OBSTETRICS

Dilemmas in genetic counseling for low-penetrance neuro-susceptibility loci detected on prenatal chromosomal microarray analysis

Dana Brabbing-Goldstein, MD; Adi Reches, MD; Ran Svirsky, MD; Anat Bar-Shira, PhD; Yuval Yaron, MD

BACKGROUND: Chromosomal microarray analysis is standard of care in fetuses with malformations, detecting clinically significant copy number variants in 5−7% of cases over conventional karyotyping. However, it also detects variants of uncertain significance in 1.6−4.2% of the cases, some of which are low-penetrance neuro-susceptibility loci. The interpretation of these variants in pregnancy is particularly challenging because the significance is often unclear and the clinical implications may be difficult to predict.

OBJECTIVE: The purpose of this study was to describe counseling dilemmas regarding low-penetrance neuro-susceptibility loci that are detected by prenatal chromosomal microarray analysis.

STUDY DESIGN: During the study period (January 2014 to December 2015), 700 prenatal chromosomal microarray analyses were performed. Cases were categorized as "indicated" (n=375) if there were abnormal sonographic findings or suggestive medical history and "patient choice" (n=325) in the presence of a structurally normal fetus with no other particular indication. The laboratory reported on copy number variants ≥400 Kb in size in loci known to be associated with genetic syndromes and ≥1 Mb in other areas of genome. Results were classified as gross aneuploidy, copy number variants, and normal. Copy number variants were categorized according to the American College of Medical Genetics standards and guidelines: pathogenic, variants of uncertain significance, or benign. Variants of uncertain significance were further subdivided into categories of likely pathogenic, variants of uncertain significance with no subclassification, and likely benign. Statistical analysis was performed with the use of Chi square test and Fisher's exact test to compare intergroup differences in incidence of the different result categories and demographic data.

RESULTS: Patient choice cases became more prevalent with time (35.5% in the beginning of the study, compared with 48.4% at the end of the study period). Clinically significant copy number variants were found in 14 of 375 (3.7%) of indicated cases vs only 2 of 325 (0.6%) of patient choice cases (P=.009). All "likely benign" variants consisted of low-penetrance neuro-susceptibility loci. The incidence thereof was similar between the indicated and patient choice groups (3.7% vs 3.4%; P=.85). In the indicated group, some variants of uncertain significance may have contributed to the abnormal anatomic findings. Conversely, in the patient choice group, the finding of low-penetrance neuro-susceptibility loci was often unexpected and confounding for prospective parents.

CONCLUSION: Prenatal chromosomal microarray analysis added clinically significant information in both groups. However, it also detected low-penetrance neuro-susceptibility loci in approximately 3.5% of the cases. This fact should be conveyed during pretest counseling to allow patients to make informed choices, particularly when chromosomal microarray is to be performed for patient choice.

Key words: chromosomal microarray analysis, copy number variant, genetic counseling, prenatal diagnosis, variant of uncertain significance, low-penetrance neuro-susceptibility loci

Chromosomal microarray analysis provides a powerful tool for the detection of chromosomal imbalances such as deletions or duplications with up to 1000 times the resolution of conventional karyotyping.[1] Such genomic imbalances, also known as copy number variants (CNVs), are a significant cause of congenital malformations and neurodevelopmental disorders (NDDs). Therefore, chromosomal microarray analysis is recommended as the first-tier test in the evaluation of postnatal conditions that include intellectual disability, autistic spectrum disorders (ASD), and multiple congenital anomalies.[2,3] In the prenatal setting, chromosomal microarray analysis has become the standard-of-care in the work up of fetuses with congenital malformations, with an added detection rate of 5−7% over standard karyotyping.[4,5] The American Congress of Obstetrics and Gynecology (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend performing chromosomal microarray analysis in prenatal diagnosis of fetuses with major structural abnormalities that are identified on sonographic examination.[6,7] Although the advantage of chromosomal microarray analysis in structurally abnormal fetuses is well accepted, its use in structurally normal fetuses is still a matter of some debate. In such low-risk pregnancies, the frequency of pathogenic CNVs is reported to be approximately 1%.[8] For this reason, some authorities advocate performing chromosomal microarray analysis for all invasive prenatal diagnostic testing.[1,9] The ACOG and SMFM state that, in patients with a structurally normal fetus undergoing invasive testing, either fetal karyotyping or chromosomal microarray analysis may be performed. However, it should be noted that chromosomal microarray analysis also detects variants of uncertain clinical significance (VUSs) at a rate of approximately 1.6−4.2%.[5,10,11] The interpretation thereof in the prenatal

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TABLE 1
Demographic information of the patients in *"indicated"* and *"patient choice"* groups[a]

	Indicated (%)	Patient choice (%)	*P*-value
Age (years)	33.2 ± 4.8	37.4 ± 5.1	<0.00001
Nulliparity	168 (47.7%)	103 (31.8%)	<0.0001
Twin pregnancies	25 (6.7%)	22 (6.8%)	NS
Type of pregnancy			NS
Spontaneous	296 (84.1%)	267 (82.2%)	
Fertility treatments	56 (15.9%)	58 (17.8%)	
Sample type			<0.00001
Amniocentesis	275 (73.3%)	305 (93.8%)	
CVS	43 (11.5%)	19 (5.8%)	
POC	57 (15.2%)	1 (0.4%)	
Family history of NDD	84 (23.8%)	67 (20.6%)	NS
History of chromosomal abnormalities	39 (11.1%)	19 (5.8%)	0.016

CVS, Chorionic villus sampling; *NDD*, neurodevelopmentall disorders; *NS*, not significant; *POC*, Products of conception.

[a] Demographic data was unavailable in 24 cases

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setting is particularly challenging, because most of the available phenotypic information is derived from series of affected individuals, which skews the data towards the more severe end of the spectrum.[12] Incomplete penetrance and variable expressivity make it difficult to predict the postnatal outcome, especially with regard to NDDs.[13] Genetic counseling is further complicated by the fact that CNVs that initially are classified as VUSs subsequently may be reclassified as either benign or pathogenic variants, as the scientific data accumulate over time.[11] It is for this reason that the ACOG and SMFM recommend pre- and posttest genetic counseling regarding the benefits, limitations, and potential to identify such VUSs.[6,7] The purpose of this study was to describe the prevalence and counseling dilemmas regarding VUSs that are associated with a low penetrance for NDDs in prenatal diagnosis.

Materials and Methods

Patients

Between January 1, 2014, and December 31, 2015, 700 prenatal chromosomal microarray analyses were performed on samples that were obtained by amniocentesis and chorionic villus sampling or from products of conception. Demographic data and the indication for chromosomal microarray analysis were collected from computerized medical records and patient files. The study was approved by the local institutional review board (approval no. 0039-15-TLV). Cases were categorized as "indicated" (n=375) or "patient choice" (n=325). Indicated cases included those with major malformations (n=258); increased nuchal translucency ≥3.0 mm (n=58); abnormal fetal measurements (n=23) that included oligohydramnios (amniotic fluid index < 2 standard deviations), polyhydramnios (amniotic fluid index >2 standard deviations), or fetal growth restriction (estimated fetal weight <2 standard deviations for gestational age), and cases of suggestive medical history (n=36) that included known fetal or parental chromosomal abnormalities that predispose to chromosomal aberrations such as balanced reciprocal translocations. The patient choice group included cases with no particular indication (such as ultrasound anomalies or family history). The following rationale was used for the term *patient choice*: In fetuses with structural abnormalities, chromosomal microarray analysis is considered standard of care according to professional guidelines (ie, indicated). In contrast, ACOG and SMFM state that "…in patients with a structurally normal fetus undergoing invasive testing, either fetal karyotyping or CMA may be performed…" (hence, patient choice). Thus patient choice refers not only to the question whether to have an invasive test, but also to the extent of laboratory analysis. This is particularly relevant with recent advances in molecular genetics. Patients who undergo invasive testing already have multiple choices of genetic tests that now also include chromosomal microarray analysis, specific mutation testing, multiple gene panels, and even whole exome and whole genome sequencing.

The patient choice group included 250 cases of advanced maternal age (≥35 years old), 21 cases of abnormal aneuploidy screening, 14 patients who were at risk for monogenic disorders (ie, Tay Sachs or fragile X), 5 patients suspected of intrauterine infection (cytomegalovirus or toxoplasmosis), 3 patients with a previous aneuploidy, and 32 cases of parental anxiety. Demographic information of both groups is summarized in Table 1.