

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 mutations 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 disease-causing mutations reported to date are nonsense and frameshift mutations at the distal end of the coding region (exon 3), which result in haploinsufficiency. In addition, three missense mutations have been reported, replacing adjacent, conserved Arginine residues in the core of the basic helix-loop-helix domain², as well as four whole gene deletions and one partial deletion.⁵ Unpublished data include the finding of early truncating mutations located in exon 2.³

Test Methods:

Using genomic DNA obtained from the submitted biological material, bi-directional sequence of the coding region and splice sites of the MYCN gene (exons 1-3) is analyzed. If a sequence change is identified, the variant is confirmed by a second analysis, using sequencing, heteroduplex or restriction fragment analysis or another appropriate method. If no variant is found by sequencing, multiplex ligation-dependant probe amplification (MLPA) may be performed to evaluate for a deletion or duplication of one or more exons in this gene.

Test Sensitivity:

A review of previous studies have identified MYCN variants by sequencing in a total of 32 of 50 (65%) unrelated families.⁴ Although the sequencing approach used by GeneDx is expected to identify >99% of existing small intragenic variants in the MYCN gene, this method will miss a partial or whole gene deletion. Whole or partial gene deletions represent approximately 10% of variants.⁴ Therefore, if indicated, MLPA analysis is available to screen for such deletions.

References:

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3. Celli, J. et al. (2000) Familial syndromic esophageal atresia maps to 2p23-p24. Am J Hum Genet 66:436-444.
4. Marcelis C. et al., (2008) Genotype-Phenotype Correlations in MYCN-Related Feingold Syndrome. Hum Mut 29(9):1125-1132.
5. Blaumeiser, B. et al. (2008) Feingold Syndrome Associated With Two Novel MYCN Mutations in Sporadic and Familial Cases Including Monozygotic Twins. Am J Med Genet. 146A: 2304-2307.
6. Chen, C. et al. (2012) A de novo 4.4-Mb microdeletion in 2p24.3-->p24.2 in a girl with bilateral hearing impairment, microcephaly, digit abnormalities and Feingold syndrome. Eur J Med Genet 55(11): 666-669.