EFNB1 Gene Analysis in Craniofrontonasal syndrome

DISORDER ALSO KNOWN AS
CFNS; Craniofrontonasal dysplasia; CFND; Craniofrontonasal dysostosis.

CLINICAL FEATURES
Craniofrontonasal syndrome (CFNS) is a rare X-linked dominant disorder characterized by a more severe phenotype of multiple skeletal malformations in heterozygous females in contrast to no or mild clinical features in hemizygous males. Females typically display craniofacial asymmetry, marked hypertelorism with a central nasal groove, bifid nasal tip, coronal craniosynostosis (unilateral or bilateral), corpus callosum agenesis, thick wiry hair, and occasionally cleft lip and/or palate. Extracranial features include sloping shoulders with dysplastic clavicles, asymmetry of the thoracic skeleton and pectoral muscle, unilateral breast hypoplasia, longitudinally grooved fingernails, mild cutaneous syndactyly, and umbilical and diaphragmatic hernia. Hemizygous males have no or only mild manifestations such as hypertelorism and less frequently cleft lip and/or palate. Males who are mosaic for EFNB1variants may present with a severe phenotype similar to female patients.

GENETICS
X-linked dominant with more severe phenotype in females and under-representation of carrier males in CFNS families.

CFNS is caused by pathogenic variants in the EFNB1 gene located on chromosome Xq13.1.The EFNB1 gene encodes the transmembrane protein ephrin-B1 which, as part of Eph/ephrin transduction system, controls cell patterning of the developing skeleton, nervous system, intestine, and blood vessels. The more severe phenotype seen in females has been hypothesized to occur by the process of random X-inactivation (rather than skewed X-inactivation). As ephrins are expressed in a spatially and temporally dynamic pattern during embryogenesis, it has been proposed that in heterozygous females, ephrin-B1-expressingcells and ephrin-B1-deficient cells lead to a disturbance of cell sorting and migration and subsequent skeletal malformations particularly craniosynostosis. In hemizygous males who have a homogeneous cell population, it is thought that ephrin-B1 may be replaced by another B-class ephrin. The generally mild clinical presentation in males suggests that ephrin-B1 is functionally redundant in the majority of tissues in which it is expressed[1,2,3]. Regarding the reasons for the observed paucity of carrier males in CFNS families, three contributing factors have been proposed: (1) predominant paternal origin of de novo EFNB1 variants, (2) occurrence of somatic variants that are expected to occur twice as often in females, and (3)reduced reproductive fitness in affected females.

TEST SENSITIVITY
In the largest published study, EFNB1 variants were identified in 33 out of 38 (86.8%) individuals with clinically diagnosed CFNS5. Specifically, pathogenic variants were detected in25 of 29 (86.2%) patients with sporadic CFNS and in 8 of 9 (88.9%) families. In two additional studies with a total of 23 families, EFNB1 variants were found in all clinically affectedindividuals[1,2]. The approach used by GeneDx will identify >99% of existing variants in theEFNB1 gene, including partial or whole gene deletions.

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 buildGRCh37/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.

REFERENCES

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T: 1 (844) 241-1233 | **F:** 1 (201) 421-2020 | GeneDx.com
207 Perry Parkway | Gaithersburg, MD 20877