The Genetics Corner: A Genetics Evaluation for Chronic Diarrhea that Revealed Incest

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Case History:

A Genetics consult was requested on a 12-week old Hispanic male infant with chronic osmotic diarrhea. This pregnancy was complicated by young maternal age, intra-uterine growth retardation, pruritic urticarial papules and plaques of pregnancy, maternal hyperthyroidism, iron deficiency anemia, and transaminitis. Mother was late to receive prenatal care and followed up inconsistently during pregnancy with her health care provider. The infant was delivered at 36w 6d by induced vaginal delivery for IUGR to a 17-year-old primigravida mother. Birth weight was 2035g (0.08 %ile), birth length was 46.5 cm (3rd percentile), and birth head circumference was 31 cm (0.32 %ile). There were no other postnatal complications, and the baby was discharged home with his mother.

"He was hospitalized with cachexia, severe hypernatremia and hyperchloremia with metabolic acidosis, likely due to malabsorption."

The infant reportedly breastfed well at home but did not gain weight. He had normal green stools for the first three weeks of life, after which he presented with chronic recurrent diarrhea. He was hospitalized with cachexia, severe hypernatremia and hyperchloremia with metabolic acidosis, likely due to malabsorption.

The family history was non-contributory for chronic diarrhea in infants, young infant deaths or other significant medical problems. Mother declined to provide any information about the infant's father.

The chromosome microarray analysis detected many large regions of the absence of heterozygosity (AOH). These regions of homozygosity (ROH), that were 3 megabases or larger, encompassed 735 megabases in total, or at least 26% of the genome.

Consultant's Report:

The baby was not dysmorphic, but underweight, alert and responsive to the examiner. The tone was normal. Although the chromosome microarray results were not diagnostic of a specific genetic disorder, the extent of ROH implied that the pregnancy resulted from incest. It also increased the possibility of an autosomal recessive disorder due to homozygosity for a pathogenic variant in a gene or genes that were identical by descent.

Within the ROH, there were 28 genes associated with diarrhea (http://firefly.ccs.miami.edu/cgi-bin/ROH/ROH_analysis_tool.cgi). Pathogenic variants in three of them, EPCAM, NEUROG3 and SLC5A1 were associated primarily with congenital/ neonatal onset chronic diarrhea. Molecular genetic testing by sequencing and del/dup analysis was recommended using a gene panel in which these three genes were also included.

The genetic testing detected homozygosity for a likely pathogenic variant in NEUROG3, c. 319C>A (p.Arg107Ser). Pathogenic variants in NEUROG3 cause congenital malabsorptive diarrhea 4, inherited in an autosomal recessive manner.

The social situation required a social services consultation and the mother, a minor, was placed in the care of Child Protection Services. Her father was arrested.

Chromosome microarray analysis (CMA) can detect copy number variants (CNVs), which are losses or gains of chromosome material that are submicroscopic and undetectable on routine chromosome analysis. CMA analysis that utilizes a single nucleotide polymorphism (SNP) platform can also detect "regions of homozygosity" (ROH) across the genome when SNPs are continuously homozygous with no intervening heterozygosity. These ROH may be due to:

- Uniparental disomy (UPD), which is the inheritance of a chromosome or a portion of a chromosome pair from the same parent
- Parental consanguinity
- Regions inherited from a recent common ancestor that are identical by descent

Identifying ROH can provide the clinical diagnosis, in the case of UPD for a chromosome where the clinical features are consistent with the UPD. ROH can also indicate an increased risk for autosomal recessive disorders due to homozygosity for pathogenic variants in genes within the ROH.

An unintended consequence of CMA analysis on an SNP platform is identifying parental relationships that are unreported, including incest. Theoretically, the fraction of the genome or autosome that is homozygous (Froh), can be calculated for a given parental relationship in a presumed outbred population:

The degree of parental relationship	Theoretical Froh
First degree Parent/ child, full siblings	25%
Second degree Half siblings, uncle/niece	12.5%
Third degree First cousins	6.25%
Fourth degree First cousins once-removed	3.125%
Fifth-degree Second cousins	1.5625%

Adapted from Sund KL, Rehder CW, 2014

Laboratories that detect and report ROH are encouraged to include the percent homozygosity, but not the degree of relationship. It falls to the clinician to interpret and return these results to patients. The laboratory reported homozygosity for 26% of the

genome in this infant, which indicated that the parents are first degree relatives.

Sexual relations between close relatives are illegal in most jurisdictions. The specific laws may vary in how "relatedness" is defined. Practitioners have a duty to report suspected child abuse, although they may not be responsible for reporting incest involving consenting adults, even if this is illegal in their jurisdiction.

Practical Applications:

- Almost all CMA platforms are SNP-based. While the main purpose of the clinical testing is to evaluate for copy number gains and losses , CMA can identify parental consanguinity, including incest.
- The laws regarding duty to report incest/ abuse/ statutory rape vary by state. Knowledge of the legal requirements and compliance is essential when incest is inadvertently identified on clinical testing.
- Young maternal age and homozygosity for the same abnormal allele by themselves should raise concern for incest even without a microarray.

References:

1. *Sund KL, Rehder CW. Detection and reporting of homozygosity associated with consanguinity in the clinical laboratory. Hum Hered 2014: 77: 217-224*
2. *Botkin JR et al., Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. Am J Hum Genet. 2015 Jul 2; 97(1): 6–21*

The authors have no relevant disclosures.

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