# FGFR-Related Disorder

**PANEL GENE LIST: *FGFR1, FGFR2, FGFR3***

## CLINICAL FEATURE:

FGFR3-related skeletal dysplasias refer to four distinct disorders caused by variants in the FGFR3gene. 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.3,5Hypochondroplasia (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.3Thanatophoric 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 narrowthorax, 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] Pathogenic variants in the FGFR3 gene have been also reported in association with cranyosynostosis syndromes including Muenke syndrome and Crouzon syndrome with acanthosis nigricans.[6,7] Muenke syndrome constitutes the most common syndromic form of craniosynostosis, with an incidence of 1 in 30,000 births. Patients with Crouzon syndrome with acanthosis nigricans present with cranyosynostosis in addition to acanthosis nigricans with peculiar characteristics; some more severe physical manifestations, such as Chiari malformation, hydrocephalus, and atresia or stenosis of the choanas may also present.

Pathogenic variants in the FGFR2gene can result in multiple phenotypes and syndromes. Many of these disorders involve craniosynostosis or premature fusion of the cranial sutures, including Crouzon, Apert, Pfeiffer, Jackson-Weiss, Antley-Bixler, and Beare-Stevenson cutis gyrata syndromesas well as bent bone dysplasia.Of these disorders, Antley-Bixler syndrome, Beare-Stevenson cutis gyrata syndrome, and bent bone dysplasia are severe skeletal dysplasias which often manifest perinatallyand may belethal.[8,9,11,17] FGFR2 is alsoassociated withlacrimo-auriculo-dento-digital (LADD) syndrome, characterized by anomalies in the lacrimal ducts, ears, teeth, and digits.[16]

The FGFR1gene is associated with multiple disorders: craniosynostosis syndromes, isolated gonadotropin-releasing hormonedeficiency (IGD)and Kallmann syndrome, and Hartsfield syndrome. The premature suture closure in craniosynostosis is a feature of multiple disorders caused by the FGFR1gene: Pfeiffer syndrome, osteoglophonic dysplasia, and trigonocephaly [1].10-12IGD is most commonlycharacterized by low serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as well as hypogonadism; Kallmann syndrome additionally involves an impaired sense of smell.IDG is estimated to occur in approximately 1 in 30,000 males and 1 in 125,000 females; Kallmann syndrome accounts for approximately two-thirds of isolated IGD cases.[13,14] Hartsfield syndrome is a disorder comprised of holoprosencephaly and ectrodactyly malformations with or without cleft lip and palate; patients may also present with craniofacial dysmorphism, cardiac defects, and developmental delay.[15]

## INHERITANCE PATTERN/GENETICS:

All FGFR-related skeletal dysplasias are autosomal dominant and often sporadic..


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## 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 withinadequate 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.

## 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 FGFR3gene.[5]
Approximately 70% of cases of hypochondroplasia are caused by a recurrent p.N540K variant in FGFR3but 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.3Thanatophoric dysplasia type I is known to be caused by at least six FGFR3variants. 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, whichis p.Lys650Glu.3 Muenke syndrome is caused by the recurrent p.Pro250Arg mutation inFGFR3.6 Crouzon syndrome with acanthosis nigricans is also caused by one known variant,p.Ala391Gluin FGFR3. [7] Testing of FGFR2isexpected to identify variants in almost everypatientdiagnosed withthe craniosynostosis syndromes Apert, classical Crouzon, Jackson-Weiss, and Beare-Stevenson cutis gyrata.11To date, only two pathogenic variants, p.Tyr381Asp and p.Met391Arg, in FGFR2have been associated with bent bone dysplasia.[8,9] Testing of the FGFR2 geneis also estimated to identifya pathogenic variant in >95% of patients with Pfeiffer syndrome.11Only a small number of patients have been reported with LADD syndromeand FGFR2-related Antley-Bixler syndrome.[16,17]
FGFR1is estimated to be the cause of <5% of Pfeiffer syndrome and of approximately 10% of IGD and Kallmann syndrome.[11,13,14] While osteoglophonic dysplasiaand Hartsfield syndrome arerare, variants in FGFR1have been observed in the majority of patients.[12,15]

| Gene | Inheritance | Disease Associations |
|---|---|---|
| ***FGFR3*** | Autosomal dominant | AchondroplasiaCrouzon syndromewith acanthosis nigricansHypochondroplasiaLADD syndromeMuenke syndromeThanatophoric dysplasia, type I / II SADDAN |
| ***FGFR2*** | Autosomal dominant | Antley-Bixler syndromeApert syndromeBeare-Stevenson cutis gyrata syndromeCraniosynostosis, non- |


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|---|---|---|
| | | specificBent bone dysplasiaCrouzon syndromeJackson-Weiss syndromeLADD syndromePfeiffer syndrome |
| ***FGFR1*** | Autosomal dominant | Craniosynostosis syndromes (Jackson-Weiss syndrome, Pfeiffer syndrome, osteoglophonic dysplasia, trigonocephaly 1) Hartsfield syndromeIsolated gonadotropin-releasing hormone (GnRH) deficiency (IGD)Kallmann syndrome |

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