Diagnostic Exome Sequencing Identifies a Homozygous Whole-Gene Deletion of **DPY19L2** that Was Not Detected by a High-Density Single Nucleotide Polymorphism (SNP) Array

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**BACKGROUND**

- While both exome sequencing and high-density single nucleotide polymorphism (SNP) arrays are capable of detecting copy number variants (CNVs), neither methodology is comprehensive and each can miss certain regions of the genome.
- In a clinical setting, SNP array testing usually precedes exome sequencing primarily due to its lower cost and ability to reliably detect large CNVs that are at least 100 kilobases (kb) in length.
- It is therefore important for SNP arrays to be able to detect, at the very least, known clinically relevant CNVs that meet the length cutoff so as to minimize additional unnecessary investigations towards a genetic diagnosis.

**CASE REPORT**

- We present a case example of a 38 years old male with globozoospermia, a spermatogenic defect that can cause male infertility due to acrosome-less sperm, who pursued diagnostic exome sequencing at our clinical genetic testing laboratory.
- The proband had no other presentations nor a family history of infertility, and was sent for exome sequencing as a proband-only case.
- The proband has a 7 month old daughter born via in-vitro fertilization (IVF) using his sperm.
- Prior to exome sequencing the proband had a negative result from the Affymetrix Cytoscan®HD Array from LabCorp, an array that contains 743,000 SNPs and 1,953,000 non-polymorphic copy number probes.
- The ordering clinician suspected several genes implicated in spermatogonial defects including **DPY19L2**, **SPATA16**, **AURKC**, **CATSPER1**, **KDH1L10**, **HR5A1**, **SEPT12**, **SYCP3**, **USP9Y**.

**RESULTS**

- **Polymerase chain reaction (PCR)** of select exons of **DPY19L2** as well as the nearby **TMEM5** gene in the proband and an unrelated control individual confirmed that the proband had a homozygous deletion of **DPY19L2** (Figure 2).

**INTERPRETATION**

- **Homozygous whole gene deletions of **DPY19L2** are common in men with globozoospermia** (Elmadf et al., 2012).
- These deletions are due to 28kb low-copy repeats (LCR1 and LCR2) with ~97% sequence identity on either side of **DPY19L2** that can cause non-allelic homologous recombination resulting in a deletion of approximately 200kb (Figure 3).
- Our proband’s deletion was missed by the Affymetrix CytoScan®HD Array due to poor probe coverage between LCR1 and LCR2. This region contains only 3 intragenic SNPs in **DPY19L2** i.e. 1 marker/36,666 base-pairs and a total of 27 probes in the region between and including LCR1 and LCR2 i.e. 1 marker/7,407 base-pairs (Figure 3). This is in contrast with the average coverage of OMIM genes on this array which is 1 marker/723 base-pairs.

**METHODS**

- Diagnostic whole exome sequencing was performed on the proband as previously described (Farwell KD. et al. 2014) with the exception of the capture reagent which was the IxGene Exome Research Panel V1.0. Approximately 97% of the proband’s exome was covered at 20x or higher.
- Population frequency cutoffs for variant filtering included 0.1% for dominant, 1% for recessive, and 0.2% for incomplete penetrance models. The latter model included variants that are found in the Human Gene Mutation Database (HGMD), those that cause truncations such as frameshift, nonsense, and canonical splice, and those found in known imprinted disorder-causing genes. Population databases used were 1000 Genomes Project, Exome Sequencing Project (ESP), and Exome and Genome Aggregation Consortia (ExAc and gnomAD, respectively).

**REFERENCES**


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