Skeletal Dysplasias: FGFR-Related
Sequence Analysis of 2 Genes

Panel Gene List:
FGFR2 and FGFR3.

Clinical Features:
FGFR3-related skeletal dysplasias refer to four distinct disorders caused by variants in the *FGFR3* gene. The most common of these is achondroplasia (ACH), which is nonlethal and the most common condition associated with disproportionate short stature or dwarfism.[3,5] Prenatally, this disorder often presents in the third trimester and is associated with rhizomelic micromelia, macrocephaly with frontal bossing and midface hypoplasia. Mild limb bowing, brachydactyly, increased space between the third and fourth digits, and a depressed nasal bridge are also common.[1,3,4,5] ACH is estimated to occur in 1 in 10,000 to 1 in 40,000 births with more than 250,000 affected individuals worldwide.[3,5] Hypochondroplasia (HCH) has a similar, but milder, phenotype to that of ACH and presents with micromelia, short stature and lumbar lordosis.[3,5] The prevalence of HCH is estimated to be 1 in 50,000 births, and together ACH and HCD are estimated to account for 20% of all cases of skeletal dysplasia in live births.[3] Thanatophoric dysplasia (TD) is the most common lethal skeletal dysplasia has an incidence estimated to be between 1 in 17,000 and 1 in 50,000 births.[1,3] This disorder is characterized by disproportionate dwarfism with very short extremities, normal trunk length, very narrow thorax, macrocephaly, depressed nasal bridge, prominent forehead with protruding eyes, brachydactyly, platyspondyly, and normal bone mineralization without fractures.[1,2,3,4] Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) is a very severe form of achondroplasia caused by a rare variant in the *FGFR3* gene.[1,5]

Bent bone dysplasia syndrome results in pathogenic variants in FGFR2. This rare, typically perinatal lethal, skeletal dysplasia presents with poor mineralization of the calvarium, bent long bones (typically the femora), craniosynostosis, prenatal teeth, hypoplastic pubis and clavicles, osteopenia, and facial dysmorphism including low-set ears, hypertelorism, midface hypoplasia, and micrognathia.[6,7]

Inheritance Pattern/Genetics:
All FGFR-related skeletal dysplasias are autosomal dominant and often sporadic.

Test Methods:
Using genomic DNA obtained from the submitted specimen, the coding exons and flanking splice junctions of the genes on this panel are enriched using a proprietary targeted capture

method developed by GeneDx. These targeted regions are simultaneously by massively parallel (NextGen) sequencing on an Illumina platform with paired-end reads. Bidirectional sequence is assembled, aligned to reference gene sequences based on human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Capillary sequencing is used to confirm all potentially pathogenic variants and to obtain sequence for regions where fewer than 15 reads are achieved by NextGen sequencing. Sequence alterations are reported according to the Human Genome Variation Society (HGVS). Benign and likely benign variants, if present, are not included in this report but are available upon request.

Test Sensitivity:

The clinical sensitivity of sequencing analysis of the genes included in this panel depends in part on the patient's clinical phenotype. Ninety-five percent (95%) of cases of achondroplasia are caused by missense variants causing arginine-for-glycine substitutions in amino acid 380 of the gene.[5] Approximately 70% of cases of hypochondroplasia are caused by a recurrent p.N540K variant but at least six other pathogenic amino acid substitutions causing this condition have been identified as well. The p.N540K variant is known to cause a more severe phenotype than other variants causing hypochondroplasia.[3] Thanatophoric dysplasia type I is known to be caused by at least six variants. These variants with their corresponding percentage of cases are: p.Arg248Cys (55%), p.Tyr373Cys (24%), p.Ser249Cys (6%) or variants in a stop codon (10%). Thanatophoric dysplasia type II is only caused by one known variant which is p.Lys650Glu.[3] To date, only two pathogenic variants, p.Tyr381Asp and p.Met391Arg, in FGFR2 have been associated with bent bone dysplasia.[6,7]

The technical sensitivity of the sequencing test is estimated to greater than 99%. It will not detect deletions, insertions, or rearrangements greater than or equal to ten base pairs. Note that small sections of a few individual genes have inherent sequence properties that yield suboptimal data and variants in those regions may not be identified.

References:

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