GENEReviews

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Fumarase Deficiency

[*Autosomal Recessive Fumarate Hydratase Deficiency, Fumaric Aciduria, Fumarate Hydratase Deficiency*]

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Summary

Disease characteristics. Fumarase deficiency is characterized by polyhydramnios, enlarged cerebral ventricles in utero, and fetal brain abnormalities. In the newborn period, findings include severe neurologic abnormalities, poor feeding, failure to thrive, and hypotonia. Early-onset infantile encephalopathy, seizures, and severe developmental delay with microcephaly are also common. Other findings include infantile spasms, trunk hypotonia with hypertonic and dystonic posture of the limbs, athetoid movements, and autistic features. EEG abnormalities such as hypsarrhythmia, facial dysmorphism, and craniofacial dysmorphism have been reported. Findings can include neonatal polycythemia, leukopenia and neutropenia, and mild hepatosplenomegaly. Neuroimaging may reveal nonspecific mild hypomyelination, progressive cerebral atrophy, ventricular dilatation, periventricular cysts, Dandy-Walker malformation, agenesis of the corpus callosum, deficient closure of the sylvian opercula, large lateral ventricles, and diffuse, bilateral polymicrogyria. Many children with fumarase deficiency do not survive infancy or die in childhood; those surviving beyond childhood have severe psychomotor retardation.

Diagnosis/testing. Fumarase deficiency is suspected in infants with multiple severe neurologic abnormalities in the absence of an acute metabolic crisis. Isolated increased concentration of fumaric acid on urine organic acid analysis is highly suggestive. Fumarase deficiency is diagnosed by measurement of enzyme activity in fibroblasts, lymphoblasts, or white blood cells and confirmed by molecular genetic testing. Fumarase enzyme activity in severely affected individuals is generally less than 10% of the control mean; however, residual fumarase enzyme activity in some individuals can be 11-35% of the control mean. Fumarase activity observed in obligate heterozygotes is 22-60% of the control mean. *FH*, the gene encoding fumarate hydratase, is the only gene associated with fumarase deficiency. Molecular genetic testing for *FH* is clinically available.

Management. No effective treatment for fumarase deficiency is available. Nutritional intervention (e.g., feeding gastrostomy) may be appropriate in hypotonic children with feeding difficulties. Physical therapy and wheelchairs can be useful for some individuals.

Genetic counseling. Fumarase deficiency is inherited in an autosomal recessive manner and is caused by homozygosity or compound heterozygosity for two *FH* mutations. When both parents are known to be heterozygotes (i.e., carriers of a *FH* mutation), each sib of an affected individual has at conception a 25% chance of having fumarase deficiency and a 25% chance of having no mutation in the *FH* gene. Each sib also has a 50% chance of being a heterozygote. Heterozygotes have a higher than average risk of developing cutaneous leiomyomas and in females, uterine leiomyomas or fibroids; however, the absolute risk is unknown. Carrier testing for at-risk family members is available on a clinical basis once the *FH* mutations have been identified in the proband. Prenatal diagnosis for pregnancies at increased risk for fumarase deficiency is available by molecular genetic testing, if both mutations in an affected family member are known, and by measurement of fumarase enzyme activity.

Diagnosis

Clinical Diagnosis

Fumarase deficiency is suspected in infants with multiple severe neurologic abnormalities in the absence of an acute metabolic crisis.

Testing

Urine organic acid analysis. Isolated increased concentration of fumaric acid on urine organic acid analysis is highly suggestive of fumarase deficiency.

Measurement of fumarase enzyme activity. Fumarase enzyme activity can be measured in fibroblasts, lymphoblasts, and white blood cells.

- Fumarase enzyme activity in severely affected individuals is generally less than 10% of the control mean; however, residual fumarase enzyme activity in some individuals can be 11-35% of the control mean. Fumarase deficiency is evident in both isoenzymes, the mitochondrial form and the cytosolic form.
- Fumarase activity observed in obligate heterozygotes is 22-60% of the control mean.

For laboratories offering biochemical testing, see Testing.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *FH*, the gene encoding fumarate hydratase, is the only gene associated with fumarase deficiency.

Molecular genetic testing: Clinical uses

- Confirmatory diagnostic testing
- Carrier detection
- Prenatal diagnosis

Molecular genetic testing: Clinical methods

- **Targeted mutation analysis.** The 3-bp AAA insertion (c.1431_1433dupAAA / p.K477dup) coding for a lysine has been detected in approximately one-third of

families studied and is the most frequent abnormal allele. In all cases, affected individuals with this allele were compound heterozygotes with a different mutation on the other allele.

- **Sequence analysis/mutation scanning.** A total of 17 different mutations have been reported in 17 families with fumarase deficiency. Affected individuals have two mutant alleles and the majority are compound heterozygotes [Bourgeron et al 1994; Coughlin et al 1998; Kimonis et al 2000; Zeman et al 2000; Alam et al 2003; Remes et al 2004; Loeffen et al 2005; Zeng et al 2006; Deschauer et al 2006; Phillips et al 2006; C Gellera et al, personal communication]. Sequence analysis identifies both mutations in more than 90% of individuals.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Fumarase Deficiency

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Targeted mutation analysis	c.1431_1433dupAAA	30% [1]	Clinical Testing
Sequence analysis	*FH* sequence variations	>90%	

1. In all cases, affected individuals with this allele were compound heterozygotes with a different mutation on the other allele.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy for a Proband

1. Urine organic acid analysis to confirm isolated increased fumaric acid excretion
2. Measurement of fumarase enzyme activity to confirm the diagnosis of fumarase deficiency
3. Molecular genetic testing to confirm the diagnosis of fumarase deficiency if fumarase enzyme activity is not diagnostic

Genetically Related (Allelic) Disorders

Multiple cutaneous and uterine leiomyomas (MCUL) and hereditary leiomyomatosis with renal cell cancer (HLRCC) are caused by heterozygous mutations in *FH* [Alam et al 2003, Toro et al 2003, Wei et al 2006].

MCUL is characterized by:

- Multiple cutaneous leiomyomas
- Early-onset uterine leiomyomas (fibroids)

HLRCC has the additional feature of renal tumors:

- Renal tumors which can be 'type 2' papillary renal cancer, collecting duct renal cell carcinoma, and clear cell renal carcinoma

Clinical Description

Natural History

Some pregnancies of affected fetuses are complicated by polyhydramnios [Coughlin et al 1998, Remes et al 1992]. Enlarged cerebral ventricles in utero and fetal brain abnormalities identified by ultrasound examination have been reported [Remes et al 1992, Coughlin et al 1998].

Most infants with fumarase deficiency show severe neurologic abnormalities in the newborn period, including poor feeding, failure to thrive, and hypotonia. Early-onset infantile encephalopathy, seizures, and severe developmental delay with microcephaly are also common. Other findings include infantile spasms, trunk hypotonia with hypertonic and dystonic posture of the limbs, athetoid movements, and autistic features [Bourgeron et al 1994, Narayanan et al 1996, Coughlin et al 1998, Kimonis et al 2000, Remes et al 2004, Loeffen et al 2005]. EEG abnormalities including hypsarrhythmia have been reported [Remes et al 2004, Loeffen et al 2005].

Facial dysmorphism has been reported [Walker et al 1989, Coughlin et al 1998, Kimonis et al 2000]. Craniofacial dysmorphism including frontal bossing, low-set ears, and a small jaw was reported in one individual [Zeman et al 2000]. All eight affected persons in one family had macrocephaly and dysmorphic facial features with frontal bossing, ocular hypertelorism, and a depressed nasal bridge; some had notched or anteverted nares and high-arched palate [Kerrigan et al 2000]. Some affected individuals do not have dysmorphic features [Bourgeron et al 1994].

Other findings can include neonatal polycythemia, leukopenia and neutropenia, mild hepatosplenomegaly, and pancreatitis [Bourgeron et al 1994, Kerrigan et al 2000, Zeman et al 2000, Phillips et al 2006].

Visual disturbances and optic nerve abnormalities were described in one family [Bourgeron et al 1994, Kerrigan et al 2000]. Abnormalities in succinylpurines were observed in the CSF of one person with fumarase deficiency [Zeman et al 2000].

Of note, acute metabolic crises with findings such as ketosis, hyperammonemia, or acidosis are not observed in fumarase deficiency. Increased CSF lactate and pyruvate concentrations were reported in two siblings.

Many children with fumarase deficiency do not survive infancy, or they die in childhood. Those surviving beyond childhood have severe psychomotor retardation.

Neuroimaging may reveal nonspecific mild hypomyelination, progressive cerebral atrophy, ventricular dilatation, periventricular cysts [Coughlin et al 1998, Kerrigan et al 2000, Loeffen et al 2005]; Dandy-Walker malformation and agenesis of the corpus callosum [Coughlin et al 1998]; deficient closure of the sylvian opercula, large lateral ventricles, and diffuse, bilateral polymicrogyria [Kerrigan et al 2000]. Some individuals have normal MRI imaging of the brain [Bourgeron et al 1994].

Heterozygotes. Most heterozygous parents are normal. However, the finding of cutaneous leiomyomata without uterine fibroids in the mother of an affected child [Tomlinson et al 2002] and death of the mother of an affected child in another family from "renal cell carcinoma" [Shih, unpublished] raise the possibility of increased risk for MCUL/HLRCC in the heterozygous relatives of children with fumarase deficiency.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been described.

Most mutations described in MCUL/HLRCC and fumarase deficiency are missense or nonsense mutations; whole gene deletions have been reported only in MCUL/HLRCC [Tomlinson et al 2002].

The predisposition to MCUL/HLRCC is likely caused by a difference in gene dosage rather than the location of the *FH* mutation as originally suggested [Tomlinson et al 2002].

Prevalence

Fumarase deficiency is rare. Fewer than 100 cases have been reported. The disorder occurs in individuals of different ethnic backgrounds.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Increased excretion of fumaric acid in urine. Transient excretion of fumaric acid in urine is common in young infants and has been observed in metabolically stressed infants, such as those with cardiac failure resulting from severe congenital cardiac anomalies. When the infant with cardiac failure is in stable condition, urine organic acid analysis should be repeated to confirm the presence of increased isolated fumaric acid excretion.

Increased excretion of fumaric acid along with other citric acid intermediates is seen in mitochondrial disorders such as subacute necrotizing encephalomyelopathy (Leigh syndrome) [DeVivo et al 1979] and deficiencies of the pyruvate dehydrogenase complex [Nyhan et al 2005]. See Mitochondrial Disorders Overview.

Polymicrogyria. See Polymicrogyria Overview.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

- Neurologic evaluation
- Feeding assessment and evaluation of nutritional status

Treatment of Manifestations

Nutritional intervention (e.g., feeding gastrostomy) may be appropriate in hypotonic children with feeding difficulties.

Physical therapy and wheelchairs can be useful for some individuals.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Fumarase deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a Proband

- The parents of an affected child are generally unaffected obligate heterozygotes and therefore carry one mutant allele. Two exceptions have been reported:
  - A father whose paternity was confirmed by haplotyping had normal fumarase activity and no evidence of either of his child's *FH* mutations [Coughlin et al 1998]. The proband most likely had fumarase deficiency as the result of a new mutation in the paternal allele, although germline mosaicism was not ruled out.
  - In another family, fumarase deficiency resulted from partial uniparental isodisomy of chromosome 1 [Zeng et al 2006].Thus, only one of the parents carried an *FH* mutation.
- The heterozygous parents of a proband may have or be at risk of developing multiple cutaneous and uterine leiomyomas (MCUL), or (low risk) papillary renal cell carcinoma with leiomyomatosis (HLRCC).

Sibs of a proband

- When both parents are known to be heterozygotes (i.e., carriers of a *FH* mutation), each sib of an affected individual has at conception a 25% chance of having fumarase deficiency and a 25% chance of having no mutation in the *FH* gene. Each sib also has a 50% chance of being a carrier. Carriers have a relatively high risk of developing cutaneous leiomyomas and in females, additional uterine leiomyomas or fibroids. Carriers have a low risk (2-6%) of developing hereditary leiomyomatosis with renal cell cancer (HLRCC).
- When fumarase deficiency occurs as the result of an unusual mechanism (e.g., new mutation in one allele, uniparental isodisomy), the risk to the sibs of a proband are based on the recurrence risk associated with that mechanism.

Offspring of a proband. Individuals with fumarase deficiency generally do not live long enough to reproduce.

Other family members of a proband. Sibs of the proband's parents are at 50% risk of having a mutation in the *FH* gene. Such carriers have a relatively high risk of developing MCUL but a low risk (2-6%) of developing HLRCC.

Carrier Detection

Biochemical testing. Enzyme assay may not be informative for heterozygote detection because the carrier and normal ranges overlap.

Molecular genetic testing. Carrier testing for at-risk family members is available on a clinical basis once the *FH* mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and clarification of carrier status is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant

in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.

Biochemical testing

Fumaric acid detection. Prenatal diagnosis for pregnancies at increased risk for fumarase deficiency is possible by detection of increased fumaric acid in amniotic fluid at about 15-18 weeks' gestation [Manning et al 2000]. No laboratories offering measurement of amniotic fluid fumarate for prenatal diagnosis of fumarase deficiency are listed in the GeneTests Laboratory Directory. However, such prenatal testing may be available in a clinical laboratory.

Fumarase (fumarate hydratase) activity. Prenatal diagnosis for pregnancies at increased risk for fumarase deficiency is possible by measurement of fumarase enzyme activity in uncultured and cultured chorionic villi.

Although analysis of enzyme activity can be performed using cultured fetal cells obtained by amniocentesis [Manning et al 2000] or chorionic villus sampling (CVS) at about 10-12 weeks' gestation [Coughlin et al 1998], some affected fetuses have considerable residual fumarase activity, making prenatal diagnosis using enzyme testing problematic.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Ultrasound examination. Enlarged cerebral ventricles and certain fetal brain abnormalities (agenesis of the corpus callosum and Dandy-Walker cyst) associated with fumarase deficiency can be identified by ultrasound scan [Remes et al 1992, Coughlin et al 1998].

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering PGD, see Testing

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Fumarase Deficiency

Gene Symbol	Chromosomal Locus	Protein Name
FH	1q42.1	Fumarate hydratase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Fumarase Deficiency

136850	FUMARATE HYDRATASE; FH
606812	FUMARASE DEFICIENCY

Table C. Genomic Databases for Fumarase Deficiency

Gene Symbol	Entrez Gene	HGMD
FH	2271 (MIM No. 136850)	FH

For a description of the genomic databases listed, click here.

Normal allelic variants: *FH* consists of ten exons encompassing 22.15 kb of DNA. The cDNA for human *FH* [Kinsella & Doonan 1986] covers the complete coding region of the mature mitochondrial *FH* gene (GenBank M15502). The identity between the rat and human nucleotide sequence is 87%.

Pathologic allelic variants: Mutations in the entire coding region of the *FH* gene have been demonstrated. Mutations have included missense mutations, insertions, and deletions [Tomlinson et al 2002, Toro et al 2003]; however, whole gene deletions have been reported only in MCUL/HLRCC [Tomlinson et al 2002]. Most mutations are missense mutations. Some deletions have been reported and a 3-bp AAA insertion has been found in multiple families with fumarase deficiency.

Note: The numbering system for the *FH* sequence has changed over the years; hence, the commonly seen AAA insertion in fumarase deficiency is referred to variously in the literature as 1302insAAA, 435insAAA, 435insK, 1433insAAA, and insK477. The most recent nomenclature guidelines of the Human Genome Variation Society (www.genomic.unimelb.edu.au/mdi), updated 8 April 2006, considers this mutation a duplication: hence, the c.1431_1433dupAAA / p.K477dup designation.

Normal gene product: The *FH* gene encodes an enzyme, fumarase or fumarate hydratase (EC 4.2.1.2.). The active form of the enzyme is a tetramer. It catalyzes the conversion of fumarate to L-malate in the Krebs tricarboxylic acid cycle. The identity between the rat and human amino acid sequences is 96%. In mammals, the two isozymes of fumarase, mitochondrial and cytosolic, are encoded by a single gene and synthesized by one species of mRNA. The mitochondrial and cytoplasmic isoforms are produced by alternative initiation.

Abnormal gene product: In the majority of the cases reported, the mutated enzyme has some degree of residual activity. Molecular modeling demonstrated that the Q376P mutation disrupts the structure of the active site of fumarase and this may explain the loss of activity in the mutant fumarase [Remes et al 2004].

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

American Epilepsy Society
342 North Main Street
West Hartford CT 06117-2507
Phone: 860-586-7505
Fax: 860-586-7550
Email: info@aesnet.org
www.aesnet.org

Children Living with Inherited Metabolic Diseases (CLIMB)
Climb Building
176 Nantwich Road
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Phone: (+44) 0870 7700 326
Fax: (+44) 0870 7700 327
Email: steve@climb.org.uk
www.climb.org.uk

Epilepsy Foundation of America
4351 Garden City Drive
Landover MD 20785
Phone: 800-EFA-1000 (800-332-1000); 301-459-3700
Fax: 301-577-4941
Email: webmaster@efa.org
www.efa.org

National Dissemination Center for Children with Disabilities
P.O. Box 1492
Washington DC 20013
Phone: 800-695-0285 (v/tty)
Fax: 202-884-8441
Email: nichcy@aed.org
www.nichcy.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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