Van der Woude Syndrome Panel

Panel Gene List: GRHL3, IRF6

Clinical Features:
Van der Woude syndrome (VWS) is characterized by cleft lip and/or cleft palate and fistulae of the lower lip (lip pits). Cleft palate may be overt or submucosal. Lip pits are typically bilateral and paramedian and can include mounds with a sinus tract leading from a mucous gland of the lip. The disorder is variable, and affected family members often show diverse phenotypic expression. Penetrance is high, although incomplete, with estimates indicating that 92% of individuals with a pathogenic variant will have one or more clinical features. Hypodontia may be present, and individuals may be missing deciduous or permanent teeth, most often affecting second incisors and second molars.

VWS may be caused by pathogenic variants in the IRF6 gene or the GRHL3 gene. The spectrum of IRF6-related disorders also includes popliteal pterygium syndrome (PPS). As with VWS, cleft lip, cleft palate and lip pits are features of PPS. In addition to the orofacial features, individuals with PPS may have popliteal pterygia, abnormal external genitalia, ankyloblepharon, pyramidal skin on the hallux, and intraoral adhesions ranging from minor adhesions to complete syngnathia. Syndactyly and bony deformities also may be present.

VWS is the most common single-gene cause of cleft lip and palate, accounting for about 2% of cases. The prevalence of VWS is estimated to be between 1 in 35,000 to 1 in 100,000 individuals in European and Asian populations.

Genetics:
VWS is inherited in an autosomal dominant manner, due to pathogenic variants in either IRF6 or GRHL3. The majority of individuals with VWS have an affected parent, although de novo cases have been reported.

Truncating variants and gross deletions in IRF6 typically result in VWS, and missense variants in the DNA-binding domain are more commonly associated with PPS; however, some missense variants are found only in individuals with VWS. Variable expressivity has been reported within families, where some individuals have features of VWS only, and others have the additional features of PPS.

Pathogenic variants in GRHL3, including frameshift, missense, and splice site variants, have been identified in 17% of individuals with VWS for whom an IRF6 variant was not identified. Individuals with VWS due to a GRHL3 variant may be more likely to have cleft palate and less likely to have cleft lip than individuals with a pathogenic variant in IRF6. Heterozygous variants in GRHL3 have also been identified in multiple families with nonsyndromic cleft palate.
Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

Clinical Sensitivity:
Sequence analysis of IRF6 detects pathogenic variants in approximately 72% of individuals with VWS, and 97% of individuals with PPS.1 Sequence analysis of GRHL3 is expected to detect pathogenic variants in 5% of individuals with VWS.4 Whole and partial gene deletions of IRF6 have been reported in a few families with Van der Woude syndrome.2 Our method is expected to detect the vast majority of existing small intragenic variants as well as large deletions and duplications of one or more exons.

References: