

MYCN Gene Analysis in Feingold Syndrome

DISORDER ALSO KNOWN AS:

Oculodigitoesophagoduodenal (ODED) Syndrome; Microcephaly-Oculo-Digito-Esophageal-Duodenal (MODED) Syndrome; Microcephaly, Mental Retardation, and Tracheoesophageal Fistula (MMT) Syndrome

CLINICAL FEATURES:

Feingold Syndrome is characterized by a combination of congenital anomalies, most notably microcephaly, distal limb malformations, and esophageal/duodenal atresia.¹ Approximately 85% of affected individuals have microcephaly, often associated with learning disabilities or mild mental retardation. Short middle phalanges of the 2nd and 5th fingers are the most common feature. Other limb malformations may include clinodactyly of the 2nd and 5th fingers, hypoplastic thumbs, restricted finger and elbow movement, and syndactyly of the 2nd/3rd and 4th/5th toes. Gastrointestinal atresia is found in almost 40% of affected individuals. Although esophageal atresia with or without tracheo-esophageal fistula is seen in only 25-30% of patients, Feingold syndrome may emerge as one of the more common forms of syndromic esophageal atresia.³ Less frequently reported clinical features include short palpebral fissures, broad nasal bridge, anteverted nostrils, micrognathia, ear abnormalities, cardiovascular anomalies (most commonly patent ductus arteriosus), renal and vertebral anomalies, deafness, and short stature. These features exhibit significant inter-and intra-familial variability. The constellation of anomalies observed in Feingold syndrome shows considerable overlap with the VATER/VACTERL association, most significantly esophageal/ duodenal atresia.

GENETICS:

Feingold syndrome is caused by variants in the MYCN gene on chromosome 2p24.3 (also known as NMYC oncogene) resulting in haploinsufficiency and probably disrupting the Sonic Hedgehog (Shh) signaling pathway. The inheritance is autosomal dominant and de novo variants occur in ~50% of patients.

Most pathogenic variants reported to date are nonsense and frameshift variants at the distal end of the coding region (exon 3), which result in haploinsufficiency. In addition, missense variants have been reported, replacing adjacent, conserved Arginine residues in the core of the basic helix-loop-helix domain^{2,6}, as well as several whole or partial gene deletions.^{4,6} Early truncating variants located in exon 2 have also been reported.⁵

TEST SENSITIVITY:

Previous studies have identified MYCN variants by sequencing in a total of 32 of 50 (65%) unrelated families.⁴ Whole or partial gene deletions represent approximately 10% of individuals with at least 3 core features of Feingold syndrome.⁴ Additionally, gross duplications involving the MYCN gene have been associated with an increased risk for tumors.^{8,9} The sequencing and deletion/duplication approach used by GeneDx is expected to identify >99% of existing small intragenic variants in the MYCN gene as well as large deletions and duplications of one or more exons.

TEST METHODS:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for

Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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.

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