Prenatal Genetic Counseling for a Novel Genetic Etiology Identified in a Fetus with Compound Heterozygous Alterations in MYH6

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BACKGROUND

- Fetal and neonatal Diagnostic Exome Sequencing (DES) is being used more frequently in cases of infant demise, with or without congenital anomalies.
- Several studies have shown the clinical utility of DES for prenatal and neonatal patients due to increasing ease of DES and knowledge of the human genome (1-3).
- The increasing use of prenatal DES results in unique counseling challenges when diagnoses are made prior to the onset of certain symptoms, especially when novel genetic findings are identified.

RESULTS

- Amniocentesis revealed a normal male karyotype (46, XY).
- DES revealed compound heterozygous alterations in MYH6 c.2162G>A (p.R721Q) and c.2462_2469delGGCCCTTC (p.R821Hfs*65), secondary findings analysis was not performed for the proband.
- Co-segregation analysis revealed that the alterations were inherited from asymptomatic heterozygous parents.

MYH6 (OMIM 160710) GENE INFORMATION

- Encodes the cardiac alpha myosin heavy chain (a-MHC), a subunit of cardiac muscle myosin protein, a major component of the sarcomeres, essential for generation of the mechanical force required for muscle contraction, myofibrillar assembly and proper heart development (reviewed in England, 2013).
- a-MHC forms homodimers or heterodimers with beta myosin heavy chain (b-MHC) encoded by the MYH7 gene (OMIM: 160760).
- In vivo animal models:
  - Homozygous Myh6 knock-out mice displayed in utero lethality between day 11 and day 12, possibly due to observed gross heart defects (6).
  - Myh6+/- mice show cardiac myofibrillar disarray, cardiac dysfunction and fibrosis.
  - Zebrafish deficient in myh6 (atrial myosin heavy chain; amhc) have revealed disruption of atrial myofibrillar organization and weak atrial contractility which indirectly causes ventricular wall thickening and narrowing of the ventricular lumen and influences atrioventricular valve formation (7).
- Heterozygous alterations in MYH6 have been associated with:
  - autosomal dominant hypertrophic cardiomyopathy (HCM; OMIM: 613251),
  - dilated cardiomyopathy (DCM; OMIM: 613252), and
  - atrial septal defects (ASDs; OMIM: 614089).
- Biallelic alterations in MYH6 n reported in just three affected individuals with complex heart defects (8), (9).

MYH6 c.2161C>T (p.R721W) ALTERATION

- Review of the literature revealed that the p.R721Q variant affects a highly conserved arginine that had previously been reported to be altered in a tryptophan (p.R721W) in a patient with sick sinus syndrome. Ventricular cardiomyocytes expressing this MYH6 p.R721W variant have been shown to have disrupted patterns of myofibrils and disintegrated sarcomeric structure in rats. In addition, a p.R721W MYH7 alteration, homologous to p.R721W of MYH6, has been shown to cause malignant hypertrophic cardiomyopathy, frequently associated with conduction abnormalities.
- a-MHC consists of a head, neck, and tail domains (10). Coiled coils are formed by tail domains of two a-MHC molecules to stabilize the interaction of the head domains with actin for generation of mechanical force required for muscle contraction. The p.R721 amino acid is located in the actin-binding convertor domain of a-MHC.

REFERENCES