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TFR2-Related Hemochromatosis

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Summary

Clinical characteristics

TFR2-related hemochromatosis (*TFR2*-HC) 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*-related hemochromatosis. The majority of individuals present with signs and symptoms of iron overload in the third decade (e.g., weakness, fatigue, abdominal pain, hepatomegaly, arthritis, arthralgia, and progressive increase in skin pigmentation). Others present as young adults with nonspecific symptoms and abnormal serum iron studies or as adults with abnormal serum iron studies and signs of organ involvement including cirrhosis, diabetes mellitus, arthropathy, hypogonadism, cardiomyopathy, and increase in skin pigmentation.

Diagnosis/testing

The diagnosis of *TFR2*-HC is established in a proband with biallelic pathogenic variants in *TFR2* identified by molecular genetic testing.

Management

Targeted therapy: In order to prevent iron overload-related complications, removal of excess iron by routine phlebotomy to maintain serum ferritin concentration at 50 ng/mL or lower and transferrin-iron saturation below 50%; iron chelation therapy as needed in those with anemia.

Supportive care: Vaccination for hepatitis A and B; therapy to prevent cirrhosis complications and liver decompensation including endoscopic surveillance of varices and prophylaxis with nonselective beta-blockers; salt restriction and diuretics for ascites with paracentesis and shunts as needed; antibiotics for spontaneous bacterial peritonitis; low protein diet for hepatic encephalopathy with lactulose and rifaximin as needed; hormone replacement therapy for hypogonadism; gonadotropins for fertility/pregnancy; routine treatment for

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diabetes mellitus and cardiac failure; nonsteroidal anti-inflammatory drugs and joint replacement for arthropathy.

Surveillance: Serum iron, transferrin, transferrin saturation, and ferritin concentration every six to 12 months once serum ferritin concentration is lower than 50 ng/mL. Serum AFP and liver ultrasound in individuals with cirrhosis every six months to assess for hepatic complications and for early detection of hepatocarcinoma. Individuals with hypogonadism, diabetes mellitus, and cardiac failure should have surveillance for complications related to the specific organ failure.

Agents/circumstances to avoid: Medicinal iron and nutritional supplements containing iron, excessive alcohol intake, vitamin C supplements, uncooked seafood, and lifestyle-related behaviors that increase the risk of viral hepatitis infection.

Evaluation of relatives at risk: It is appropriate to evaluate apparently asymptomatic older and younger sibs of an affected individual by molecular genetic testing of the *TFR2* pathogenic variants found in the family in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Pregnancy management: Phlebotomy can be paused in pregnant women with mild-to-moderate iron overload due to fetal utilization of maternal iron.

Genetic counseling

TFR2-HC is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *TFR2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier. Once the *TFR2* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

An algorithm for the diagnosis of *TFR2*-related hemochromatosis (*TFR2*-HC) has been developed (see Figure 1). See also Brissot [2016], Powell et al [2016], Zoller & Henninger [2016], European Association for the Study of the Liver [2022], and Girelli et al [2022].

Suggestive Findings

TFR2-HC **should be suspected** in a proband with clinical features, symptoms, and laboratory features associated with iron overload in whom *HFE*-related hemochromatosis has been excluded.

Clinical features and symptoms of iron overload

- Weakness, chronic fatigue
- Abdominal pain
- Hepatomegaly
- Cirrhosis, hepatocellular carcinoma
- Endocrine manifestations, including diabetes mellitus, hypogonadotropic hypogonadism (decreased libido and impotence in men, amenorrhea in women)
- Cardiomyopathy, EKG abnormalities (conduction disturbances)
- Arthritis (especially if involving the metacarpophalangeal joint), arthralgia
- Progressive increase in skin pigmentation

Laboratory features

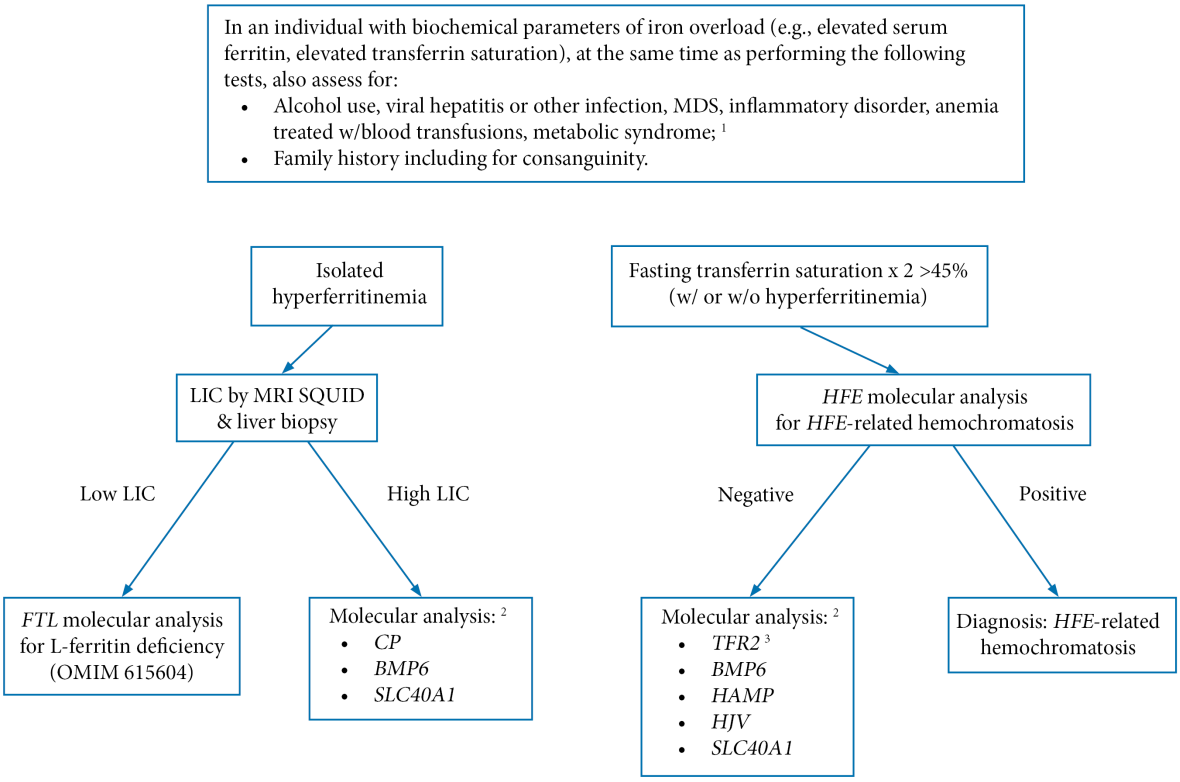

Figure 1. Flowchart for diagnosis of *TFR2*-related hemochromatosis

MDS = myelodysplastic syndrome; LIC = liver iron content

1. Obesity, insulin resistance, dyslipidemia, hypertension

2. See Differential Diagnosis.

3. Topic of this *GeneReview*

- **Transferrin saturation** >45% (normal range: 20%-35% saturation in males and females)
- **Serum ferritin concentration** usually >200 µg/L in females and >300 µg/L in males. Normal ranges:
  - Children and adolescents: 15-150 µg/L
  - Adult females: 20-200 µg/L
  - Adult males: 20-300 µg/L
- Elevated liver enzymes and/or abnormal liver function tests
- Hyperglycemia

Liver biopsy. Findings on liver biopsy have been reported in some individuals with *TFR2*-HC [Bardou-Jacquet et al 2013, Joshi et al 2015, Badar et al 2016, Peters at al 2017, Sandhu et al 2018, Khayat et al 2019, Hernández et al 2021, Tang et al 2022]. Liver biopsy is used to assess:

- Histology; fibrosis or cirrhosis
- Elevated liver iron concentration (normal values: 10-35 µmol/g dry liver weight or 0.56-1.96 mg/g dry liver weight):
  - Mild. 70-99 µmol/g dry liver weight or 3.9-5.5 mg/g dry liver weight
  - Moderate. 100-200 µmol/g dry liver weight or 5.6-11.2 mg/g dry liver weight
  - Severe. >200 µmol/g dry liver weight or >11.2 mg/g dry liver weight

Imaging. Noninvasive techniques including MRI and SQUID (superconducting quantum interference device) developed to quantitate liver iron concentration have been applied to *TFR2*-HC [Biasiotto et al 2008, Joshi et al 2015, Badar et al 2016, Hernández et al 2021, Ravasi G et al 2021, Tang et al 2022]. Due to high installation and maintenance costs, clinical use of SQUID to quantitate liver iron may not be available.

Hepcidin evaluation. Individuals with *TFR2*-HC have decreased hepcidin concentrations in plasma and urine (similar to other types of autosomal recessive hemochromatosis). Hepcidin concentration in plasma and urine can be measured by mass-spectrometry-based assay and normalized for sex and age [Piubelli et al 2017].

Establishing the Diagnosis

The diagnosis of *TFR2*-HC **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *TFR2* identified by molecular genetic testing (see Table 1).

Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Single-gene testing. Sequence analysis of *TFR2* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. 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 exon and whole-gene deletions or duplications.

A multigene panel that includes *TFR2* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of *TFR2*-HC has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

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

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
TFR2	Sequence analysis [3]	>99% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. McDonald et al [2015], Badar et al [2016], Faria et al [2016], Lanktree et al [2017], Peters et al [2017], and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

TFR2-related hemochromatosis (*TFR2*-HC) is characterized by deregulated, increased intestinal iron absorption resulting in iron accumulation in the liver, heart, pancreas, and endocrine organs [Camaschella & Poggiali 2009].

Age of onset in individuals with *TFR2*-HC is earlier than in individuals with *HFE*-related hemochromatosis (*HFE*-HC). Six individuals with childhood onset (range of onset: age 2-13 years) have been reported [Piperno et al 2004, Biasiotto et al 2008, Joshi et al 2015, Ravasi et al 2015, Khayat AA et al 2019], all with increased transferrin saturation and serum ferritin concentration. None of the children had clinical symptoms, except for fatigue in a 14-year-old boy [Joshi et al 2015]. Long-term follow up (>10 years) in two sibs diagnosed with *TFR2*-HC at age 12 and 13 years revealed no clinical features of iron overload when phlebotomy treatment was started early and continued over time [De Gobbi, unpublished data]. However, the majority of the individuals present with signs of iron overload from the third decade, as young adults with nonspecific symptoms and abnormal serum iron indices [Biasiotto et al 2008, Gérolami et al 2008, Del-Castillo-Rueda et al 2012, Peters et al 2017, Sandhu et al 2018] or as adults with abnormal serum iron studies and signs of organ involvement (e.g., liver fibrosis or cirrhosis, diabetes, hypogonadism, cardiomyopathy, and arthropathy) [Del-Castillo-Rueda et al 2012, Joshi et al 2015, Badar et al 2016, Peters et al 2017, Wang et al 2017, Sandhu et al 2018].

Liver disease. When *TFR2*-HC is progressive, complications can include cirrhosis and all its sequelae due to portal hypertension and liver dysfunction: ascites, varices and variceal bleeding, hypersplenism, hepatic

encephalopathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, cirrhotic cardiomyopathy, coagulation disorders, and hepatocellular carcinoma (HCC). However, while the distribution of liver iron deposition is similar to that seen in *HFE*-HC (mainly in hepatocytes with a decreasing gradient from portal to centrolobular areas), HCC has not been observed in the limited number of affected individuals reported to date. Even in a large series of individuals with HCC, the subgroup with increased liver iron concentration did not have *TFR2* pathogenic variants [Funakoshi et al 2016].

Endocrine manifestations. Hypogonadotropic hypogonadism usually starts during adolescence or between age 20 and 30 years and leads to decreased libido and impotence in men and amenorrhea in women. In men, additional clinical manifestations can include a decrease of androgen-dependent hair growth, testicular atrophy, and azoospermia. Severe 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; no data are available regarding treatment for infertility in women with *TFR2*-HC. Diabetes mellitus results from loss of insulin secretory capacity due to iron-induced fibrosis of the islets of Langerhans and therefore requires treatment with insulin [Tang et al 2022]. When present, the onset of diabetes mellitus usually occurs between age 30 and 40 years. Iron removal via phlebotomy may improve control of diabetes mellitus but cannot reestablish normal glucose metabolism.

Cardiac manifestations. If present, cardiomyopathy is characterized by the classic features of cardiac dysfunction caused by increased deposition of iron: dilated cardiomyopathy with dilated ventricles and reduced fractional shortening resulting in reduced ejection fraction and predisposition to arrhythmias. In the advanced stage of cardiac involvement, EKG abnormalities can be present (low QRS complex voltage and nonspecific ST and T wave), and iron deposition in the conduction system may cause atrioventricular blocks. The common signs and symptoms of congestive heart failure are present and should be managed with standard medical therapy for heart failure. An implantable cardioverter defibrillator for prevention of fatal arrythmias can be used in those with severe cardiac disease. Lowering myocardial iron content through phlebotomy or iron chelation can improve left ventricular function.

Joint manifestations. Severe joint involvement has been reported [Ricerca et al 2009, Peters et al 2017]. Arthralgia can involve multiple sites but mainly affects metacarpophalangeal joints causing severe pain, deformation of hands, and functional impairment. After arthritis and arthralgia have developed progressive structural damage may continue even after the removal of systemic iron excess with phlebotomy. Some individuals have required joint replacement for severe joint disease.

Prognosis. Disease progression is slower than in juvenile hereditary hemochromatosis [De Gobbi et al 2002]. If *TFR2*-HC is diagnosed early and treated appropriately with phlebotomy, individuals with *TFR2*-HC will have normal life expectancy. Similar to *HFE*-HC, the most important factors that can influence survival are the onset of cirrhosis, diabetes, and/or cardiomyopathy.

Genotype-Phenotype Correlations

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

Inheritance of compound heterozygosity for the *HFE* pathogenic variants p.Cys282Tyr (NM_000410.3:c.845G>A) and p.His63Asp and homozygosity for the *TFR2* pathogenic variant p.Gln317Ter produced a phenotype of juvenile hemochromatosis in a single family [Pietrangelo et al 2005].

Individuals with *TFR2*-HC who are also heterozygous for an *HFE* pathogenic variant do not seem to have a more severe phenotype. In fact, a male homozygous for *TFR2* pathogenic variant p.Trp781Ter and heterozygous for *HFE* pathogenic variant p.Cys282Tyr presented at age 46 years with a classic *TFR2*-HC phenotype

(hyperferritinemia, severe hepatic iron accumulation detected by MRI, and chronic arthropathy) [Hernández et al 2021].

Penetrance

The penetrance of *TFR2*-HC is less than 100% and can be influenced by genetic (e.g., hemoglobinopathies) or environmental factors (e.g., chronic hepatitis, low dietary iron intake, and chronic bleeding). The oldest individual to be diagnosed with *TFR2*-HC is an individual diagnosed at age 82 years homozygous for *TFR2* variant p.Arg30ProfsTer31 [Roetto et al 2001]. The youngest individual is a child with Alagille syndrome and homozygous for *TFR2* pathogenic variant p.Ser470Ile diagnosed with iron overload at age two years [Khayat et al 2019]. In a family reported by Roetto et al [2001], one middle-aged female homozygous for *TFR2* pathogenic variant p.Arg30ProfsTer31 had iron deficiency and a history of low dietary iron intake and hypermenorrhea. Girelli et al [2002] also found iron deficiency in a young female homozygous for p.Ala621_Gln624del who had a history of anorexia and *Helicobacter pylori*-related chronic gastritis.

Nomenclature

TFR2-HC is also known as hemochromatosis type 3 or HFE3; however, the term "HFE3" seems inappropriate because *HFE* has no role in *TFR2*-HC. "*TFR2*-related hemochromatosis" is the preferred term in the hemochromatosis classification developed by the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) [Girelli et al 2022].

Prevalence

TFR2-HC is rare, with pathogenic allele frequencies estimated within the range of 0.000008 to 0.0002 [Wallace & Subramaniam 2016]. Just over 50 affected individuals have been reported worldwide, most commonly of European descent (mainly in Italy but also in France, Portugal, and Spain). According to Sandhu et al [2018], the most frequent *TFR2* pathogenic variants are p.Tyr250Ter, p.Glu60Ter, and p.Met172Lys. In individuals from Sicily, allelic frequency of p.Tyr250Ter was estimated to be 0.45% [De Gobbi et al 2001].

In Japan, where hemochromatosis is rare and heterogeneous, it has been proposed that *TFR2*-HC is the most frequent form of hereditary hemochromatosis [Hayashi et al 2006]; however, studies are limited. The most frequent pathogenic variant in individuals of Japanese descent is p.Ala621_Gln624del.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TFR2*.

Differential Diagnosis

TFR2-related hemochromatosis (*TFR2*-HC) needs to be distinguished from other primary iron overload disorders as well as from secondary iron overload disorders (see Figure 1).

Primary Iron Overload Disorders

Genes associated with primary overload disorders (i.e., disorders characterized by increased absorption of iron from a normal diet) are listed in Table 2.

No studies have evaluated the prevalence of *TFR2* pathogenic variants in individuals with non-*HFE*-related hemochromatosis.

Table 2. Primary Iron Overload Disorders to Consider in the Differential Diagnosis of *TFR2*-Related Hemochromatosis

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/*TFR2*-HC	Distinguishing from *TFR2*-HC
BMP6	*BMP6*-related iron overload (OMIM 620121)	AD	• Biochemical features of iron overload • Liver iron accumulation	• Normal transferrin saturation in some • Mild-to-moderate late onset of iron overload
CP	Aceruloplasminemia	AR	• Hyperferritinemia • Diabetes mellitus	• Anemia • Iron deposition in hepatic reticuloendothelial (not parenchymal) cells • Brain iron accumulation manifesting as retinal degeneration & neurologic disease (movement disorders & ataxia)
HFE	*HFE*-related hemochromatosis	AR	Biochemical & clinical features of iron overload	• Lower penetrance • Later onset
HAMP *HJV*	Juvenile hemochromatosis	AR	Biochemical & clinical features of iron overload	• Full penetrance • Earlier onset • More severe clinical manifestations, esp cardiomyopathy & hypogonadotropic hypogonadism
SLC40A1	*SLC40A1*-related hemochromatosis assoc w/ gain-of-function pathogenic variants (OMIM 606069)	AD	Biochemical & clinical features of iron overload	Later-onset clinical manifestations of iron overload
	SLC40A1-related hemochromatosis assoc w/ loss-of-function pathogenic variants (OMIM 606069)	AD	Hyperferritinemia	• At early stage: anemia & low transferrin saturation • Iron deposition in hepatic reticuloendothelial (not parenchymal) cells • Reduced tolerance to phlebotomy

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; *TFR2*-HC = *TFR2*-related hemochromatosis

Primary overload disorders of unknown genetic cause:

- **African iron overload** (OMIM 601195). Similar to *TFR2*-HC, African iron overload is associated with liver iron accumulation in reticuloendothelial and parenchymal cells and cirrhosis. Distinguishing features of African iron overload include susceptibility to tuberculosis and other infections and a lower frequency of cardiomyopathy and diabetes. African iron overload is characteristically diagnosed in individuals with an excessive intake of dietary iron from drinking beer brewed in non-galvanized steel drums and a genetic predisposition to iron loading (the molecular basis underlying this predisposition is unknown).
- **Neonatal hemochromatosis** (congenital alloimmune hepatitis) (OMIM 231100). Similar to *TFR2*-HC, neonatal hemochromatosis is associated with iron deposition in multiple organs (liver, pancreas, heart, and endocrine glands). Distinguishing features of neonatal hemochromatosis include alloimmune pathogenesis and prenatal onset (i.e., iron overload occurs in the fetus). Severe liver failure at birth is seen in neonatal hemochromatosis and the disorder is often fatal without liver transplant.

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, familial porphyria cutanea tarda), metabolic dysfunction such as dysmetabolic iron overload syndrome, and inflammatory disorders such as rheumatoid arthritis or lupus erythematosus (of note, inflammatory disorders are not true iron overload disorders but are categorized in this group because hepcidin excess induced by inflammatory cytokines leads to the sequestration of iron in macrophages and other reticuloendothelial cells).

Management

No clinical practice guidelines for *TFR2*-related hemochromatosis (*TFR2*-HC) have been published. Management and treatment follow the guidelines established for *HFE*-related hemochromatosis (HFE-HC).

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *TFR2*-HC, the evaluations summarized in Table 3 are recommended (based on recommendations for *HFE*-HC) [Kowdley et al 2019, European Association for the Study of the Liver 2022], if not performed as part of the evaluation that led to the diagnosis.

Table 3. *TFR2*-Related Hemochromatosis: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Biochemical iron parameters	Serum iron, serum transferrin, transferrin saturation, & serum ferritin	
Liver disease	Biochemical profile of liver function: AST, ALT, ALP, bilirubin, & albumin	
	Liver biopsy for eval of abnormal liver function tests & establishing prognosis	In those w/serum ferritin >1,000 ng/mL, esp if there is underlying liver disease (e.g., alcohol abuse, viral hepatitis)
	Liver elastography to assess for hepatic fibrosis	
Endocrine	Serum gonadotropins (FSH & LH) to assess pituitary function	• At time of identification of iron overload • If LH &/or FSH are low, a GnRH stimulation test may be necessary.
	Serum testosterone to assess testicular function & serum estradiol to assess ovarian function	At time of identification of iron overload
	• Fasting serum glucose • Oral glucose tolerance test	At time of identification of iron overload to assess for diabetes mellitus
Cardiac	Cardiac eval incl EKG & echocardiography	In all persons, esp in those w/severe iron overload
Joint manifestations	Radiographs of affected joint(s) to assess persistent arthralgia or arthropathy	In those w/arthralgia

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *TFR2*-HC to facilitate medical & personal decision making

ALP = alkaline phosphatase; ALT = aminotransferase; AST = aspartate aminotransferase; FSH = follicle-stimulating hormone; GnRH = gonadotropin hormone-releasing hormone; LH = luteinizing hormone; MOI = mode of inheritance; *TFR2*-HC = *TFR2*-related hemochromatosis

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Individuals with increased serum ferritin concentration should be treated by the same protocol as for *HFE*-HC, and the following recommendations are mainly based on guidelines proposed for *HFE*-HC in Europe [European Association for the Study of the Liver 2022] and North America [Kowdley et al 2019]. However, since *TFR2*-HC may progress differently from *HFE*-HC, individualized treatment should be provided.

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

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 phlebotomy weekly or every two weeks; however, twice-weekly phlebotomy or erythrocytapheresis may be useful initially to accelerate iron depletion. Hematocrit or hemoglobin level should be assessed prior to each phlebotomy. In the initial stage of treatment, when serum ferritin is high, ferritin measurement should be performed approximately every ten phlebotomies.

Weekly phlebotomy is carried out until the serum ferritin concentration is 50 ng/mL or lower. If anemia is detected or hematocrit is reduced from the initial level by more than 20%, phlebotomy should be postponed.

As the target ferritin range of 50-100 ng/mL is approached, serum ferritin analysis may be repeated more frequently.

Note: Although experience is limited because of the small number of affected individuals identified worldwide, it should be noted that transferrin saturation can remain high in individuals with *TFR2*-HC when serum ferritin concentration is low (<50 ng/mL), even after intensive phlebotomy [Girelli et al 2011; Camaschella, Roetto, & De Gobbi, personal observations].

Maintenance therapy. The goal is to maintain serum ferritin concentration around 50 ng/mL and transferrin-iron saturation below 50%. Phlebotomy to prevent reaccumulation of iron is performed about every three to four months. However, the required frequency of therapeutic phlebotomy varies by individual.

Iron chelation therapy is not recommended unless an individual has an elevated serum ferritin concentration and concomitant anemia or cardiac dysfunction that makes therapeutic phlebotomy impossible. Subcutaneous desferrioxamine has been used in individuals with concomitant anemia alone [Riva et al 2004] or in combination with deferiprone [Tauchenová et al 2016]. A Phase I/II trial with the oral chelator deferasirox

demonstrated that this treatment is feasible, safe, and effective – although associated with a high incidence of gastrointestinal side effects [Phatak et al 2010].

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. *TFR2*-Related Hemochromatosis: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Liver disease	Phlebotomy & iron chelation as needed (See Targeted Therapy.)	Although cirrhosis is not reversible by phlebotomy, persons w/cirrhosis benefit from iron removal to ↓ risk of HCC.
	Vaccination against hepatitis A & B	
	• **Varices:** endoscopic surveillance; prophylaxis w/nonselective beta-blockers • **Ascites:** salt restriction & diuretics, & paracentesis & shunts if needed • **Spontaneous bacterial peritonitis:** antibiotic therapy • **Hepatic encephalopathy:** nutritional modifications (low-protein diet) & lactulose & rifaximin as needed	• Liver disease mgmt aims to prevent complications of cirrhosis & liver decompensation. • There are no reports of liver transplantation for end-stage liver disease in persons w/*TFR2*-HC.
Hypogonadotropic hypogonadism	• Hormone replacement therapy • Gonadotropin treatment for infertility	Usually not reversable by iron removal & therefore requires lifelong treatment
Diabetes mellitus	Insulin treatment	Iron removal may improve control of diabetes mellitus but cannot reestablish normal glucose metabolism.
Cardiac failure	• Diuretics, ACE inhibitors, cardiac glycosides • Iron chelation by intravenous or subcutaneous desferrioxamine, or oral deferiprone & deferasirox	• Lifelong treatment is required in those w/ cardiac disease. • To date, oral deferiprone & deferasirox are not approved for treatment of *TFR2*-HC.
Arthropathy	• Nonsteroidal anti-inflammatory drugs • Physiotherapy	Joint replacement has been performed in some affected persons.

ACE = angiotensin-converting enzyme; HCC = hepatocellular cancer; *TFR2*-HC = *TFR2*-related hemochromatosis

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, surveillance is based on guidelines proposed for *HFE*-HC in Europe [European Association for the Study of the Liver 2022] and North America [Kowdley et al 2019].

Table 5. *TFR2*-Related Hemochromatosis: Recommended Surveillance

System/Concern	Evaluation	Frequency
Biochemical iron parameters	Serum iron, transferrin, transferrin saturation, & ferritin	Every 6-12 mos

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
Liver disease	Liver function tests	Every 6-12 mos or more frequently if signs/ symptoms of liver decompensation
	• Serum AFP • Liver ultrasound to assess for HCC	Every 6 mos in those w/cirrhosis & eligible for cancer treatment or liver transplantation, regardless of iron depletion
Hypogonadotropic hypogonadism	No surveillance recommendations for those w/o hypogonadism	
	Serum gonadotropins (FSH & LH), serum testosterone, & serum estradiol to assess possible partial restoration of pituitary function	In those w/hypogonadism, on an individual basis according to severity of hypogonadism at diagnosis
Diabetes mellitus	Fasting serum glucose	Every 12 mos in those w/o diabetes
	Serum glucose, Hgb A1c, serum lipid profile, blood pressure, assessment of kidney function, assessment for peripheral neuropathy, & eye exam as for standard care, to prevent complications	In those w/diabetes, every 6-12 mos from diagnosis or as needed based on clinical manifestations
Cardiac failure	No surveillance recommendations for those w/o cardiac disease	
	EKG & echocardiography	In those w/cardiac disease, annually or as needed based on clinical manifestations
Arthropathy	X-ray exam	As needed based on symptoms

AFP = alpha-fetoprotein; FSH = follicle-stimulating hormone; HCC = hepatocellular carcinoma; Hgb = hemoglobin; LH = luteinizing hormone

Agents/Circumstances to Avoid

Avoid the following:

- Medicinal iron and nutritional supplements containing iron
- Excessive alcohol intake, which increases iron absorption and is toxic to hepatocytes. Individuals with cirrhosis should avoid alcohol consumption, even in small amounts.
- Vitamin C supplements, which may enhance iron absorption
- Uncooked seafood, which carry a risk of infection from microorganisms thriving under conditions of excess iron (e.g., *Yersinia enterocolitica*, *Vibrio vulnificus*)
- Lifestyle-related behaviors that increase the risk of viral hepatitis infection

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of an affected individual by molecular genetic testing of the familial *TFR2* pathogenic variants in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

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

Pregnancy Management

In pregnant women with mild-to-moderate iron overload, phlebotomy can be paused because fetal utilization of maternal iron effectively reduces the mother's iron load during pregnancy.

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

Genetic Counseling

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

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *TFR2* pathogenic variant. (Note: Due to the rarity of *TFR2*-HC, parental consanguinity is a possible consideration if the proband has homozygous *TFR2* pathogenic variants.)
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *TFR2* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) without other genetic or environmental risk factors (e.g., hemoglobinopathies, chronic hepatitis) are asymptomatic, do not have abnormal serum iron studies, and are not at risk of developing *TFR2*-HC [Joshi et al 2015].

Sibs of a proband

- If both parents are known to be heterozygous for a *TFR2* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) without other genetic or environmental risk factors (e.g., hemoglobinopathies, chronic hepatitis) are asymptomatic, do not have abnormal serum iron studies, and are not at risk of developing *TFR2*-HC [Joshi et al 2015].

Offspring of a proband. The offspring of an individual with *TFR2*-HC are obligate heterozygotes (carriers) for a pathogenic variant in *TFR2*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *TFR2* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *TFR2* pathogenic variants in the family.

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

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- It is appropriate to offer *TFR2* molecular genetic testing for reproductive partners of individuals known to have *TFR2*-HC or to be heterozygous for a *TFR2* pathogenic variant, particularly if consanguinity is likely.

Prenatal Testing and Preimplantation Genetic Testing

Once the *TFR2* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **Associazione per lo Studio dell'Emocromatosi e delle Malattie da Sovraccarico di Ferro ETS**
  Italy
  www.emocromatosi.it
- **Canadian Hemochromatosis Society**
  Canada
  Phone: 877-223-4766; 604-279-7135
  Email: office@toomuchiron.ca
  www.toomuchiron.ca
- **EFAPH: European Federation of Associations of Patients with Haemochromatosis**
  Phone: 32 2 280 23 34
  Email: info@eu-patient.eu
  EFAPH

- **Haemochromatosis International**
  Email: info@haemochromatosis-international.org
  www.haemochromatosis-international.org
- **Haemochromatosis UK**
  United Kingdom
  Phone: 03030 401 101
  Email: office@huk.org.uk
  www.haemochromatosis.org.uk
- **National Human Genome Research Institute**
  About Hemochromatosis
- **National Institute of Diabetes and Digestive and Kidney Diseases**
  Phone: 800-860-8747
  Email: nddic@info.niddk.nih.gov
  Hemochromatosis
- **NCBI Genes and Disease**
  Hereditary hemochromatosis
- **Iron Disorders Institute**
  Email: info@irondisorders.org
  www.irondisorders.org
- **MedlinePlus**
  Hereditary hemochromatosis
- **Non-HFE Registry**
  Email: contact@non-hfe.com
  www.non-hfe.com

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. TFR2-Related Hemochromatosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TFR2	7q22.1	Transferrin receptor protein 2	TFR2 @ LOVD	TFR2	TFR2

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 TFR2-Related Hemochromatosis (View All in OMIM)

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

Molecular Pathogenesis

Iron homeostasis is regulated by the hepcidin pathway. The hepatic peptide hepcidin (encoded by *HAMP*) is a circulating hormone that regulates the absorption of dietary iron from the duodenum. Hepcidin expression is inappropriately decreased in hemochromatosis and is abnormally increased in the anemia of chronic diseases. Hepatic proteins essential for normal iron homeostasis, including hereditary hemochromatosis protein (encoded by *HFE*), transferrin receptor protein 2 (TfR2, encoded by *TFR2*), and hemojuvelin, function at least in part by modulating the expression of hepcidin [Colucci et al 2021]. Low/absent levels of urinary hepcidin have been reported in *TFR2*-related hemochromatosis (*TFR2*-HC) [Nemeth et al 2005], suggesting a mechanism for *TFR2*-HC.

TfR2 is expressed in the liver, especially in hepatocytes. TfR2 is also expressed in erythroid cells and interacts with the erythropoietin receptor [Forejtnikovà et al 2010]. TfR2 binds and internalizes transferrin. However, binding occurs at low affinity (25- to 30-fold lower) [Kawabata et al 1999], as compared to that of the transferrin receptor protein 1 (encoded by *TFRC*). *TFR2* is not transcriptionally regulated by iron. According to the most recent in vitro models, TfR2 is able to bind hereditary hemochromatosis protein and hemojuvelin on the cell surface [Hentze et al 2010, D'Alessio et al 2012] to regulate hepcidin production. Significant expression of TfR2 has been identified outside of the liver, and in a *Tfr2* knockout mouse model, local impairment of iron metabolism was found, for example, in brain and reticuloendothelial cells [Roetto et al 2018].

Mechanism of disease causation. Loss of function

Table 6. *TFR2* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003227.4 NP_003218.2	c.88dupC	p.Arg30ProfsTer31	See Penetrance.
	c.178G>T	p.Glu60Ter	See Prevalence.
	c.515T>A	p.Met172Lys	
	c.750C>G	p.Tyr250Ter	
	c.949C>T	p.Gln317Ter	See Genotype-Phenotype Correlations.
	c.1409G>T	p.Ser470Ile	See Penetrance.
	c.1861_1872delGCCGTGGCCCAG	p.Ala621_Gln624del	
	c.2343G>A	p.Trp781Ter	See Genotype-Phenotype Correlations.

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

Chapter Notes

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Prof Marco De Gobbi (marco.degobbi@unito.it) is actively involved in clinical research regarding individuals with *TFR2*-related hemochromatosis (*TFR2*-HC). He would be happy to communicate with persons who have any questions regarding diagnosis of *TFR2*-HC or other considerations.

Contact Dr Antonella Roetto (antonella.roetto@unito.it) to inquire about review of *TFR2* variants.

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