FGF3 Gene Sequencing Assay: Genetics and Clinical Overview

Test Information:
FGF3 Gene Sequencing Assay (CMGDL test code 3001)
For sample collection, transport and testing information refer to the CMGDL website www.medgen.med.miami.edu.
See the link for additional test ordering information such as CPT codes, test methodology and limitations.

Gene and Disease Information
Genetic causes of hearing loss. Hearing loss has many known genetic and environmental causes and affects at least 30% of the population at some time in their lives. Clinically significant hearing loss is present in at least 1.9 per 1000 infants at birth and the prevalence rises to at least 2.7 per 1000 by the age of 4 (Morton and Nance, 2006). Genetic causes of hearing loss are estimated to account for 68% of cases expressed at birth and 55% of those expressed by the age of 4. Autosomal recessive, dominant, and X-linked inheritances are responsible for 77%, 22%, and 1% of the genetic cases, respectively. Most cases of genetic deafness are caused by pathologies of the inner ear or hearing nerves, which can be identified with audiological investigations and are referred to as sensorineural hearing loss. Deafness can be classified into syndromic (20%-30%) and nonsyndromic (70%-80%) forms based on the presence or absence of distinctive clinical or laboratory features.

Clinical Significance
FGF3 mutations and hearing loss: the LAMM syndrome. The gene encoding for Fibroblast Growth Factor 3, FGF3 (MIM 164950), is located on chromosome 11 and it consists of three exons. In 2007 Tekin et al. (Tekin et al., 2007) reported that germ line mutations in FGF3 are responsible for a genetic form of hearing loss referred to as LAMM (deafness, congenital, with labyrinthine aplasia, microtia, and microodontia; OMIM 610706). Four additional mutations in FGF3 were subsequently reported to cause similar phenotypes (Tekin et al., 2008; Alsmadi et al., 2009; Ramsebner et al., 2009) making mutations in this gene an established cause of deafness and LAMM syndrome. In addition, FGF3 mutations have been reported to have a variable expressivity with manifestations ranging from fully penetrant LAMM to deafness with residual inner ear structures and minimal syndromic features (Riazuddin S, et al., 2011).

Test Indications
-To confirm a clinical diagnosis or suspect of LAMM syndrome (deafness, congenital, with labyrinthine aplasia, microtia, and microodontia; OMIM 610706)
-To establish a diagnosis in patients with deafness and minimal syndromic features

Contraindications
-Testing should not be ordered for individuals with previously identified familial FGF3 mutations. To test for a specific mutation, it is recommended to order Family Testing, Gene Sequencing Targeted Mutation Analysis (CMGDL test code 3000) and provide a copy of the laboratory report stating the familial mutation.
-Prenatal testing is not performed by the CMGDL

Results Interpretation
-Identification of a known pathogenic FGF3 mutation in a clinically affected individual confirms a diagnosis of Lamm
-Failure to identify FGF3 mutation in a clinically affected individual does not rule out a diagnosis of LAMM. Patient management should be based on clinical findings and family history
-This test may identify FGF3 gene variants of unknown clinical significance

Related Tests
-Family Testing, Gene Sequencing Targeted Mutation Analysis (test code 3000) (visit our website at www.medgen.med.miami.edu)

References
-OMIM http://www.omim.org/entry/610706