KAL1 and FGFR1 Gene Analysis in Kallmann Syndrome

Clinical Features:
Kallmann syndrome (KS) is typically characterized by hypogonadotropic hypogonadism and anosmia. The presence of a defective sense of smell, whether partial (hyposmia) or complete (anosmia) distinguishes KS from normosmic idiopathic hypogonadotropic hypogonadism with a normal sense of smell (nIHH), which can be associated with variants in the GnRHR and GPR54 genes. Due to hypothalamic GnRH deficiency, males with KS demonstrate cryptorchidism, testicular atrophy and microphallus at birth and then subsequent failure to undergo a normal puberty during adolescence. Females with KS usually present with primary amenorrhea or infertility. Variants in at least two genes have been shown to be associated with KS. Variant in the X-linked KAL1 gene is associated with the classic genital and olfactory features of Kallmann syndrome, and in some cases, renal agenesis in males only. This is known as Type 1 Kallmann syndrome (KAL1). Type 2 Kallmann syndrome (KAL2) is caused by variant in the autosomal FGFR1 gene, a gene also responsible for several skeletal disorders including cleft lip and palate. Although premature skeletal fusion syndromes, i.e. craniosynostoses, have not been observed in patients with Kallmann syndrome, orofacial clefting and hypodontia can be seen in KAL2 patients. Both types show clinical variability and reduced penetrance, although this is much more significant in FGFR1-associated KS. Type 1 KS is the result of abnormal anosmin-1 protein production due to KAL1 gene variant. Loss-of-function, or inactivating, variant in the FGFR1 gene causes Type 2 KS, as opposed to gain-of-function, or activating variants which are associated with craniosynostosis. Overall, about 25% of Kallmann syndrome cases are due to variant in KAL1 (5-10%) or FGFR1 (8-16%).

Genetics:
Most cases (2/3) of KS are sporadic. Type 1 KS, due to variants in the KAL1 gene, is an X-linked recessive condition. Type 2 KS, due to variants in the FGFR1 gene, is an autosomal dominant condition. Autosomal recessive inheritance has also been reported.

Test Methods:
Sequencing of the KAL1 and FGFR1 genes is offered as separate tests. Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice junctions of the KAL1 gene (exons 1-14) and FGFR1 gene (exons 1-18) is analyzed. As gross deletions have been reported in the KAL1 and FGFR1 genes, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available for both genes to evaluate for a deletion or duplication of one or more exons. In males, deletions of one or more exons of the KAL1 gene would be detectable by sequencing analysis. Variants 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.
Rarely, deletions in the terminal region of chromosome of Xp22.3 may cause a contiguous gene syndrome, possibly including short stature, chondrodysplasia punctata, mental retardation, steroid sulfatase deficiency, and Kallmann syndrome. If indicated, either FISH analysis for KAL1 or FISHonChipDx testing on a microarray targeted to 65 microdeletion and microduplication syndromes, including KS is available.

**Test Sensitivity:**
There is genetic heterogeneity in Kallmann syndrome. Approximately 25% of Kallmann syndrome cases are due to variant in KAL1 (5-10%) or FGFR1 (8-16%). Sequence analysis as performed by GeneDx is expected to identify > 95% of variants in the KAL1 and FGFR1 genes. Deletions of the KAL1 gene alone or as part of a contiguous gene deletion syndrome are rare as are deletions of the FGFR1 gene. However, such deletions would be identifiable by the deletion/duplication analysis offered at GeneDx.

**Variant Spectrum:**
A variety of missense, nonsense, splicing, small and gross deletions, small insertions, complex rearrangements and frameshift variants have been reported in the KAL1 gene. Observed variants in the FGFR1 gene include missense, nonsense, splicing, small deletions/ insertions, and a gross deletion.

**References:**
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