3-1-2022

eP446: High rates of 'atypical' panorama noninvasive prenatal screening results among consanguineous Arab American women

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with an unbalanced Robertsonian translocation resulting in three copies of chromosome 13, demonstrating that isochromosome 13 was not detected by the SNP-based cfDNA aneuploidy screening. Follow-up parental karyotypes were normal, confirming that the translocation occurred de novo.
Case two presented to maternal fetal medicine care at 12 weeks gestational age due to an increased nuchal translucency of 5.54 mm. SNP-based cfDNA aneuploidy screening was performed at 10 weeks, and the results returned low risk (<1 in 10,000) for trisomy 21, trisomy 13, trisomy 18, and monosomy X, with a fetal fraction of 11.4%. Chorionic villus sampling was performed at 13 weeks. CVS karyotype results were abnormal: 46,XY,idic(18)(p11.3)[5]/46,XY [15]. CVS microarray was also abnormal with a 4.9Mb deletion of 18p11.32p11.31, 3.9Mb duplication of 18p11.31p11.2, and 69Mb duplication of 18p11.2q23. This result is consistent with an isodicentric chromosome 18, likely to produce a phenotype similar to trisomy 18, and was not detected by the SNP-based cfDNA aneuploidy screening. A follow-up ultrasound at 16 weeks identified a two-vessel cord, marginal cord insertion, umbilical cord cyst, omphalocele, absent nasal bone, strawberry-shaped skull, and a unilateral choroid plexus cyst. The pregnancy ended in an uncomplicated dilation and evacuation at 16 weeks gestational age. Parental follow-up testing was not pursued.
Conclusion: We present two cases of false-negative cfDNA aneuploidy screening results due to isochromosome 13 and isodicentric chromosome 18. It is critical that providers and patients understand that cfDNA testing is a screening test where false negative results are rare but possible. While SNP-based cfDNA is a highly effective cfDNA screening methodology, it has unique limitations for trisomies caused by isochromosomes and isodicentric chromosomes.

https://doi.org/10.1016/j.gim.2022.01.477

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Fatty acid oxidation disorders and acute fatty liver of pregnancy- is it always the LCHAD deficiency 1528G>C variant?

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Introduction: An association between long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency and acute fatty liver of pregnancy (AFLP) has been demonstrated in many reports. The most common variant in clinical observations is the 1528G>C. Our goal was to evaluate the different fetal/neonatal mitochondrial fatty acid oxidation (FAO) genetic variants associated with AFLP in the literature.
Methods: We conducted a search using the databases PubMed, Ovid MEDLINE, Cochrane, CINAHL Scopus and ClinicalTrials.gov from 1970-April 2021. Relevant papers evaluating the possible relationship between AFLP and FAO were identified without any time, language, or study design limitations. Our search terms were as follows: Trifunctional protein deficiency with myopathy and neuropathy or LCHAD or mitochondrial fatty acid oxidation or fatty acid oxidation or newborn infant and AFLP or liver disease in pregnancy or hepatic disease or hepatic steatosis or liver steatosis or hepatic crisis and pregnancy or maternal liver disease or labor or antepartum or postpartum. The study was registered in PROSPERO under the identification tag CRD42021247166. The reference sequence for all variants is NM_000182.5.
Results: Out of the 14 cases included in our review, 6 cases of AFLP (42.8%) were associated with homozygous 1528G>C variant in the fetus/neonate. Four cases (28.5%) were compound heterozygous with the 1528G>C variant. The 4 compound heterozygous cases associated with AFLP were as follows: 1528G>C/1132C>T (premature stop codon variant), 1528G>C/D67 ter (Asp67ter variant in the alpha subunit exon 4), 1528G>C/T +2C (exon 12 splice site transversion) and the last case was a compound heterozygous with a premature stop codon variant in exon 4 inherited from the father. One AFLP case was associated with short-chain acyl-CoA dehydrogenase (SCAD) deficiency and another one with long-chain 3-ketoacyl CoA thiolase (LCKT) enzyme. Two cases did not have any genetic testing but were suspected to have a FAO disorder based on acylcarnitine species and enzyme analysis.
Conclusion: Not all cases of AFLP reported in the literature are secondary to LCHAD deficiency or the 1528G>C variant. Other pathways such as SCAD and LCKT may be involved. Further research is needed to evaluate the genetic etiologies of AFLP associated with FAO disorder.

https://doi.org/10.1016/j.gim.2022.01.478

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High rates of 'atypical' panorama noninvasive prenatal screening results among consanguineous Arab American women

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Introduction: Panorama is one of the most accurate and commonly used methods of cell free DNA noninvasive prenatal screening (NIPS). The results are reported as either high risk for a specific aneuploidy, high risk due to fetal fraction, insufficient fetal DNA, atypical, high risk, or no results. It is the only form of NIPS that uses a single nucleotide polymorphism (SNP) method, representing genetic changes that are present in over 1% of the general population, to screen for common fetal aneuploidies and microdeletion syndromes. We hypothesize that the SNP method could be leading to the increase in atypical results among women in consanguineous relationships, common amongst Arab Americans, where there is high homogeneity of genetic material. The aim of this study is to explore factors influencing atypical Panorama NIPS results and its association with abnormal fetal outcomes amongst Arab American women.
Methods: A retrospective cohort study was performed by looking at Panorama NIPS performed between September 2018 and January 2021 at a large urban health system in Detroit, Michigan. The records were obtained from Natera, Inc, the clinical genetic testing company for Panorama. Singleton gestations who underwent Panorama screening and had 'atypical' results were included. The outcome of interest was fetal anomalies or abnormal genetic outcomes.
Results: A total of 5,886 women underwent Panorama NIPS within the defined time frame and 772 (13.1%) were identified as Arab Americans. Forty-nine (0.79%) women had atypical results, of which 43 were singleton gestations. The mean age was 29.6 ± 5.3 years old. Nineteen women (44.2%) were White, 14 (32.6%) were Arab and 8 (18.6%) were Black. The percentage of Arab American women with atypical results (32.6%) was significantly higher than the overall percentage of Arab American women who ever underwent Panorama testing (13.0%) (p=0.00018). Eight women were in a known consanguineous relationship, all of whom identified as Arab Americans, hence making 57.1% of Arab women with atypical results. The outcomes for all 43 pregnancies showed

normal fetal anatomy and no genetic abnormalities. In those who underwent further testing with amniocentesis (14.0%) or MaterniT21 (14.0%), the results were all normal.

Conclusion: We identified a high percentage of Arab American women with atypical results compared to the baseline Arab American women ratio in the population screened. More importantly, we identified a high rate of consanguinity amongst Arab women with atypical results and subsequent normal fetal anatomy suggesting the possible influence of consanguinity on falsely elevated atypical results due to the SNP method used with Panorama testing. Such knowledge might suggest that, for Arab American women, particularly consanguineous couples, Panorama testing may not be the most ideal method for NIPS. This could help reduce unnecessary invasive testing and Maternal Fetal Medicine and genetics consultations.

https://doi.org/10.1016/j.gim.2022.01.479

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Family history helps solve the case: Prenatal case report of Lowe syndrome

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Background: Oculocerebrorenal syndrome (Lowe Syndrome), is a rare X-linked disorder affecting 1/500,000 males, that most frequently affects the eyes, central nervous system, and kidneys. Phenotypic presentation includes congenital cataracts, developmental delay, intellectual disability, and Fanconi-type renal dysfunction. Lowe Syndrome is caused by a variant in the *OCRL* gene. *OCRL* loss of function variants result in decreased enzyme levels and an accumulation of the enzyme's substrate, phosphatidylinositol (4,5) biphosphate (PiP2), and cytoskeletal defects. While individuals may live into the 3rd and 4th decade of life, some will die in the first few years from either renal failure or infection. We report a case of a family with an extensive history of congenital cataracts, immune compromise, and neonatal death in male members with an ultimate diagnosis of Lowe Syndrome.

Case presentation: The patient was referred at 31 weeks 1 day gestation with a prenatal diagnosis of cerebral ventriculomegaly. The patient is a 29-year-old G2P1 who conceived spontaneously and denied all exposures during the pregnancy. A three-generation pedigree was obtained. The family was from Uzbekistan and consanguinity was denied. The patient reported that 4 of her 5 brothers died at very young ages. Two of her brothers died within the first few days of life, another brother died at 22 days of life, and the last brother died at 3 years of life following recovering from a surgery to remove his congenital cataracts. All 4 brothers were said to have immune deficiency, which was reported to be their cause of death. Based on this pedigree, the family history was concerning for X-linked severe combined immunodeficiency syndrome (SCIDS), however, the congenital cataract diagnosis presented as a confounder, as it is not a typical finding in SCIDS. The patient further reported that her mother had two sisters, one of which had a son born with congenital cataracts and was of severely short stature. This additional family history suggested that there might be an additional X-linked disorder causing cataracts and growth deficiency in the family.

High-resolution ultrasound, fetal MRI, and fetal echocardiography were performed. No major structural defects of the heart were visualized. Ultrasound demonstrated a male fetus with mild lateral cerebral ventriculomegaly, segmentation anomalies of the lower thoracic and lumbar spine, foreshortened long bones, small umbilical cord cysts, and a left cataract. Neuro MRI reported possible germinolytic cysts bilaterally, with a normal corpus callosum and gyral patterns appropriate for gestational age.

Given the presence of the congenital cataract, the patient was counseled on the possibility that this fetus was affected with the same condition as her brothers and her maternal first cousin. The patient opted to interrupt the pregnancy by KCl injection followed by induction of labor. A virtual autopsy was completed, including CT and MRI examinations. Sagittal clefts of the thoracic and lumbar vertebrae were seen as was the left eye cataract of 0.3cm in size. Exome sequencing (ES) was completed postmortem and reported a maternally inherited variant in *OCRL*, causative of Lowe Syndrome. There are reports in the literature describing affected males with mild ventriculomegaly. As some individuals with Lowe Syndrome die within the first years of life due to susceptibility to infections and immunocompromise, it is possible that the brothers who died at young ages and did not have known cataracts, also had Lowe Syndrome.

Conclusion: This case highlights the critical importance of ascertaining a full and detailed family history with a multigeneration pedigree when evaluating fetuses with congenital anomalies. Now that this condition has been identified for this family, other members can be tested, including the patient's maternal aunts and cousins. It also allows the family to pursue ART with preimplantation genetic diagnosis for future pregnancies. This case may also represent an expansion of the phenotypic spectrum of this disease as Lowe syndrome has not been previously reported to present with clefting of the vertebrae of the lumbar or thoracic spine.

https://doi.org/10.1016/j.gim.2022.01.480

eP448

Multiple pregnancies with fetal akinesia deformation sequence caused by variants in *MUSK*

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Background: Fetal akinesia deformation sequence (FADS), also known as Pena-Shokier Syndrome, is a clinical manifestation of arthrogryposis, abnormal facial features, and pulmonary hypoplasia, and demonstrates a high degree of genetic heterogeneity. Variants within the genes that are involved in the neuromuscular system are most frequently involved. One gene in particular, *MUSK,* is involved in the formation and maintenance of the neuromuscular junction. Biallelic loss of function variants in this gene have been documented by 5 affected fetuses in a Swedish family and an affected fetus in a Dutch family. We report a patient who had multiple pregnancies affected with a FADS phenotype who was found to have variants in the *MUSK* gene, causative of the ultrasound findings.

Case presentation: The patient was evaluated at 20 weeks 4 days gestation for suspected fetal arthrogryposis. She reported a previous pregnancy that was similarly affected with arthrogryposis, rocker bottom feet, non-immune hydrops fetalis (NIHF), and polyhydramnios that ended in intrauterine fetal demise at