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TFR2-Related Hereditary Hemochromatosis

[*Type 3 Hereditary Hemochromatosis*]

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Summary

Disease characteristics. *TFR2*-related hereditary hemochromatosis (*TFR2*-HHC) is characterized by increased intestinal iron absorption resulting in iron accumulation in the liver, heart, pancreas, and endocrine organs. Age of onset is earlier than in *HFE*-associated HHC. Some individuals present in the second decade and others present as adults with fatigue and arthralgia and/or organ involvement including liver cirrhosis, diabetes mellitus, and arthropathy. In other individuals, *TFR2*-HHC may not be progressive even if untreated.

Diagnosis/testing. The diagnosis of *TFR2*-HHC in individuals with clinical symptoms and/or biochemical evidence of iron overload is typically based on serum transferrin-iron saturation (>45% in men and women) and serum ferritin concentration (usually >200 µg/L in females and >300 µg/L in males) as well as histologic assessment of hepatic iron stores on liver biopsy. Molecular genetic testing for *TFR2*, the only gene associated with *TFR2*-HHC, is available on a clinical basis.

Management. *Treatment of manifestations:* routine phlebotomy to remove excess iron to maintain serum ferritin concentration at 50 ng/mL or lower and transferrin-iron saturation below 50%, lifelong hormone replacement therapy for hypogonadism, gonadotropins for fertility/pregnancy, nonsteroidal anti-inflammatory drugs (NSAIDs) and joint replacement for arthropathy, diuretics, routine treatment for cardiac failure and diabetes mellitus. *Prevention of primary manifestations:* routine phlebotomy as in *Treatment of manifestations*. *Surveillance:* monitoring serum ferritin concentration every three to four months once serum ferritin concentration is less than 50 ng/mL. *Agents/circumstances to avoid:* medicinal iron, mineral supplements, excess vitamin C, uncooked seafood; restriction of alcohol intake for those with liver involvement. *Testing of relatives at risk:* if the disease-causing mutations in the family are known, molecular genetic testing of at-risk relatives, to allow early diagnosis and treatment.

Genetic counseling. *TFR2*-HHC 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. Heterozygotes (carriers) are asymptomatic and do not have abnormalities of iron parameters. Carrier testing for at-risk family members is available on a clinical basis once the disease-causing mutations

have been identified in the family. Prenatal testing is available if both disease-causing mutations have been identified in the family; however, requests for prenatal testing for conditions such as *TFR2*-HHC that do not affect intellect and have effective treatment available are not common.

Diagnosis

Clinical Diagnosis

TFR2-related hereditary hemochromatosis *(TFR2*-HHC) should be suspected in any individual with findings of iron overload (including hepatomegaly, hepatic cirrhosis, diabetes mellitus, cardiomyopathy, hypogonadism, arthritis - especially if involving the metacarpophalangeal joints, and progressive increase in skin pigmentation) in whom *HFE*-associated hereditary hemochromatosis has been excluded. More typically, individuals present either (a) with early clinical findings of hereditary hemochromatosis (including vague nonspecific symptoms, e.g., abdominal pain, fatigue, arthralgia, decreased libido) or (b) most frequently with biochemical evidence of iron overload in routinely used panels that include serum transferrin-iron saturation and serum concentrations of iron and ferritin.

Testing

Diagnosis of *TFR2*-HHC is suspected in individuals with the following:

- **Transferrin saturation** higher than 45%. Normal range is between 20% and 35% saturation in both sexes.
- **Serum ferritin concentration** usually higher than 200 µg/L in females and higher than 300 µg/L in males

  Normal ranges:

  - Children and adolescents: 15-150 µg/L
  - Adult males: 20-300 µg/L
  - Adult females: 20-200 µg/L

    Note: The same biochemical iron parameters are used in diagnosis of *HFE*-associated hereditary hemochromatosis [Pietrangelo 2004].

Liver Biopsy—Findings on liver biopsy have been reported in a few individuals with *TFR2*-HHC [Girelli et al 2002, Pietrangelo et al 2005, Hsiao et al 2007]. Liver biopsy is used to assess histology (fibrosis or cirrhosis), liver iron concentration (LIC), and the distribution of iron storage (increased iron deposition occurs in the hepatocytes, and a decreasing gradient of iron stores is observed from portal to centrolobular areas [Girelli et al 2002], as in *HFE*-associated hereditary hemochromatosis).

Imaging—Noninvasive techniques including MRI [Gandon et al 2004, St Pierre et al 2005] and SQUID developed to quantitate liver iron concentration have been applied to *HFE*-associated hereditary hemochromatosis [Carneiro et al 2007] but rarely to *TFR2*-HHC [Piperno et al 2004, Biasiotto et al 2008].

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. *TFR2* is the only gene associated with *TFR2*-HHC.

Clinical testing

- **Targeted mutation analysis.** A panel of four mutations (See Table 1) identifies mutations in fewer than 50% of individuals known to have *TFR2*-HHC.

Research testing

- **Mutation scanning.** Mutation scanning methods such as DHPLC [Biasiotto et al 2003], followed by sequencing of variant fragments, permits rapid screening of the coding sequences and splice junctions. Mutation detection rate is assumed to be higher than 98%, based on experience with this technology. Mutation scanning does not detect extensive deletions.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *TFR2*-Related Hereditary Hemochromatosis

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Targeted mutation analysis	p.Arg30ProfsX31, p.Met172Lys, p.Tyr250X, p.Ala621_Gln624del in *TFR2* [1]	<50% [2]	Clinical Testing
Mutation scanning	*TFR2* sequence variants	>98%	Research only

1. See Table 2.

2. Data are from the Italian population [Author, personal observation].

Testing Strategy

Confirmation of the diagnosis in a proband. In an individual with a clinical diagnosis of hemochromatosis, and/or increased iron at liver biopsy, and/or a family history of hemochromatosis **AND** no identifiable *HFE* mutations, molecular genetic testing for *TFR2* mutations is appropriate.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family.

Note: Carriers are heterozygotes for an autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *TFR2*.

Clinical Description

Natural History

TFR2-related hereditary hemochromatosis (*TFR2*-HHC) is characterized by deregulated, increased intestinal iron absorption resulting in iron accumulation in the liver, heart, pancreas, and endocrine organs [Camaschella et al 2000].

The age of onset in *TFR2*-HHC is earlier than in *HFE*-associated hereditary hemochromatosis. One child age 3.5 years had transferrin saturation and serum ferritin concentration that were increased for age [Piperno et al 2004]. Some individuals present with signs of iron overload in the second decade [Girelli et al 2002, Hattori et al 2003, Le Gac et al 2004, Piperno et al 2004, Biasiotto et al 2008]. Others present as adults with abnormal serum iron studies or fatigue and arthralgia and/or signs of organ involvement (liver cirrhosis, diabetes, arthropathy) [Roetto et al 2001, Girelli et al 2002, Hattori et al 2003, Koyama et al 2005].

Disease progression is slower than in juvenile hereditary hemochromatosis, even in untreated individuals [De Gobbi et al 2002]. Even untreated, *TFR2*-HHC may not be progressive [Roetto et al 2001, Girelli et al 2002].

When *TFR2*-HHC is progressive, complications can include cirrhosis, hypogonadotropic hypogonadism, and arthritis. Cardiomyopathy and diabetes mellitus are rare [Riva et al 2004] and hepatocellular carcinoma has not been observed in the limited number of affected individuals reported to date.

Most individuals reported to date have been of Italian or Japanese ancestry. Individuals of Japanese ancestry were older at diagnosis than those of Italian ancestry and had hepatic iron loading; a few middle-aged Japanese males had cirrhosis [Hattori et al 2003, Koyama et al 2005].

Genotype-Phenotype Correlations

The limited number of individuals reported and the private nature of the mutations do not permit genotype-phenotype correlations.

Presence of the p.His63Asp allele of *HFE* (NP_000401.1; NM_000410.3: c.187C>G) has been described in individuals with *TFR2*-HHC [Camaschella et al 2000, Piperno et al 2004]; however, the contribution of the p.His63Asp allele to the *TFR2*-related iron overload is unclear.

Inheritance of compound heterozygosity for the *HFE* mutations p.Cys282Tyr (NP_000401.1; NM_000410.3: c. 845G>A) and p.His63Asp and homozygosity for the *TFR2* mutation p.Gln317X produced a phenotype of juvenile hemochromatosis in a single family [Pietrangelo et al 2005].

Penetrance

The penetrance of *TFR2*-HHC is less than 100%. In a family reported in the study by Roetto et al [2001], one middle-aged female homozygous for the p.Arg30ProfsX31 mutation had no evidence of clinical disease; a second female had no signs of iron overload, and in fact had iron deficiency.

Nomenclature

TFR2-HHC is also known as hemochromatosis type 3 (HFE3); however, the term HFE3 seems inappropriate because the *HFE* gene has no role in *TFR2*-HHC.

Prevalence

TFR2-HHC is rare. Fewer than 25 affected individuals have been reported worldwide, most commonly in Japan and Italy. Single families from France [Le Gac et al 2004] and Portugal [Mattman et al 2002] have been reported. One case was reported in Taiwan [Hsiao et al 2007].

Screening for *TFR2* mutations on a large scale is not available. Screening for the first identified *TFR2* mutation (p.Tyr250X) among a small cohort of blood donors in Italy with increased transferrin saturation revealed a single p.Tyr250X heterozygote, accounting for a carrier frequency of 0.9% in this select population [De Gobbi et al 2001]. Screening of individuals with non-*HFE*-associated hereditary hemochromatosis worldwide did not identify the p.Tyr250X mutation in Caucasians [Aguilar-Martinez et al 2001a, Aguilar-Martinez et al 2001b, Barton et al 2001, Lee et al 2001].

In Japan, where hemochromatosis is rare and heterogeneous, it has been proposed that *TFR2*-HHC is the most frequent form of hereditary hemochromatosis [Hayashi et al 2006]; however, studies are limited.

Differential Diagnosis

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

TFR2-related hereditary hemochromatosis (*TFR2*-HHC, sometimes called type 3 HHC) needs to be distinguished from other primary iron overload disorders as well as from secondary iron overload disorders. No specific studies have evaluated the percentage of *TFR2* mutations detected in individuals with non-*HFE*-associated hereditary hemochromatosis.

Primary Iron Overload Disorders

Primary overload disorders are characterized by increased absorption of iron from a normal diet.

***HFE*-related hereditary hemochromatosis** (hemochromatosis type 1) is the most common form. *HFE*-associated hereditary hemochromatosis is characterized by excessive storage of iron, particularly in the liver, skin, pancreas, heart, joints, and pituitary, resulting in hypogonadotropic hypogonadism. Without therapy, males may develop symptoms between ages 40 and 60 years and females after menopause. Hepatic fibrosis or cirrhosis may occur in untreated individuals after age 40 years. A large fraction of homozygotes (≤98% in some series) [Asberg et al 2001, Beutler et al 2002] for mutations in this gene do not develop clinical symptoms (i.e., penetrance is low). Inheritance is autosomal recessive.

Juvenile hereditary hemochromatosis (sometimes called type 2 HHC) has an earlier age of onset and more severe clinical manifestations than *HFE*-related hereditary hemochromatosis. Two causative genes (hence, two clinically indistinguishable "subtypes") have been identified: type 2A, caused by mutations in *HJV* encoding hemojuvelin; and type 2B, caused by mutations in *HAMP*. Onset of severe iron overload typically occurs in the first to third decades of life. Males and females are equally affected. Prominent clinical features include hypogonadotropic hypogonadism, cardiomyopathy, arthropathy, and liver fibrosis or cirrhosis. Hepatocellular cancer has not been reported. The main cause of death is cardiac-related disease. If juvenile hemochromatosis is detected early enough and if blood is removed regularly through the process of phlebotomy to achieve iron depletion, morbidity and mortality are greatly reduced. Inheritance is autosomal recessive [Roetto et al 1999, Camaschella et al 2000, De Gobbi et al 2002].

Ferroportin-related hereditary hemochromatosis (hemochromatosis type 4) is caused by mutations in *SLC40A1,* or solute carrier family 40 (iron-regulated transporter), member 1, which encodes ferroportin. Onset is late. Unlike all other varieties of hemochromatosis, iron storage in most cases affects reticuloendothelial rather than parenchymal cells [Montosi et al 2001, Njajou et al 2001]. Recently, two types of ferroportin disease have been recognized. The more common, “ferroportin disease,” is caused by mutations that reduce the iron export from

macrophages resulting in macrophage iron accumulation and low-normal transferrin saturation [Schimanski et al 2005]. Less common are hepcidin-resistant mutations that permit continued export of iron from macrophages and result in disease that resembles *HFE*-associated hereditary hemochromatosis, with high transferrin saturation and iron in hepatocytes [Drakesmith et al 2005, Wallace & Subramaniam 2007]. Some persons have an intermediate phenotype with a mixed pattern of liver iron accumulation. Inheritance is autosomal dominant.

Aceruloplasminemia is characterized by iron accumulation in the brain and the visceral organs, manifest as retinal degeneration, diabetes mellitus, and neurologic disease (movement disorders and ataxia) in individuals older than age 25 years. Early treatment with iron chelators can diminish iron accumulation and ameliorate symptoms. Aceruloplasminemia is caused by the complete lack of ceruloplasmin ferroxidase activity resulting from mutations in the *CP* gene that encodes ceruloplasmin. Inheritance is autosomal recessive.

African iron overload was originally described in Africans who drink a traditional beer brewed in non-galvanized steel drums. The disease does not develop in all beer drinkers, suggesting the existence of a genetic susceptibility. A missense change (NP_055400.1:p.Gln248His; NM_014585.4:c.744G>T) in the *SLC40A1* gene encoding ferroportin has been reported in Africans and African-Americans with iron overload by independent groups [Beutler et al 2003, Gordeuk et al 2003], but the functional effect of this mutation in vitro is controversial [Drakesmith et al 2005, McNamara et al 2005, Barton et al 2007]. In the large HEIRS study the association of increased serum ferritin concentration and the polymorphism was found only in males [Rivers et al 2007].

In neonatal hemochromatosis iron overload occurs in the fetus, likely secondary to different causes. At birth, liver failure dominates the clinical picture. The disease is extremely severe, often fatal, unless liver transplantation is performed. Inheritance is unknown. Recently, an immunologic pathogenesis has been proposed for recurrent cases because treatment of at-risk pregnancies with high-dose IV IGg resulted in significant improvement of the outcome [Whitington & Hibbard 2004].

Secondary Iron Overload Disorders

Secondary iron overload disorders include iron excess resulting from different conditions. The most severe disorders result from transfusions for chronic anemia such as beta-thalassemia or sickle cell disease. Secondary iron overload may result from ingested iron in foods, cookware, and medicines, as well as parenteral iron from iron injections.

This group also includes a range of liver diseases associated with parenchymal liver disease (e.g., alcoholic liver disease, acute viral hepatitis or chronic hepatitis C, neoplasia, porphyria cutanea tarda) and inflammatory disorders such as rheumatoid arthritis (which are questionable because inflammatory disorders are not true iron-loading disorders).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with *TFR2*-related hereditary hemochromatosis (*TFR2*-HHC), the following evaluations are recommended:

- Liver biopsy for evaluation of abnormal liver function tests and establishing prognosis. No recommendations are available for liver biopsy in *TFR2*-HHC; however, it seems appropriate to follow the recommendation for *HFE*-associated hereditary hemochromatosis for liver biopsy when serum ferritin concentration is greater than 1000 ng/mL and/or when hepatomegaly is present [Guyader et al 1998].

- Serum concentration of gonadotropins (FSH and LH) to assess pituitary function. Depending on the results, a GnRH stimulation test may be necessary.
- Serum concentration of testosterone to assess testicular function; serum concentration of estradiol to assess ovarian function
- Radiographs of the affected joint(s) to assess persistent arthralgia or arthropathy
- Cardiac evaluation (ECG and echocardiography) for all symptomatic individuals and those with severe iron overload
- Screening for diabetes mellitus by fasting serum glucose concentration and oral glucose tolerance test (OGTT)

Treatment of Manifestations

Individuals with increased serum ferritin concentration should be treated by the same protocol as for *HFE*-associated hereditary hemochromatosis.

Therapeutic phlebotomy. Periodic phlebotomy (i.e., removal of a unit of blood) is a simple, inexpensive, safe, and effective way to remove excess iron. Each unit of blood (400-500 mL) with a hematocrit of 40% contains approximately 160-200 mg of iron.

The usual therapy is weekly phlebotomy; however, twice weekly phlebotomy may be useful initially to accelerate iron depletion. On average, men require removal of twice as many units of blood as women.

Weekly phlebotomy is carried out until the hematocrit is 75% of the baseline hematocrit. At this point, the serum ferritin concentration is usually measured. Once the serum ferritin concentration is 100 ng/mL or lower, it should be measured following each phlebotomy or every other phlebotomy [Barton et al 1998]:

- Once the serum ferritin concentration is lower than 50 ng/mL, monitoring serum ferritin concentration every three to four months is adequate.
- If the serum ferritin concentration is 50 ng/mL or higher despite a significant reduction in hematocrit, phlebotomies need to be spaced further apart.

Note: Although experience is limited because of the small number of affected individuals identified worldwide, transferrin saturation remains high in *TFR2*-related hereditary hemochromatosis when serum ferritin concentration is low (<50 ng/mL), even after intensive phlebotomy [Camaschella & Roetto, unpublished observation].

Maintenance therapy. The goal is to maintain serum ferritin concentration below 50 ng/mL and transferrin-iron saturation below 50%. Phlebotomy to prevent reaccumulation of iron is performed about every three to four months for men and once or twice a year for women.

Iron chelation therapy is not recommended unless an individual has an elevated serum ferritin concentration and concomitant anemia that makes therapeutic phlebotomy impossible. Iron chelators such as subcutaneous desferrioxamine are used as a first choice in case of concomitant anemia [Riva et al 2004] or cardiac dysfunction.

Note: At present, oral iron chelators are not available to treat hemochromatosis.

Treatment of clinical complications

- **Cirrhosis** should be treated and followed up as in other conditions. Although cirrhosis is not reversible by phlebotomy, individuals with cirrhosis benefit from iron removal in that it reduces the risk of hepatocellular cancer.
- **Hypogonadism** is irreversible and requires lifelong hormone replacement therapy in males and females. Use of gonadotropins has successfully restored fertility and induced pregnancy in women who have been treated for other forms of hemochromatosis.
- **Arthropathy** requires nonsteroidal anti-inflammatory drugs (NSAIDs) and is barely influenced by phlebotomy. In some cases, joint replacement has been performed.
- **Cardiac failure** is treated with diuretics, ACE inhibitors, cardiac glycosides, and iron chelation by intravenous or subcutaneous deferioxamine.
- **Diabetes mellitus** may require lifelong insulin treatment. Iron removal may improve control of diabetes mellitus but cannot reestablish normal glucose metabolism.

Prevention of Primary Manifestations

In affected individuals with increased serum ferritin concentration, prevention of primary manifestations is accomplished by weekly phlebotomy to deplete iron stores (see Treatment of Manifestations).

Surveillance

Once the serum ferritin concentration is lower than 50 ng/mL, monitoring serum ferritin concentration every three to four months is adequate.

Although hepatocellular carcinoma has not been reported in *TFR2*-associated hereditary hemochromatosis, surveillance for its development should be performed in persons with cirrhosis by monitoring liver ultrasound examinations and serum concentrations of alpha-fetoprotein, as in persons with cirrhosis with *HFE*-associated hereditary hemochromatosis.

Agents/Circumstances to Avoid

- Medicinal iron
- Mineral supplements
- Excess vitamin C
- Uncooked seafood (because of the risk of infection from microorganisms thriving under conditions of excess iron)

For those with hepatic involvement, alcohol intake should be restricted because it increases iron absorption and is toxic to the hepatocytes.

Testing of Relatives at Risk

If the disease-causing mutations in the family are known, it is appropriate to offer molecular genetic testing to at-risk relatives, to allow early diagnosis and treatment.

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

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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

TFR2-related hereditary hemochromatosis (*TFR2*-HHC) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes and thus carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic and do not have abnormalities of iron parameters.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3
- Heterozygotes (carriers) are asymptomatic and do not have abnormalities of iron parameters.

Offspring of a proband. The offspring of an individual with *TFR2*-HHC are obligate heterozygotes (carriers) for a disease-causing mutation in the *TFR2* gene.

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

Carrier Detection

Carrier testing using molecular genetic testing for at-risk family members is available on a clinical basis once the mutations have been identified in the family.

Carrier testing using biochemical testing is not possible because iron parameters are normal in heterozygotes.

Related Genetic Counseling Issues

See Management for information on testing at-risk relatives for the purpose of early diagnosis and treatment

Family planning

- The optimal time for determination of genetic risk 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 or are carriers, or are at risk of being affected or carriers.

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 when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

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

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

Requests for prenatal testing for conditions such as *TFR2*-HHC that do not affect intellect and have effective treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD). PGD may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Note: It is the policy of GeneReviews to include information on prenatal testing that is available from laboratories listed in the GeneTests Laboratory Directory; inclusion does not necessarily reflect the endorsement of its use by the author(s), editor(s), or reviewer(s).

Molecular Genetics

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

Table A. Molecular Genetics of *TFR2*-Related Hereditary Hemochromatosis

Gene Symbol	Chromosomal Locus	Protein Name
TFR2	7q22	Transferrin receptor protein 2

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 *TFR2*-Related Hereditary Hemochromatosis

604250	HEMOCHROMATOSIS, TYPE 3; HFE3
604720	TRANSFERRIN RECEPTOR 2; TFR2

Table C. Genomic Databases for *TFR2*-Related Hereditary Hemochromatosis

Gene Symbol	Entrez Gene	HGMD
TFR2	7036 (MIM No. 604720)	TFR2

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

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

TFR2-encoded protein is highly expressed in the hepatocytes and its function is likely related to the hepcidin pathway that regulates iron homeostasis.

The hepatic peptide hepcidin is a circulating hormone that regulates the absorption of dietary iron from the duodenum. Hepcidin expression is inappropriately decreased in hereditary hemochromatosis and is abnormally increased in the anemia of chronic diseases. Other hepatic proteins essential for normal iron homeostasis, including HFE, transferrin receptor protein 2 (TfR2), and hemojuvelin, function at least in part by modulating the expression of hepcidin [Fleming 2005].

Individuals with homozygous *TFR2* mutations have increased intestinal iron absorption that causes iron overload. Low/absent levels of urinary hepcidin have been reported in *TFR2*-related hereditary hemochromatosis [Nemeth et al 2005], suggesting that *TFR2* is a modulator of hepcidin. A similar finding of down-regulation (or lack of up-regulation following iron loading) of mRNA of hepcidin in liver has been documented in mice with a *tfr2*^{Y245X} targeted mutation [Kawabata et al 2005] and in *tfr2*-knockout mice [Wallace et al 2005].

Normal allelic variants: *TFR2* is 21 kb long and consists of 18 exons. There are two main alternatively spliced variants (see Figure 1):

- Alpha, corresponding to transcription of all exons. Alpha-*TFR2* is prevalently and highly expressed in hepatocytes. Two alpha-*TFR2* cDNAs of 2.9 and 2.3 kb are recognized. The first (Genbank accession AF053356) lacks 81 nucleotides in exon 8 and is 18 nucleotides longer in exon 18 [Glockner et al 1998] when compared to the second (Genbank accession AF067864) [Kawabata et al 1999].
- Beta, which has an in-frame transcription start site in exon 4 [Kawabata et al 1999]. Beta-*TFR2* cDNA lacks exons 1-3 and has 142 additional bases at its 5' end. Beta *TFR2* is expressed ubiquitously at very low levels.

Several exonic normal DNA variants have been described (see Figure 1); they are either silent or missense mutations present also in control individuals [Lee et al 2001,Biasiotto et al 2008]. Two nucleotide normal variants have been identified in the non-coding region of *TFR2* [Meregalli et al 2000,Biasiotto et al 2008].

Pathologic allelic variants: Fifteen causal mutations have been reported; most are rare or private [Roetto et al 2002, Lee & Barton 2006, Hsiao et al 2007, Biasiotto et al 2008] (see Table 2):

- The most frequent mutation is p.Tyr250X, identified in four different Italian families [Camaschella et al 2000, Piperno et al 2004] who live in the same geographical area and thus may be distantly related.
- p.Arg30ProfsX31 has been found in a single large Italian family [Roetto et al 2002].
- p.Met172Lys has been found in two unrelated Italian families [Roetto et al 2001, Majore et al 2006].
- A recurrent mutation is a deletion of 12 nucleotides in a 12-nucleotide repeat in exon 16, which results in a four-amino acid deletion p.Ala621_Gln624del (see Figure 1) [Girelli et al 2002,Hattori et al 2003].
- The private mutation p.Arg105X was characterized in two affected young siblings from France [Le Gac et al 2004].
- Two novel mutations (p.Leu490Arg and p.Ser556AlafsX6) were characterized in Japanese individuals [Koyama et al 2005].
- p.Gln317X was reported in association with *HFE* p.Cys282Tyr and p.His63Asp compound heterozygosity in two siblings with a juvenile phenotype and in association with wild-type *HFE* in a brother with a classic type of HHC [Pietrangelo et al 2005]. See Genotype-Phenotype Correlations for *HFE* mutation references.
- Two novel *TFR2* mutations (p.Arg396X and p.Gly792Arg) associated to an already characterized polymorphic variant (p.Arg455Gln) [Hofmann et al 2002] have been found in a single Scottish individual.
- A new mutation missense mutation has been characterized in a Taiwanese woman with the disease [Hsiao et al 2007].
- In an Italian mutation study, one subject compound heterozygous for two new mutations (p.Asn411del and p.Ala444Thr) together with two siblings homozygous for a new causal variant (c.713-1G>A) have been recently identified [Biasiotto et al 2008].

For more information, see Genomic Databases table and Figure 1.

Table 2. *TFR2* Allelic Variants Discussed in This *GeneReview*

Class of Variant Allele	DNA Nucleotide Change (Alias [1])	Protein Amino Acid Change (Alias [1])	Reference Sequence	Reference
Normal	c.97C>A	p.His33Asn	NM_003227.3 NP_003218.2	[Biasiotto et al 2008]
	c.224C>T	p.Ala75Val		[Biasiotto et al 2003]
	c.158+49C>A (IVS3+49)	--		[Biasiotto et al 2008]
	c.1851C>T (1878C>T)	p.(=) [2] (Ala617Ala)		[Meregalli et al 2000]
	c.714C>G	p.Ile238Met		[Lee et al 2001]
	c.1364G>A	p.Arg455Gln		[Hofmann et al 2002]
	c.1770C>T	p.(=) (Asp590Asp)		[Lee et al 2001]
	c.1851C>T	p.(=) (Ala617Ala)		[Lee et al 2001]
	c.2228C>T	p.Ala743Val		[Lee et al 2001]

Pathologic	c.64G>A	p.Val22Ile		[Biasiotto et al 2003]
	c.88_89insC (ins88C)	p.Arg30ProfsX31 (E60X)		[Roetto et al 2001]
	c.313C>T	p.Arg105X (E60X)		[Le Gac et al 2004]
	c.515T>A	p.Met172Lys		[Roetto et al 2001]
	c.750C>G	p.Tyr250X		[Camaschella et al 2000]
	c.949C>T	p.Gln317X		[Pietrangelo et al 2005]
	c.1186C>T	p.Arg396X		[Lee & Barton 2006]
	c.1231_1233del	p.Asn411del		[Biasiotto et al 2008]
	c.1330G>A	p.Ala444Thr		[Biasiotto et al 2008]
	c.1403G>A	p.Arg468His (Arg481His)		[Hsiao et al 2007]
	c.1469T>G	p.Leu490Arg		[Koyama et al 2005]
	c.1665delC	p.Ser556AlafsX6 (Val561X)		[Koyama et al 2005]
	c.1861_1872del12	p.Ala621_Gln624del (AVAQ621-624del)		[Girelli et al 2002]
	c.2069A>C	p.Gln690Pro		
	c.713-1G>A (IVS17+5636)	--		[Biasiotto et al 2008]
	c.2374G>A	p.Gly792Arg		[Lee & Barton 2006]

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (http://www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

2. The designation p.(=) means that no effect on protein level is expected.

Normal gene product: *TFR2* is a type II transmembrane glycoprotein characterized by short intracellular and transmembrane domains and a large extracellular domain. The *TFR2* full-length transcript (the alpha form) originates an 801-amino acid transmembrane protein. Residues 1-80 correspond to the cytoplasmic domain, residues 81-104 correspond to the transmembrane, and amino acids 105-801 correspond to the extracellular domain. Cysteines 89-98 and 108-111 are involved in disulfide bonds, likely responsible for *TFR2* homodimerization. A YQRV amino acid motif in the cytoplasmic domain, similar to the internalization signal (YTRF) of transferrin receptor (TFRC), could have the same function.

TFR2 is highly expressed in hepatoma (HEPG2) and in erythroleukemia cell lines (K562) [Kawabata et al 1999]. It is expressed in the liver, especially in the hepatocytes, and at low levels in Kuppfer cells [Zhang et al 2004].

Alpha-TFR2 binds and internalizes transferrin. However, binding occurs at low affinity (25- to 30-fold lower) [Kawabata et al 2000], as compared to that of the transferrin receptor (TFRC). Alpha-TFR2 protein shows significant amino acid homology with TFRC and the prostate-specific membrane antigen (PSMA), especially in the extracellular portion [Kawabata et al 1999].

Beta-TFR2 lacks the cytoplasmic and transmembrane domains and could be an intracellular protein.

TFR2 has no IRE elements in its 5' or 3' UTR and is not transcriptionally regulated by iron. *TFR2* does not bind *HFE* in vitro because residues involved in *HFE* binding in TFRC are not conserved in *TFR2* [West et al 2000]. Analysis of *TFR2* distribution pattern in humans revealed by immunohistochemistry showed strong expression in liver and duodenal cells [Deaglio et al 2002]. At this level, an interaction has been documented with the *HFE*-encoded protein by immunohistochemical techniques [Griffiths & Cox 2003]. *TFR2* is also expressed by early erythroid progenitors but not by bone marrow precursors [Calzolari et al 2004].

TFR2-encoded protein in H2 cell lines is stabilized by diferric transferrin, which increases *TFR2*-encoded protein half-life [Johnson & Enns 2004, Robb & Wessling-Resnick 2004]. In addition, *TFR2* mediates a biphasic pattern of transferrin uptake associated with ligand delivery to multivesicular bodies [Robb et al 2004]. Tfr2 stabilization by transferrin reduces Tfr2 lysosomal degradation and directs *TFR2* toward the recycling endosome [Johnson et al 2007].

The cytoplasmic domain is that involved in membrane stabilization after TF binding [Chen & Enns 2007].

Two animal models exist: (1) A *tfr2*-deficient mouse homozygous for *tfr2*^{Y245X} [Fleming et al 2002], a mutation orthologous to the human p.Tyr250X [Camaschella et al 2000], the *tfr2*-knockout mouse [Wallace et al 2005], and a conditional hepatic knock out [Wallace et al 2007]. All these mice show iron overload in liver and other organs with the spleen relatively free of iron as in the human disorder [Fleming et al 2002]. (2) The *tfr2*-null (knockout) shows significant iron overload and is unable to increase hepcidin in response to iron [Wallace et al 2005].

Abnormal gene product: The pathologic variants produce a truncated protein or an abnormally structured protein (e.g., p.Ala621_Gln624del, p.Leu490Arg, p.Gln690Pro). The mutation p.Met172Lys is of interest because it causes a missense in the alpha form but changes the methionine that is the putative initiation codon of beta*TFR2* [Roetto et al 2001, Majore et al 2006].

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.

CDC: Iron Overload and Hemochromatosis, Frequently Asked Questions
www.cdc.gov/nccdphp/dnpa/hemochromatosis/faq.htm

National Digestive Diseases Information Clearinghouse (NDDIC)
Hemochromatosis

National Human Genome Research Institute
Learning About Hereditary Hemochromatosis

National Library of Medicine Genetics Home Reference
Hemochromatosis, type 3

NCBI Genes and Disease
Hereditary hemochromatosis

Iron Disorders Institute, Inc
PO Box 3021
Greenville, SC 29602
Phone: 864-241-0111
Fax: 864-244-2104
Email: irondis@aol.com
www.irondisorders.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

- 5 August 2008 (cd) Revision: prenatal diagnosis available clinically
- 15 May 2008 (me) Comprehensive update posted to live Web site
- 7 August 2006 (ar) Revision: change in mutation nomenclature from AVAQ594-597del to AVAQ621-624del
- 5 December 2005 (ar) Revision: targeted mutation analysis clinically available; mutation scanning no longer available
- 29 August 2005 (me) Review posted to live Web site
- 1 February 2005 (ar) Original submission

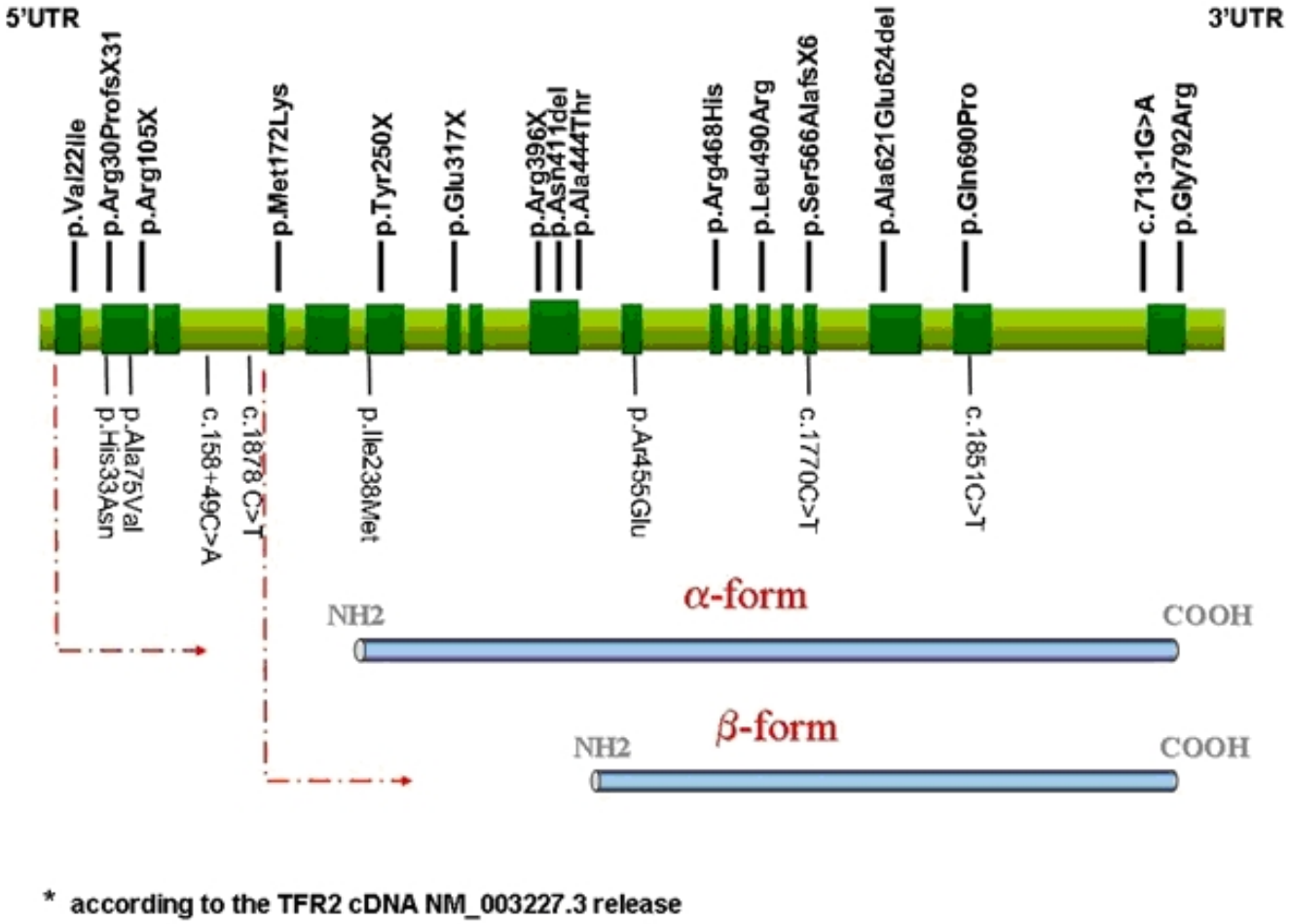

Figure 1. Schematic representation of the localization of *TFR2* mutations. Causal mutations are illustrated in bold above the gene; exonic normal variants are marked below the gene (see Table 2). The two alternatively spliced *TFR2* transcripts are also shown. Alternative transcription start sites are indicated by the dotted arrow lines.