

CFTR Sequencing and Deletion/Duplication Analysis

Also known as: Cystic Fibrosis, CFTR-Related Disorders, CFTR-Related Metabolic Syndrome

Clinical Features

Cystic fibrosis (CF) is a progressive multi-system genetic disease involving the respiratory tract, pancreas, gastrointestinal tract, hepatobiliary system, sweat glands, and reproductive system. The clinical presentation of CF may range in severity. Respiratory manifestations include persistent lung infections, bronchiectasis, extensive lung damage, recurrent sinusitis, and nasal polyposis (PMID: 19092437; 20301428). Pancreatic issues include pancreatic insufficiency, fat malabsorption, steatorrhea, acute or chronic pancreatitis, and CF-related diabetes. These symptoms stem from thickening of secretions within the pancreatic ducts, prevention of normal release of digestive enzymes, and loss of islet cells (PMID: 19092437). Meconium ileus is present in 15–20% of newborns with CF (PMID: 19092437). Most men with CF have absent or altered vas deferens resulting in infertility, though sperm production is often normal (PMID: 19092437).

Today, most individuals with CF are identified in infancy by newborn screening (NBS) programs. NBS for the identification of CF involves measurement of immunoreactive trypsinogen (IRT). If IRT is elevated, screening proceeds to diagnosis by sweat chloride testing and *CFTR* genetic testing (PMID: 28129811). Although screening or clinical presentation typically leads to the diagnosis of cystic fibrosis during infancy or childhood, some individuals with CF do not present with symptoms until adulthood (PMID: 15486385).

CFTR-related metabolic syndrome (CRMS) is characterized by a positive NBS test in an individual without clinical features of CF (PMID: 28129811; 28129812). CRMS represents those individuals identified by NBS for whom the question of a CF diagnosis is not resolved due to ambiguity in repeat sweat tests and/or genetic testing results. Infants with CRMS are monitored for symptoms as approximately 10–20% of asymptomatic infants can develop clinical features of CF (PMID: 28129812; 19914443).

CFTR-related disorders (CFTR-RD) present in childhood or adulthood and often have complex genotype and phenotype relationships. The clinical features of CFTR-RD overlap with CF but are typically isolated. CFTR-RD include congenital absence of the vas deferens (CAVD), chronic or recurrent acute pancreatitis, and disseminated bronchiectasis (PMID: 21658649).

CF occurs in all ethnicities, but the disease is most common in individuals of Northern European and Ashkenazi Jewish ancestry, in whom the carrier frequency is 1 in 28 and 1 in 29, respectively (PMID: 1384328; 9506637). The incidence of CF in the highest risk populations is approximately 1 in 2000–4000 live births (PMID: 19092437).

Genetics

CF and CAVD are autosomal recessive disorders. CFTR-RD have been reported in individuals with 1 or 2 identified pathogenic *CFTR* variants (PMID: 21658649). Penetrance for CF is essentially 100% when two CF-causing *CFTR* variants are in trans, though there can be considerable variable expressivity (<https://www.cftr2.org/>).

Clinical Sensitivity

The clinical sensitivity of this test depends in part on the patient's clinical presentation and is expected to be highest for individuals with a clearly defined phenotype and/or family history. Interpretations are made with the assumption that any clinical information provided, including family relationships, are accurate. In general, the sensitivity is highest for individuals with features suggestive of cystic fibrosis, CFTR-related disorders, and CFTR-related metabolic syndrome as outlined above. Sequencing and deletion/duplication analysis identify 97–98% and ≤ 2 –3%, respectively, of pathogenic variants in an individual with cystic fibrosis (PMID: 20301428). Approximately 20% of individuals with pancreatitis have at least one identified CFTR variant, including CF-causing and bicarbonate deficient (non-CF-causing) variants (PMID: 25033378). In a meta-analysis, 78% of men with CAVD had at least one identified CFTR variant (PMID: 22081250). The overall test sensitivity for CRMS or other CFTR-RD is unknown.

TEST METHODS

Genomic DNA is extracted directly from the submitted specimen or, if applicable, from cultured fibroblasts. The DNA is enriched for the complete coding regions and splice site junctions of CFTR, including the poly-T and poly-TG tracts in intron 9, 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; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on the probe coordinates, the coordinates of the exons involved, or precise breakpoints when known. 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. Available evidence for variant classification may change over time and reported variant(s) may be reclassified according to the ACMG/AMP Standards and Guidelines (PMID: 25741868), which may lead to issuing a revised report.

Disclaimer

Genetic testing using the methods applied at GeneDx is expected to be highly accurate. However, normal findings do not rule out the diagnosis of a genetic disorder since some genetic abnormalities may be undetectable by this test.

Unless otherwise indicated, the methods used cannot reliably detect deletions of 20bp to 500bp in size, or insertions of 10bp to 500bp in size. Sequencing cannot detect low-level mosaicism. Copy number assessment methods cannot reliably detect mosaicism and cannot identify balanced chromosome aberrations. Regions of certain genes have inherent sequence properties (for example: repeat, homology, or pseudogene regions, high GC content, rare polymorphisms) that yield suboptimal data, potentially impairing accuracy of the results.