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Congenital Deafness with Labyrinthine Aplasia, Microtia, and Microdontia

Synonyms: Congenital Deafness with Inner Ear Agenesis, Microtia, and Microdontia; LAMM Syndrome

Jessica Ordonez, MS[1] and Mustafa Tekin, MD[2]

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Summary

Clinical characteristics

Congenital deafness with *l*abyrinthine *a*plasia, *m*icrotia, and *m*icrodontia (LAMM syndrome) is characterized by: profound bilateral congenital sensorineural deafness associated with inner ear anomalies (most often bilateral complete labyrinthine aplasia); microtia (type I) that is typically bilateral (although unilateral microtia and normal external ears are observed on occasion); and microdontia (small teeth). Individuals with LAMM syndrome commonly have motor delays during infancy presumably due to impaired balance from inner ear (vestibular) abnormalities. Growth, physical development, and cognition are normal.

Diagnosis/testing

The diagnosis of LAMM syndrome is established in a proband by identification of biallelic pathogenic variants in *FGF3* on molecular genetic testing.

Management

Treatment of manifestations: Enrollment in appropriate early-intervention programs and educational programs for the hearing impaired; consideration of vibrotactile hearing devices or brain stem implants for individuals with complete labyrinthine aplasia; consideration of cochlear implantation for those with a cochleovestibular nerve and a cochlear remnant; routine ophthalmologic management of strabismus.

Prevention of secondary complications: Attention to the increased risk for accidents secondary to delayed gross motor development and deafness.

Author Affiliations: 1 Division of Clinical Genetics Center for Genomic Medicine Miami Cancer Institute at Baptist Health South Florida Miami, Florida; Email: jessicaord@baptisthealth.net. 2 Dr John T Macdonald Foundation Department of Human Genetics John P Hussman Institute for Human Genomics Miami, Florida; Email: mtekin@med.miami.edu.

Surveillance: Yearly evaluations with a physician familiar with LAMM syndrome or other forms of hereditary deafness; regular ENT and dental evaluations.

Agents/circumstances to avoid: Individuals with residual cochlear function should avoid noise exposure. Because of the high risk for disorientation when submerged in water, swimming needs to be undertaken with caution.

Evaluation of relatives at risk: It is recommended that sibs have hearing screening to allow early diagnosis and treatment of hearing impairment.

Genetic counseling

LAMM syndrome is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *FGF3* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

The diagnosis of congenital deafness with *l*abyrinthine *a*plasia, *m*icrotia, and *m*icrodontia (LAMM syndrome) **should be suspected** in individuals with the following:

- Profound congenital sensorineural deafness
- Severe inner ear anomalies diagnosed by CT scan or MRI of the inner ear. The most common inner ear anomaly is complete labyrinthine aplasia with no recognizable structure in the inner ear (also referred to as Michel aplasia) (Figure 1C).
- Microtia with shortening of the upper part of the auricles (also referred to as type I microtia) (Figure 1A)
- Microdontia (small teeth) with widely spaced teeth (Figure 1B)

Some individuals may also show gross motor developmental delay during infancy (presumably due to the absence of vestibular system) accompanied by additional features that include:

- Hypoplasia/dysplasia of middle ear anatomic structures identified by imaging studies;
- Stenosis of the jugular foramen with enlarged emissary vein identified by imaging studies.

Establishing the Diagnosis

The diagnosis of LAMM syndrome **is established** in a proband by identification of biallelic pathogenic variants in *FGF3* on molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of LAMM syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of LAMM syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

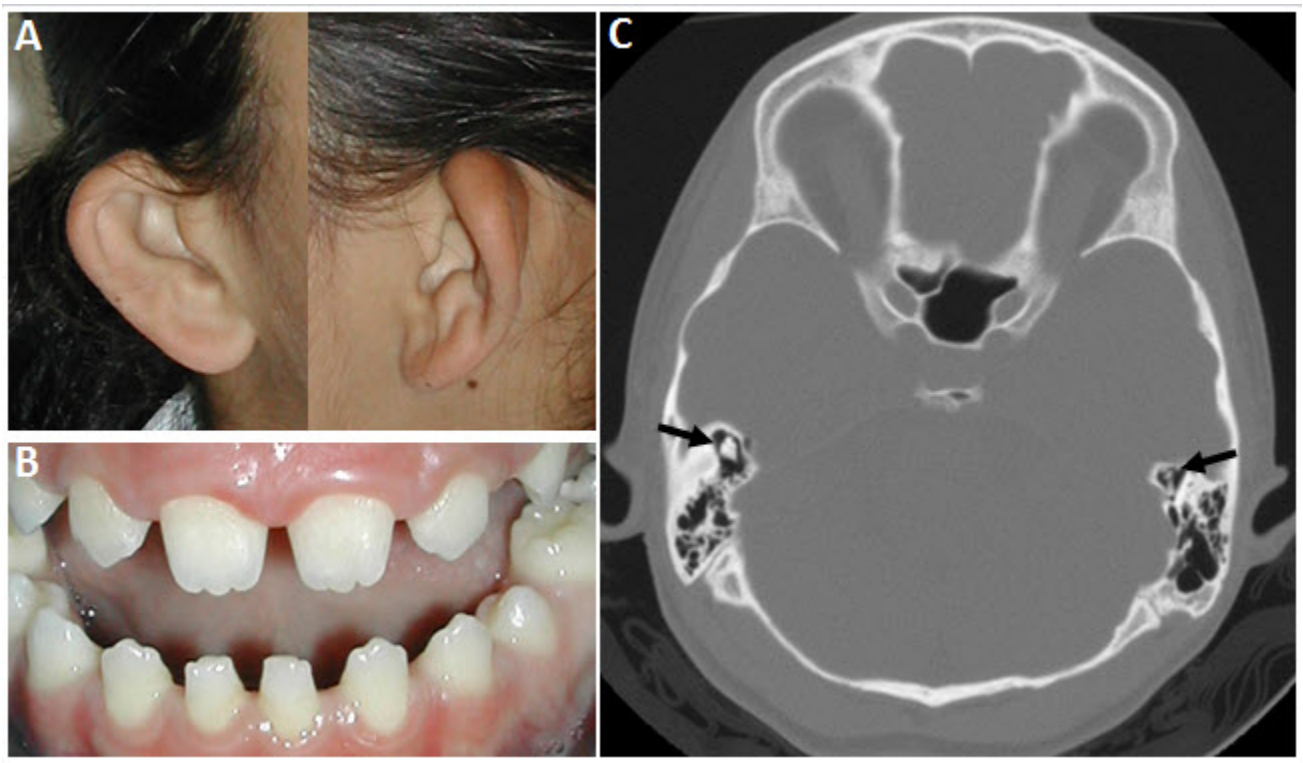

Figure 1. Congenital deafness with labyrinthine aplasia, microtia, and microdontia

A. Microtia with anteverted ears

B. Microdontia with widely spaced teeth

C. CT image demonstrating bilateral petrous bone aplasia and absence of inner ear structures. Malleus and incus are seen in the middle ear cavity (black arrows).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of LAMM syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *FGF3* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *FGF3* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of LAMM syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Congenital Deafness with Labyrinthine Aplasia, Microtia, and Microdontia

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
FGF3	Sequence analysis [3]	15 reported [4]
	Gene-targeted deletion/duplication analysis [5]	3 reported [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Tekin et al [2007], Tekin et al [2008], Alsmadi et al [2009], Ramsebner et al [2010], Dill et al [2011], Riazuddin et al [2011], Sensi et al [2011], Singh et al [2014], Basdemirci et al [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Gregory-Evans et al [2007]

Clinical Characteristics

Clinical Description

*L*abyrinthine *a*plasia, *m*icrotia, and *m*icrodontia (LAMM syndrome) was originally described by Tekin et al [2007]. Since then more than 60 individuals with homozygous and compound heterozygous *FGF3* pathogenic variants from more than 20 families (consanguineous and nonconsanguineous) have been reported [Sensi et al 2011]. Age at diagnosis is typically age 50 years or younger (range: 1 month to 50 years).

Profound congenital sensorineural deafness is bilateral in all individuals reported to date. Most have bilateral complete labyrinthine aplasia, some have unilateral complete labyrinthine aplasia and visible but severely malformed inner ear structures in the other ear, and a few have some inner ear structure present bilaterally [Tekin et al 2007, Ramsebner et al 2010, Riazuddin et al 2011].

Type I microtia with shortening of auricles above the crura of the antihelix tends to be bilateral in most. Unilateral microtia and bilateral normal external ears have been reported in individuals with the p.Arg95Trp pathogenic variant. Anteverted ears and large skin tags or lobulation of the upper side of the auricle can be seen in some [Tekin et al 2008].

Small teeth have been observed in all reported individuals. Dental anomalies include conical shape and decreased tooth diameter resulting in widely spaced teeth. Loss of tooth height and peg-shaped lateral incisors have been seen. Supernumerary upper lateral incisors and absence of the first premolars have been observed.

Mild micrognathia and excessive caries were noted in one adult.

Hypodontia or dental root anomalies have not been observed [Tekin et al 2007].

Other

- Motor delays during infancy, presumably the result of impaired balance; commonly seen
- Stenosis of the jugular foramen with enlarged emissary vein diagnosed by cranial imaging with no clinical manifestations
- Normal growth and physical development
- Average or above-average cognition; affected individuals often attend and thrive at schools for the hearing impaired.
- Absence of limb anomalies and lacrimal findings (seen in some *FGFR*-related syndromes)

Findings that may be incidental to LAMM syndrome include: mild anatomic defects including unilateral stenosis of the uretero-pelvic junction, ocular abnormalities such as strabismus-hypermetropia; brain anomalies such as pontocerebellar arachnoid cysts; cardiovascular findings such as prominent azygos vein; and mildly distinctive facial features such as long facies, downslanting palpebral fissures, deep-set eyes, high nasal bridge, hypoplastic alae nasi, and mild micrognathia.

Life span is not typically altered in individuals with LAMM syndrome. Healthy adults in their 40s and 50s have been reported [Tekin et al 2007, Alsmadi et al 2009].

Genotype-Phenotype Correlations

The variant p.Arg95Trp is associated with a less severe phenotype than the other *FGF3* pathogenic variants [Ramsebner et al 2010, Riazuddin et al 2011].

- Microtia was not observed in eight of 11 individuals homozygous for p.Arg95Trp; in contrast, none of the persons reported with other pathogenic variants had normal-appearing external ears.
- Inner ear structures were identified in seven of 20 individuals homozygous for p.Arg95Trp; in contrast, persons reported with other pathogenic variants had either no inner ear components or primitive vesicle-like structures.

Prevalence

LAMM syndrome is very rare; no prevalence estimates have been established. It has been reported in more than 60 individuals from more than 20 unrelated families.

Genetically Related (Allelic) Disorders

Chromosome microdeletions at 11q13 containing *FGF3* have been associated with globodontial and sensorineural hearing loss seen in the context of otodental dysplasia (also known as otodental syndrome) (OMIM 166750). Otodental dysplasia has also been associated with ocular anomalies in individuals with chromosome microdeletions including *FADD* and *EYA* as well as *FGF3*. Haploinsufficency of multiple genes has been proposed as the mechanism of otodental dysplasia. However, this observation is inconsistent with the detection of heterozygous null *FGF3* variants (resulting in haploinsufficiency) in phenotypically normal parents of individuals with LAMM syndrome. Additional studies are needed to clarify the pathophysiology of *FGFR3* pathogenic variants in LAMM syndrome and otodental dysplasia.

Differential Diagnosis

Table 2. Other Genes of Interest in the Differential Diagnosis of LAMM Syndrome

Gene(s)	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/LAMM syndrome	Distinguishing from LAMM syndrome
FGF10 *FGFR2* *FGFR3*	Lacrimo-*a*uriculo-dento-digital (LADD) syndrome (OMIM 149730)	AD	• Hearing loss • Dental anomalies	• Aplasia, atresia, or hypoplasia of the lacrimal & salivary systems • Cup-shaped ears • Digital (particularly thumb) anomalies
EYA1 *SIX1* *SIX5*	Branchiootorenal spectrum disorder	AD	Hearing loss	• Branchial fistulae & cysts • Renal malformations
KMT2D *KDM6A*	Kabuki syndrome	AD XL	• Hearing loss • Strabismus	• Skeletal anomalies • Typical facial features • Dermatoglyphic abnormalities • Congenital heart defects • Mild-to-moderate ID
SALL1	Townes-Brocks syndrome	AD	• Microtia • Hearing loss	• Imperforate anus or anal stenosis • Typical thumb malformations w/o hypoplasia of the radius

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked; LAMM = labyrinthine aplasia, microtia, and microdontia

Other single-gene disorders or microdeletion/microduplication syndromes should be considered in individuals who have intellectual disability in addition to typical anomalies seen in LAMM syndrome [Dill et al 2011].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital deafness with labyrinthine aplasia, microtia, and microdontia (LAMM syndrome), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Congenital Deafness with Labyrinthine Aplasia, Microtia, and Microdontia

System/ Concern	Evaluation	Comment
ENT	CT &/or MRI of temporal bones	Evaluate inner ear anomalies
Hearing	Audiologic eval	Evaluate for sensorineural hearing loss
Dental	Dental eval	Evaluate for dental anomalies
Renal	Consider renal ultrasound.	Evaluate for kidney anomalies incl unilateral stenosis of uretero-pelvic junction
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Ideally, the team evaluating and treating a deaf individual should include an otolaryngologist with expertise in the management of early-childhood otologic disorders, an audiologist experienced in the assessment of hearing loss in children, a clinical geneticist, and a pediatrician. The expertise of an educator of the Deaf, a neurologist, and a pediatric ophthalmologist may also be required.

- Enrollment in appropriate early-intervention programs and educational programs for the hearing impaired is appropriate.
- An important part of the evaluation is determining the appropriate habilitation option. Possibilities include hearing aids, vibrotactile devices, brain stem implants, and cochlear implantation:
  - Consideration of vibrotactile hearing devices or brain stem implants for individuals with complete labyrinthine aplasia [Riazuddin et al 2011]
  - Evaluation for cochlear implantation in those individuals with a cochleovestibular nerve and a cochlear remnant. Cochlear implantation can be considered in children over age 12 months with severe-to-profound hearing loss.
- Routine ophthalmologic management of strabismus, if present, is indicated.

Prevention of Secondary Complications

Regardless of its etiology, uncorrected hearing loss has consistent sequelae: Auditory deprivation through age two years is associated with poor reading performance, poor communication skills, and poor speech production. Educational intervention is insufficient to completely remediate these deficiencies.

In contrast, early auditory intervention (whether through amplification or cochlear implantation) is effective (see Hereditary Hearing Loss and Deafness Overview). However, the presence of severe inner ear anomalies and Michel aplasia in individuals with LAMM syndrome limits auditory habilitation options.

Delayed gross motor development (presumably the result of impaired balance and profound deafness) increases the risk for accidents and trauma.

- The risk for accidents can be addressed in part by use of visual or vibrotactile alarm systems in homes and schools.
- The risk for pedestrian injury can be reduced by choosing routes with visual displays of crosswalks.
- Anticipatory education of parents, health providers, and educational programs about hazards can help address the risk for falls [Gaebler-Spira & Thornton 2002, Chakravarthy et al 2007].

Surveillance

Table 4. Recommended Surveillance for Individuals with Deafness with Congenital Labyrinthine Aplasia, Microtia, and Microdontia

System/Concern	Evaluation	Frequency
Deafness	ENT eval	Annually
Strabismus	Ophthalmologic eval	
Dental	Dental eval	As neeeded

Yearly evaluations by the multidisciplinary team mentioned in Treatment of Manifestations is appropriate.

Agents/Circumstances to Avoid

Noise exposure is a well-recognized environmental cause of hearing loss. Since this risk can be minimized by avoidance, individuals with LAMM syndrome and a residual cochlea should be counseled appropriately.

Because of the high risk for disorientation when submerged in water, swimming needs to be undertaken with caution.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic sibs of an affected individual by molecular genetic testing for the *FGF3* pathogenic variant in the family in order to allow early diagnosis and treatment of hearing impairment. (Note: Affected sibs may have normal-appearing ears.)

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Congenital deafness with labyrinthine aplasia, microtia, and microdontia (LAMM syndrome) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *FGF3* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with LAMM syndrome are obligate heterozygotes (carriers) for a pathogenic variant in *FGF3*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *FGF3* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *FGF3* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Society for Deaf Children**

  Phone: 800-942-2732 (ASDC)

  Email: info@deafchildren.org

  deafchildren.org

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  www.babyhearing.org

- **Children's Craniofacial Association**

  Phone: 800-535-3643

  Email: contactCCA@ccakids.com

  www.ccakids.org

- **National Association of the Deaf**

  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)

  Fax: 301-587-1791

  Email: nad.info@nad.org

  nad.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Congenital Deafness with Labyrinthine Aplasia, Microtia, and Microdontia: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FGF3	11q13.3	Fibroblast growth factor 3	FGF3 database	FGF3	FGF3

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Congenital Deafness with Labyrinthine Aplasia, Microtia, and Microdontia (View All in OMIM)

164950	FIBROBLAST GROWTH FACTOR 3; FGF3
610706	DEAFNESS, CONGENITAL, WITH INNER EAR AGENESIS, MICROTIA, AND MICRODONTIA

Molecular Pathogenesis

Introduction. Fibroblast growth factor (FGF) proteins function in embryonic development, cell growth, morphogenesis, tissue repair, and tumor growth and invasion [Pownall & Isaacs 2010]. They mainly function through three pathways:

- RAS/MAP kinase pathway (the main pathway)
- Phosphoinositides 3 kinase/AKT pathway
- Phospholipase C gamma pathway

Physiologically, FGF3 binds to the FGF receptor (FGFR) 1b and 2b to activate its signaling cascade, thus regulating cellular proliferation, survival, migration, and differentiation [Zelarayan et al 2007]. Along with FGF8 and FGF10, FGF3 plays a crucial role in the embryonic development of the otic placode (which forms the inner ear) and its eventual differentiation into the vestibular and cochlear structures [Vendrell et al 2000, Wright & Mansour 2003, Toriello et al 2004]. Studies in mice and zebrafish have also shown the role of FGF3 in dental morphogenesis [Kettunen et al 2000, Jackman et al 2004].

Mechanism of disease causation. Loss of function; reported *FGF3* pathogenic variants include nonsense, frameshift, and missense variants in highly conserved amino acid residues.

Molecular modeling suggests that the p.Arg95Trp pathogenic variant does not impair the interaction of FGF3 with FGFR2b receptors or heparin sulfate binding sites, which may result in residual function of FGF3 [Riazuddin et al 2011].

Table 5. Notable *FGF3* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_005247.2 NP_005238.1	c.283C>T	p.Arg95Trp	Variant has been assoc w/a milder phenotype of LAMM syndrome [Ramsebner et al 2010, Riazuddin et al 2011].

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Author Notes

John P Hussman Institute for Human Genomics: Genetic Studies of Deafness

Division of Clinical and Translation Genetics: Deafness Clinic

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