the newborn period and into later life.[1] Due to advances in medical and surgical therapies, 85% to 95% of babies with CHD survive to adulthood. Prognosis, both in terms of survival and neurodevelopmental outcome, is influenced by the severity of the cardiac defect and the underlying cause.[1] Up to 30% of children with CHD have a genetic disorder underlying their cardiac defects.[2] Such conditions include common aneuploidies, microdeletion/duplication syndromes (including 22q11.2 deletion syndrome and Williams syndrome), or single gene disorders, such as Noonan syndrome, CHARGE syndrome, or Alagille syndrome.[1] Such genetic conditions can predispose children to additional medical and developmental issues.

Even though fetal echocardiography is often able to accurately predict the severity of the heart defect, having the ability to determine the underlying cause of the cardiac defect would provide parents with the most accurate prognosis for their child, an understanding of the chance of recurrence, and, when determined prenatally, the ability to make informed decisions about the pregnancy. Traditionally, karyotype, which can detect aneuploidies, translocations, and large deletions or duplications over 5 to 10 megabases (Mb), has been the only option available to investigate underlying genetic causes when no specific single gene disorder is suspected, which often occurs in prenatal cases.

More recently, array comparative genomic hybridization (CGH) has been used to provide genome-wide assessment for smaller chromosome imbalances. In postnatal patients, the detection rate is 17% above karyotype in cases of CHD with other anomalies and approximately 4% in patients with isolated CHD.[3–5] In addition to an increased diagnostic yield, prenatal array CGH is less labour-intensive than karyotyping and has a faster turn-around time because cell culture is not typically required.

Since array CGH was introduced approximately five years ago, its use in the prenatal population has quickly become the standard of care. Initial hesitation about its use was related to the risk of identifying variants of uncertain significance (VOUS; including difficulty in their interpretation and the stress they caused for parents) and the risk of incidental findings. The yield of prenatal array CGH over karyotype has generally been lower than that seen postnatally, which may be related to difficulty in selecting the most appropriate patients for testing in the prenatal setting. Thus, there continues to be a need for more data regarding which patient populations benefit most from prenatal array.[6–19]

In cases of prenatal CHD, the results of array CGH have been variable. Detection rates have varied from 2.5% to 25% in different studies; ultimately a rate of 7% in cases of CHD was seen in a meta-analysis.[15,20–30] Whereas a previous study had suggested no significant difference between isolated and syndromic CHD, this meta-analysis showed an increased yield of almost 6% beyond karyotype in CHD with additional anomalies compared with isolated CHD.[28,31]

VOUS continues to be a challenging issue prenatally. The current rate of the discovery of VOUS in prenatal array is estimated to be 0.3% to 4.7%, with most meta-analyses suggesting this risk is approximately 2%.[7,8,14,16,24,25,32] The studies that have focused on CHD have reported VOUS rates from 0% to 25%, but many of these were smaller studies, with the recent meta-analysis showing a VOUS detection rate of 3.4% for this group of patients.[23,24,26,28] Confounding these numbers is the fact that the definition of a VOUS has changed over time, with reclassification of CNVs that were previously classified as uncertain to either pathogenic or benign as we have gained further understanding of the variants.[33] In addition, some CNVs previously believed to be either pathogenic or benign have also been reclassified, based on new understanding of their full phenotypic spectrum.

Incidental findings, which provide a diagnosis of a disease or disease risk unrelated to the indication for testing (including adult-onset conditions), raise ethical questions in the prenatal setting. Incidental findings have been reported in 1% to 2.3% of prenatal arrays.[11,14]

In the publicly funded and ethnically diverse health care system in Canada, widespread introduction of array CGH in prenatal clinics has been slow, and there has been inconsistency with adaptation throughout the country. Concerns have focused on diagnostic yield, handling of VOUS and incidental findings, and the ability for laboratories to manage testing in a time-sensitive manner.

In light of recent calls for more cardiac-specific investigation of the clinical utility of prenatal array CGH, we prospectively recruited pregnant women with fetal cardiac anomalies, either isolated or with additional ultrasound

ABBREVIATIONS

CGH	comparative genomic hybridization
CHD	congenital heart disease
CNV	copy number variant
FISH	fluorescence in situ hybridization
VOUS	variant of uncertain significance