Genetic testing of the DHH Gene in 46,XY Disorder of Sex Development

Disorder also known as: 46,XY DSD; 46,XY gonadal dysgenesis; 46,XY gonadal dysgenesis with minifascicular neuropathy

Clinical Features:
Variants in the DHH gene result in a 46,XY disorder of sex development (DSD) with or without polyneuropathy. Several individuals with DHH variants have presented with isolated 46,XY complete gonadal dysgenesis characterized by female external genitalia, bilateral streak gonads, and the presence of Mullerian structures, including bilateral Fallopian tubes and an immature uterus.\(^1,2\) Variants in DHH have also been reported in an individual with 46,XY partial gonadal dysgenesis, resulting in external female genitalia with a blind-ending vagina, one testis and one streak gonad, and an immature uterus. In addition, this individual also exhibited polyneuropathy with extensive minifascicle formation on sural nerve biopsy.\(^3\) Additionally, two siblings with DHH variants are reported with gonadal dysgenesis, seminoma, and polyneuropathy.\(^4\) Parents of individuals with DHH-related 46,XY DSD who are obligate carriers of a single heterozygous mutation have not been reported to exhibit any evidence of gonadal dysgenesis or polyneuropathy.\(^3,1\)

Inheritance Pattern/Genetics:
Autosomal recessive.

Test Methods:
Analysis is performed by bi-directional sequencing of the three coding exons (exons 1-3) and the exon/intron splice junctions of the DHH gene. If sequencing identifies a variant on only one allele of DHH, targeted array CGH analysis with exon-level resolution (ExonArrayDx) will be performed to evaluate for a deletion or duplication of one or more exons of this gene. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:
46,XY disorders of sex development are genetically heterogeneous, and the sensitivity of DHH testing is currently not well established. A previous study identified homozygous DHH variants in 3 of 6 patients of Mexican-Mestizo ancestry with 46,XY complete gonadal dysgenesis.\(^1\) Additionally, one out of four patients with 46,XY complete gonadal dysgenesis and peripheral neuropathy was found to harbor DHH variants.\(^3,5\) However, no variants in DHH were reported in a cohort including 96 individuals with 46,XY complete gonadal dysgenesis and 48 individuals with 46,XY partial gonadal dysgenesis, suggesting that variants in DHH are overall
a rare cause of disorders of sex development. Of note, two individuals with 45,X/46,XY mixed gonadal dysgenesis were found to carry a single mutation (c.1086delG) in the DHH gene, and the authors suggested that heterozygous variants in DHH may contribute to the severity of gonadal dysgenesis in individuals with due to a 45,X/46,XY karyotype; however, additional studies are necessary to confirm this association.

References: