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Fumarate Hydratase Deficiency

Synonyms: Fumarase Deficiency, Fumaric Aciduria

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Summary

Clinical characteristics

Fumarate hydratase (FH) deficiency results in severe neonatal and early infantile encephalopathy that is characterized by poor feeding, failure to thrive, hypotonia, lethargy, and seizures. Dysmorphic facial features include frontal bossing, depressed nasal bridge, and widely spaced eyes. Many affected individuals are microcephalic. A spectrum of brain abnormalities are seen on magnetic resonance imaging, including cerebral atrophy, enlarged ventricles and generous extra-axial cerebral spinal fluid (CSF) spaces, delayed myelination for age, thinning of the corpus callosum, and an abnormally small brain stem. Brain malformations including bilateral polymicrogyria and absence of the corpus callosum can also be observed. Development is severely affected: most affected individuals are nonverbal and nonambulatory, and many die during early childhood. Less severely affected individuals with moderate cognitive impairment and long-term survival have been reported.

Diagnosis/testing

Isolated increased fumaric acid and alpha-ketoglutarate on urine organic acid analysis, combined with increased succinyladenosine on urine purines and pyrimidines is highly suggestive of FH deficiency. The diagnosis of FH deficiency is established in a proband with reduced fumarate hydratase enzyme activity in fibroblasts or leukocytes and/or biallelic pathogenic variants in *FH* identified by molecular genetic testing.

Management

Treatment of manifestations: Evaluation and management by a pediatric neurologist to treat seizures; gastrostomy tube to optimize nutrition and prevent aspiration in hypotonic or lethargic children; feeding

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therapy as needed; special needs services to address developmental deficits; physical therapy to minimize contractures; wheelchair and/or other mobility devices; management of scoliosis by orthopedist.

Prevention of primary manifestations: To date, there is limited information regarding use of a high-fat/low-carbohydrate diet with 60% of the dietary energy goals coming from fat, 30% from carbohydrate, and 10% from protein.

Surveillance: At least annual evaluations by pediatric neurology and physical medicine; periodic evaluation by orthopedist to monitor contractures and scoliosis; assessment of visual acuity by ophthalmologist.

Agents/circumstances to avoid: The ketogenic diet is usually considered to be contraindicated for treating epilepsy associated with FH deficiency or other enzymatic defects within the Krebs tricarboxylic acid cycle.

Evaluation of relatives at risk: If the *FH* pathogenic variants in the family are known, it is appropriate to consider offering molecular genetic testing to relatives who may be at risk for hereditary leiomyomatosis and renal cell cancer.

Genetic counseling

FH deficiency is inherited in an autosomal recessive manner. When both parents are known to be heterozygous for an *FH* pathogenic variant, each sib of an affected individual has at conception a 25% chance of having FH deficiency, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial *FH* pathogenic variants. Heterozygotes are at risk of developing hereditary leiomyomatosis and renal cell cancer. Once the *FH* pathogenic variants have been identified in an affected family member, heterozygote detection for at-risk relatives and molecular genetic prenatal testing and preimplantation genetic testing are possible. Biochemical prenatal testing by measurement of fumarate hydratase enzyme activity is also possible but may be problematic as some affected fetuses have considerable residual fumarate hydratase enzyme activity.

Diagnosis

Suggestive Findings

Fumarate hydratase (FH) deficiency **should be suspected** in individuals with the following clinical, laboratory, and imaging findings.

Clinical findings

- Neonatal and early-infantile severe encephalopathy, which may include poor feeding, hypotonia, and decreased levels of consciousness (lethargy, stupor, and coma)
- Seizures, present in many but not all affected individuals
- Intellectual disability / developmental delay
- Dysmorphic facial features including frontal bossing, depressed nasal bridge, and widely spaced eyes

Laboratory findings

- Finding of isolated increased fumaric acid and alpha-ketoglutarate on urine organic acid analysis combined with increased succinyladenosine on urine purines and pyrimidines is highly suggestive of FH deficiency.
- Reduced fumarate hydratase enzyme activity. Fumarate hydratase enzyme activity can be measured in fibroblasts or leukocytes. Fumarate hydratase enzyme activity in severely affected individuals is often less than 10% of the control mean; however, residual fumarate hydratase enzyme activity in some affected individuals can be 11%-35% of the control mean. FH deficiency is evident in both isozymes – the mitochondrial form and the cytosolic form (see Molecular Genetics).

Imaging findings. Abnormalities on brain MRI examination, including enlarged ventricles and polymicrogyria, may not be present in mildly affected individuals.

Establishing the Diagnosis

The diagnosis of FH deficiency **is established** in a proband with reduced fumarate hydratase enzyme activity in fibroblasts or leukocytes and/or biallelic pathogenic variants in *FH* identified by 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, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determines which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of FH deficiency 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 with a phenotype indistinguishable from many other inherited disorders with seizures and/or neonatal encephalopathy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *FH* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect (multi)exon and whole-gene deletions or duplications.
- **A seizure and/or neonatal encephalopathy multigene panel** that includes *FH* 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by seizures and/or intellectual disability, **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.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 Fumarate Hydratase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
FH	Sequence analysis [3]	>99%
	Gene-targeted deletion/duplication analysis [4]	See footnote 5.

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. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
5. A whole-gene deletion in an individual with fumarate hydratase deficiency was reported by Mroch et al [2012] and large *FH* deletions have been reported in hereditary leiomyomatosis with renal cell cancer [Tomlinson et al 2002] (see Genetically Related Disorders).

Clinical Characteristics

Clinical Description

To date, approximately 50 individuals have been identified with fumarate hydratase (FH) deficiency [Allegri et al 2010, Ottolenghi et al 2011, Kimonis et al 2012, Mroch et al 2012, Ezgu et al 2013, Saini & Singhi 2013, Tregoning et al 2013, Baştuğ et al 2014, Vara et al 2014, Ryder et al 2018, Grocott et al 2020]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Fumarate Hydratase Deficiency

Feature	% of Persons w/Feature	Comment
Antenatal manifestations	12/51 (23%)	Oligohydramnios, polyhydramnios, IUGR, maternal intrahepatic cholestasis,& preeclampsia
Prematurity	15/51 (30%)	
DD	44/51 (86%) [1]	Severe
Mild-moderate ID	4/51 (8%)	
Hypotonia	35/51 (68%)	
Seizures	22/51 (43%)	
Cortical visual impairment	13/51 (25%)	
Dysmorphic facial features	20/51 (39%)	Frontal bossing, depressed nasal bridge, anteverted nares
Microcephaly	17/51 (33%)	
Macrocephaly	10/51 (20%)	
Abnormal brain imaging	47/51 (92%)	Incl MRI, CT, & antenatal ultrasound findings; most notably: cerebral atrophy, white matter volume loss, polymicrogyria
Acute metabolic perturbations	4/51 (8%)	Metabolic acidosis, lactic acidosis, hypoglycemia, hyperammonemia
Hematologic abnormalities	11/51 (22%)	Neonatal polycythemia (9 persons); neutropenia (2 persons)

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Dystonic posturing	4/51 (8%)	
Excessive irritability	3/51 (6%)	
Hepatic involvement	5/51 (10%)	Cirrhosis, acute hepatic neonatal hepatic failure, biliary atresia

DD = developmental delay; ID = intellectual disability; IUGR = intrauterine growth retardation
1. Note: Some infants died in the neonatal period.

Fetal Manifestations

Few clinical reports comment on complications of affected pregnancies. However, polyhydramnios, oligohydramnios, intrauterine growth retardation, and premature birth (typically at 33-36 weeks' gestation) are reported in approximately one third of affected pregnancies [Coughlin et al 1998, Maradin et al 2006, Allegri et al 2010, Saini & Singhi 2013]. Enlarged cerebral ventricles and other brain abnormalities have been identified by fetal ultrasound [Chan et al 2017].

Neonatal and Early-Infantile Encephalopathy

Newborns with FH deficiency may be symptomatic immediately following delivery or may appear normal at birth and be discharged home from the nursery without recognized problems [Phillips et al 2006]. If symptoms are not apparent at birth, affected infants show severe neurologic abnormalities within age one week to one month, including poor feeding, failure to thrive, and hypotonia. These infants have poor eye contact and variable degrees of depressed consciousness including lethargy, stupor, and even coma. Head and neck control may be entirely absent. Infants gain weight slowly and may require tube feedings.

Epileptic seizures are common (40%-80%), with variable age of onset and seizure type [Kerrigan et al 2000, Allegri et al 2010]. Infantile spasms accompanied by hypsarrhythmia on EEG have been reported [Remes et al 2004, Loeffen et al 2005]. Seizures are often resistant to treatment.

Dysmorphic Facial Features

Abnormal facial features with a spectrum of specific findings have been widely reported and should be regarded as a hallmark feature of this condition (although perhaps not universal). Common features (>50% of affected individuals) include depressed nasal bridge, frontal bossing, and widely spaced eyes [Allegri et al 2010]. Less frequent features (<50%) include cleft ala nasi or anteverted nares, ear anomalies, or narrow forehead [Allegri et al 2010].

Head Size

Head size has been reported as microcephalic in 36% of all affected individuals [Allegri et al 2010]. However, in one large kindred (8 affected individuals in 1 consanguineous family), 88% (7 of 8 affected individuals) were reported to have "relative macrocephaly," since head sizes were within the normal range, but in association with brain imaging findings of cerebral atrophy and mild communicating hydrocephalus (enlarged extra-axial CSF spaces) [Kerrigan et al 2000]. That is, most children with FH deficiency appear have abnormally limited brain growth.

Brain Imaging Findings

The most common finding is a small brain, representative of cerebral underdevelopment. This may be described by the neuroradiologist as cerebral atrophy (73% of all individuals summarized by Allegri et al [2010]), or ventriculomegaly (82% of all individuals summarized by Allegri et al [2010]). Brain volume loss (or more likely

lack of brain volume development) can be accompanied by a relative decrease in CSF reabsorption, leading to a normal head size with a small brain but modestly expanded CSF compartments. In the series of Kerrigan et al [2000], two such individuals were shunted for possible "hydrocephalus" leading to collapse of the CSF compartments and secondary microcephaly without clinical improvement.

Additional findings on MRI can include nonspecific white matter abnormalities, described as either delayed myelination or hypomyelination [Phillips et al 2006], deficient closure of the Sylvian opercula [Kerrigan et al 2000, Phillips et al 2006], and a hypoplastic brain stem [Kerrigan et al 2000, Phillips et al 2006, Tregoning et al 2013]. Abnormalities of the corpus callosum are also reported, including thinning [Maradin et al 2006, Phillips et al 2006] and absence [Coughlin et al 1998]. Hyperintense basal ganglia lesions in the caudate and thalamic nuclei, and elevated lactate on MRS have also been reported [Tregoning et al 2013]. Diffuse bilateral polymicrogyria of the cerebral cortex has also been reported, a universal feature in the eight affected individuals from one kindred reported by Kerrigan et al [2000] but also noted in three additional unrelated individuals [Zeng et al 2006, Ottolenghi et al 2011].

Acute Metabolic Derangements

Acute metabolic crises with findings such as hypoglycemia, ketosis, hyperammonemia, or acidosis are rarely observed in individuals with FH deficiency [Allegri et al 2010, Saini & Singhi 2013, Başтuğ et al 2014].

Other Clinical Features

Other findings can include neonatal polycythemia [Kerrigan et al 2000], recurrent neutropenia [Tregoning et al 2013, Guitart et al 2017], recurrent vomiting with hepatosplenomegaly [Allegri et al 2010, Tregoning et al 2013], and pancreatitis [Phillips et al 2006]. Visual disturbances and optic nerve hypoplasia were described in two families [Kerrigan et al 2000, Saini & Singhi 2013]. Birth defects involving other organ systems are uncommon.

Clinical Course

The clinical outcome for individuals with FH deficiency is not favorable. Many individuals do not survive infancy, or may die of secondary complications (e.g., respiratory failure) during the first decade of life [Loeffen et al 2005]. Many children are unable to feed successfully, with failure to gain weight and increased risk for aspiration. Accordingly, feedings administered through gastrostomy tube may be required.

Over time, severely affected children (usually nonverbal and nonambulatory) develop evidence of spasticity, and consequently are at risk for contractures and orthopedic deformities including scoliosis. Extrapyramidal motor features, including athetosis and dystonic posturing, can also be observed. Epileptic seizures often become more frequent and less responsive to treatment. Seizures may occur daily in some individuals.

However, less severely affected children, who may be ambulatory and capable of engaging in special needs school programs (despite the presence of bilateral polymicrogyria), have also been reported [Ottolenghi et al 2011]. Consequently, counseling of families with children with FH deficiency should include recognition of the range of severity.

Heterozygotes

Most heterozygous parents are healthy. However, the finding of cutaneous leiomyomata without uterine fibroids in the mother of an affected child [Tomlinson et al 2002], a report of a mother with uterine myomas [Maradin et al 2006], the death of the mother of an affected child from "renal cell carcinoma" in a third family [VE Shih, unpublished], and the detection of renal carcinoma in an asymptomatic obligate heterozygous female raise the possibility of increased risk for HLRCC in the heterozygous relatives of children with FH deficiency (see Hereditary Leiomyomatosis with Renal Cell Cancer).

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

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

Genetically Related (Allelic) Disorders

Hereditary leiomyomatosis with renal cell cancer (HLRCC) resulting from haploinsufficiency of fumarate hydratase caused by heterozygous pathogenic loss-of-function *FH* variants is characterized by cutaneous leiomyomata, uterine leiomyomata (fibroids), and renal cancer. Renal tumors are usually unilateral, solitary, and aggressive and range from type 2 papillary to tubulo-papillary to collecting-duct carcinomas. They occur in about 10%-16% of individuals with HLRCC.

Sporadic tumors occurring as single tumors in the absence of any other findings of hereditary leiomyomatosis and renal cell cancer were found to have biallelic somatic pathogenic variants in *FH* that were **not** present in the germline. For more information see Cancer and Benign Tumors.

Differential Diagnosis

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, including subacute necrotizing encephalomyelopathy (see Mitochondrial DNA-Associated Leigh Syndrome and NARP and Nuclear Gene-Encoded Leigh Syndrome Overview) and deficiencies of the pyruvate dehydrogenase complex [Patel et al 2012] (see Primary Pyruvate Dehydrogenase Complex Deficiency Overview).

Polymicrogyria. See Polymicrogyria Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with fumarate hydratase (FH) deficiency, 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 Fumarate Hydratase Deficiency

System/Concern	Evaluation	Comment
Neurologic	Eval by pediatric neurologist	Eval will likely incl brain MRI exam.
Nutrition	Feeding assessment & eval of nutritional status	
Other	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Fumarate Hydratase Deficiency

Manifestation/ Concern	Treatment	Considerations/Other
Seizures	Eval & mgmt by pediatric neurologist	• Ketogenic diet is considered contraindicated. • Seizures are often difficult to control.
Developmental delay	Gastrostomy tube feeding	May be appropriate in hypotonic &/or lethargic children w/feeding difficulties &/or aspiration
	Feeding therapy	May be helpful in some affected persons
	Special needs services	In persons w/significant developmental deficits (incl impairment of motor, language, & social development)
Contractures	Physical therapy	To minimize contractures
	Wheelchair &/or other mobility device	Can be useful for some persons
Scoliosis	Mgmt per orthopedist	

Prevention of Primary Manifestations

One individual with FH deficiency has been treated with a high-fat/low-carbohydrate diet with 60% of the dietary energy goals coming from fat, 30% from carbohydrate, and 10% from protein [Ryder et al 2018]. This child presented at age six months, began the dietary treatment at age 14 months, and remains stable with mild intellectual impairment and well-controlled seizures. Whether the milder disease trajectory is a consequence of the diet remains unclear.

Surveillance

Table 5. Recommended Surveillance for Individuals with Fumarate Hydratase Deficiency

System/Concern	Evaluation	Frequency
Seizures	Eval by pediatric neurologist	At least annually to monitor for &/or treat epilepsy
Musculoskeletal complications	Physical medicine eval	At least annually to monitor for equipment needs & to monitor for &/or treat manifestations of spasticity
	Orthopedics eval	As needed to monitor contractures &/or scoliosis
Ophthalmology	Ophthalmology eval for visual acuity & nystagmus	As recommended by ophthalmologist

Agents/Circumstances to Avoid

The ketogenic diet is usually considered to be contraindicated for treating epilepsy associated with FH deficiency or other enzymatic defects within the Krebs tricarboxylic acid cycle.

Evaluation of Relatives at Risk

If the *FH* pathogenic variants in the family are known, it is appropriate to consider offering molecular genetic testing to relatives who may be at risk for hereditary leiomyomatosis and renal cell cancer (see Genetically Related Disorders).

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

Therapies Under Investigation

Increasingly sophisticated models of mitochondrial function are being used to study the metabolic derangements associated with identified defects of intermediary metabolism, including FH deficiency [Smith & Robinson 2011]. These models may suggest treatment interventions with supplements or dietary changes that are not presently established.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Other

No significant clinical or biochemical improvement was noted by treatment with a protein-restricted diet [unpublished data]. A brief therapeutic trial of a low-protein diet in one mildly affected individual with FH deficiency did not alter urinary excretion of fumaric acid or improve clinical signs [Kimonis et al 2012].

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

Fumarate hydratase (FH) deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for one *FH* pathogenic variant. Two exceptions have been reported:
  - A father whose paternity was confirmed by haplotyping had normal fumarate hydratase enzyme activity and no evidence of either of his child's *FH* pathogenic variants [Coughlin et al 1998]. The proband most likely had FH deficiency as the result of a *de novo* pathogenic variant in the paternal allele, although germline mosaicism was not ruled out.
  - In another family, FH deficiency resulted from partial uniparental isodisomy of chromosome 1 [Zeng et al 2006]. Thus, only one of the parents carried an *FH* pathogenic variant.
- The heterozygous parents of a proband are at risk of developing hereditary leiomyomatosis and renal cell cancer (HLRCC). Lifelong kidney surveillance of heterozygotes is appropriate and may reduce morbidity and mortality associated with renal cancer (see Clinical Description, Heterozygotes) [Menko et al 2014, Chan et al 2017].

Sibs of a proband

- If both parents are known to be heterozygous for an *FH* pathogenic variant:
  - Each sib of an affected individual has at conception a 25% chance of having FH deficiency and a 25% chance of having no pathogenic variant in *FH*. Each sib also has a 50% chance of being heterozygous.
  - Heterozygotes are at risk of developing HLRCC.

- When FH deficiency occurs as the result of an unusual mechanism (e.g., a *de novo* pathogenic variant in one allele or uniparental isodisomy), the risk to the sibs of a proband is based on the recurrence risk associated with that mechanism.

Offspring of a proband. Many individuals with FH deficiency do not survive childhood; no affected individuals with offspring have been reported.

Other family members. Sibs of the proband's parents are at 50% risk of having a pathogenic variant in *FH*. Such heterozygotes are at risk of developing HLRCC.

Heterozygote Detection

Molecular genetic testing. Heterozygote testing for at-risk relatives requires prior identification of the *FH* pathogenic variants in the family.

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

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 of allelic disorders associated with heterozygous pathogenic variants in *FH* (i.e., HLRCC).

Family planning

- The optimal time for determination of genetic risk, clarification of genetic 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 heterozygous or are at risk of being heterozygous.

DNA banking. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative genetic alteration/s are unknown).

Prenatal Testing and Preimplantation Genetic Testing

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

Biochemical testing

- **Fumaric acid detection.** Prenatal testing for a pregnancy at increased risk for FH deficiency is possible by detection of increased fumaric acid in amniotic fluid at approximately 15 to 18 weeks' gestation [Manning et al 2000]. However, such studies are not diagnostic, and should be reviewed with extreme caution.
- **Fumarate hydratase enzyme activity.** Prenatal testing for a pregnancy at increased risk for FH deficiency is possible by measurement of fumarate hydratase enzyme activity in uncultured and cultured chorionic villi. Although analysis of fumarate hydratase enzyme activity can be performed using cultured fetal cells obtained by amniocentesis [Manning et al 2000] or chorionic villus sampling at approximately ten to 12 weeks' gestation [Coughlin et al 1998], some affected fetuses have considerable residual fumarate hydratase enzyme activity, making prenatal testing 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 FH deficiency can be identified by ultrasound examination [Chan et al 2017].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is 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.

- **United Mitochondrial Disease Foundation**
  Phone: 888-317-UMDF (8633)
  Email: info@umdf.org
  www.umdf.org
- **American Epilepsy Society**
  aesnet.org
- **Epilepsy Foundation**
  Phone: 800-332-1000; 866-748-8008
  epilepsy.com
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.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. Fumarate Hydratase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FH	1q43	Fumarate hydratase, mitochondrial	TCA Cycle Gene Mutation Database (FH)	FH	FH

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 Fumarate Hydratase Deficiency (View All in OMIM)

136850	FUMARATE HYDRATASE; FH
606812	FUMARASE DEFICIENCY; FMRD

Molecular Pathogenesis

FH encodes for both mitochondrial and cytosolic FH enzyme isoforms, which catalyze hydration of fumarate to malate. Mitochondrial FH is an important part of the tricarboxylic acid cycle (TCA cycle, also known as Krebs

cycle) and is required for efficient oxidative phosphorylation in the mitochondria. The cytosolic isoform of FH metabolizes fumarate produced in the urea cycle, in the purine nucleotide cycle, and during arginine synthesis.

FH deficiency results in a genetic block in Krebs cycle and the inability of cells to metabolize fumarate in the cytosol. As a consequence, fumarate is substantially accumulated intracellularly and extracellularly and in excessive levels it is toxic to the cells, thus causing multiple developmental defects.

Mechanism of disease causation. Loss of function. Based on genotypes observed in affected individuals, it is likely that complete loss of enzyme activity is incompatible with life.

Notable *FH* variants. Most disease-associated variants are concentrated at the C terminus of the FH enzyme [Allegri et al 2010]. There are currently 281 unique variants reported in the Leiden Open Variation Database (LOVD 3.0), many of which are private (databases.lovd.nl).

The p.Lys477dup variant is the variant most frequently associated with FH deficiency [Coughlin et al 1998]; however, no functional studies have been reported. This variant is present in the population at a frequency higher than expected for a disease-causing variant; it is not associated with HLRCC (see Genetically Related Disorders) [Zhang et al 2020]. Therefore, the functional consequence of p.Lys477dup is not understood at this time.

Table 6. Notable *FH* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000143.2 NP_000134.2	c.1431_1433dupAAA [1]	p.Lys477dup [1]	Most common variant assoc w/FH deficiency (30% of fumarate hydratase deficiency-related pathogenic variants)

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.
1. The numbering system for the *FH* sequence has changed over the years; hence, the commonly seen AAA duplication in fumarate hydratase deficiency is referred to variously in the literature as 1302insAAA, 435insAAA, 435insK, 1433insAAA, and insK477.

Cancer and Benign Tumors

Sporadic tumors (including 2 early-onset uterine leiomyomas and a soft tissue sarcoma of the lower limb) occurring as single tumors in the absence of any other findings of hereditary leiomyomatosis and renal cell cancer were found to have biallelic somatic pathogenic variants in *FH* that were **not** present in the germline [Kiuru et al 2002, Lehtonen et al 2004]. In these circumstances predisposition to these tumors is not heritable.

Loss of FH enzymatic activity leads to the accumulation of intracellular fumarate, which is thought to function as an oncometabolite, an intermediate of cellular metabolism that promotes cancer formation. Fumarate is known to competitively inhibit 2-oxoglutarate (2OG)-dependent oxygenases, including HIF prolyl hydroxylases, thus resulting in an increased stability of HIFs, which are thought to be oncogenic drivers in certain tumors. High levels of cytoplasmic fumarate also result in the modification of protein cysteine residues, forming S-(2-succinyl)-cysteine, in the process called succination, thereby affecting multiple cellular pathways. Furthermore, elevated fumarate succinates glutathione (GSH; a major cellular protection against reactive oxygen species), and by depleting the GSH pool it causes oxidative stress, a common feature of many cancers. While the exact causal mechanism by which elevated fumarate promotes cancer formation is not well defined, it is highly likely that fumarate synergistically affects multiple cellular pathways to exert its pathogenic effects.

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