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TFR2-Related Hereditary Hemochromatosis

Synonym: Type 3 Hereditary Hemochromatosis

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Summary

Clinical 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. 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, 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, and arthropathy.

Diagnosis/testing. The diagnosis of TFR2-HHC is established in a proband by identification of biallelic pathogenic variants in TFR2 on molecular genetic testing.

Management. Treatment of manifestations: Removal of excess iron by routine phlebotomy 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 and joint replacement for arthropathy; routine treatment for cardiac failure, diabetes mellitus, and hepatic complications.

Prevention of primary manifestations: Routine phlebotomy; see Treatment of manifestations.

Surveillance: Monitoring serum ferritin concentration every three to four months once serum ferritin concentration is lower than 50 ng/mL.

Agents/circumstances to avoid: Medicinal iron and nutritional supplements containing iron, excessive alcohol intake, vitamin C supplements, uncooked seafood.

Evaluation of relatives at risk: If the pathogenic variants 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 and prenatal testing for pregnancies at increased risk are possible once both pathogenic variants in the family have been identified.

Diagnosis

An algorithm for the diagnosis of TFR2-related hereditary hemochromatosis (TFR2-HHC) has been developed (see Figure 1). See also [Bardou-Jacquet et al \[2013\]](#), [Brissot \[2016\]](#), [Powell et al \[2016\]](#), and [Zoller & Henninger \[2016\]](#).

Suggestive Findings

TFR2-HHC **should be suspected** in a proband with clinical features, symptoms, and laboratory features associated with iron overload in whom [HFE-associated hereditary hemochromatosis](#) has been excluded.

Clinical features and symptoms of iron overload

- Weakness, chronic fatigue
- Abdominal pain
- Hepatomegaly
- Cirrhosis, hepatocellular carcinoma
- Diabetes mellitus
- Cardiomyopathy, ECG abnormalities (conduction disturbances)
- Hypogonadism (decreased libido and impotence in men, amenorrhea in women)
- Arthritis (especially if involving the metacarpophalangeal joint), arthralgia
- Progressive increase in skin pigmentation

Laboratory features

- **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-HHC [[Girelli et al 2002](#), [Pietrangelo et al 2005](#), [Hsiao et al 2007](#), [Pelucchi et al 2009](#), [Del Castillo-Rueda et al 2011](#), [Hattori et al 2012](#), [Joshi et al 2015](#), [Badar et al 2016](#), [Peters et al 2017](#)]. 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 developed to quantitate liver iron concentration have been applied to TFR2-HHC [Biasiotto et al 2008, Pelucchi et al 2009, Ricerca et al 2009, Del Castillo-Rueda et al 2011, Del-Castillo-Rueda et al 2012, Joshi et al 2015, Badar et al 2016].

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

Establishing the Diagnosis

No specific diagnostic guidelines are available for TFR2-HHC.

The diagnosis of TFR2-HHC **is established** in a proband by identification of biallelic pathogenic variants in TFR2 by molecular genetic testing (see [Table 1](#)).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of TFR2 is performed first and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes TFR2 and other genes of interest (see Differential Diagnosis) can be considered. 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; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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](#).

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation).

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 Hereditary Hemochromatosis

Gene ¹	Test Method	Proportion of Pathogenic Variants ² Detectable by This Method
TFR2	Sequence analysis ³	>99% ⁴
	Gene-targeted deletion/duplication analysis ⁵	Unknown ⁶

1. See [Table A. Genes and Databases](#) for chromosome locus and protein.
2. See [Molecular Genetics](#) for information on allelic variants.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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. McDonald et al [2015], Badar et al [2016], Faria et al [2016], Lanktree et al [2017], Peters et al [2017]
5. 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.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

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 & Poggiali 2009](#)].

Age of onset in individuals with TFR2-HHC is earlier than in individuals with HFE-associated hereditary hemochromatosis. Five individuals with childhood onset (range of onset: age 3-13 years) have been reported [[Piperno et al 2004](#), [Biasiotto et al 2008](#), [Joshi et al 2015](#), [Ravasi et al 2015](#)], all with increased transferrin saturation and serum ferritin concentration. 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](#)], or as adults with abnormal serum iron studies and signs of organ involvement (e.g., liver fibrosis or cirrhosis, diabetes, hypogonadism, arthropathy) [[Pelucchi et al 2009](#), [Del-Castillo-Rueda et al 2012](#), [Hattori et al 2012](#), [Joshi et al 2015](#), [Badar et al 2016](#), [Peters et al 2017](#), [Wang et al 2017](#)].

Disease progression is slower than in juvenile hereditary hemochromatosis [[De Gobbi et al 2002](#)].

When TFR2-HHC is progressive, complications can include cirrhosis and hypogonadotropic hypogonadism. Severe joint involvement has been reported [[Ricerca et al 2009](#), [Peters et al 2017](#)]. Cardiomyopathy and diabetes mellitus are rare [[De Gobbi et al 2002](#), [Riva et al 2004](#)]. While the distribution of liver iron deposition is similar to that seen in HFE-associated hereditary hemochromatosis (mainly in hepatocytes with a decreasing gradient from portal to centrolobular areas), hepatocellular carcinoma (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](#)].

If TFR2-HHC is diagnosed early and treated appropriately with phlebotomy, individuals with TFR2-HHC will have normal life expectancy. Similar to HFE-associated hereditary hemochromatosis, the most important factors that can influence survival are the onset of cirrhosis, diabetes, and/or cardiomyopathy. The oldest individual to be diagnosed with TFR2-HHC is an Italian individual diagnosed at age 82 years [[Roetto et al 2001](#)].

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 (NP_000401.1; 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](#)].

Penetrance

The penetrance of TFR2-HHC is less than 100% and can be influenced by environmental factors. In a family reported by [Roetto et al \[2001\]](#), one middle-aged female homozygous for the TFR2 p.Arg30ProfsTer31 pathogenic variant 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-HHC is also known as hemochromatosis type 3 (HFE3); however, the term HFE3 seems inappropriate because HFE has no role in TFR2-HHC.

Prevalence

TFR2-HHC is rare, with pathogenic allele frequencies estimated within the range of 0.000008 to 0.0002 [[Wallace & Subramaniam 2016](#)]. Approximately 50 affected individuals have been reported worldwide, most commonly in Italy, Japan, and Portugal.

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.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with pathogenic variants in TFR2.

Differential Diagnosis

TFR2-related hereditary hemochromatosis (TFR2-HHC) needs to be distinguished from other primary iron overload disorders as well as from secondary iron overload disorders (see [Figure 1](#)). No specific studies have evaluated the percentage of TFR2 pathogenic variants detected in individuals with non-HFE-associated hereditary hemochromatosis.

Primary Iron Overload Disorders

Table 2.

Primary Iron Overload Disorders to Consider in the Differential Diagnosis of TFR2-HHC

Disorder ¹	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping with TFR2-HHC	Distinguishing from TRF 2-HHC
HFE-related hereditary hemochromatosis	HFE	AR	Biochemical & clinical features of iron overload	<ul style="list-style-type: none"> • Lower penetrance • Later onset
Juvenile hereditary hemochromatosis	HJV HAMP	AR	Biochemical & clinical features of iron overload	<ul style="list-style-type: none"> • Full penetrance • Earlier onset • More severe clinical manifestations, esp cardiomyopathy & hypogonadism

Disorder ¹	Gene(s)	MOI	Clinical Features of This Disorder	
			Overlapping with TFR2-HHC	Distinguishing from TRF 2-HHC
Ferroportin 1-associated hemochromatosis (OMIM 606069)	SLC40A1	AD	Biochemical & clinical features of iron overload	Later-onset clinical manifestations of iron overload
Ferroportin disease ²	SLC40A1	AD	Hyperferritinemia	<ul style="list-style-type: none"> • At early stage: anemia & low transferrin saturation • Iron deposition in hepatic reticuloendothelial (not parenchymal) cells • Reduced tolerance to phlebotomy
<u>Aceruloplasminemia</u>	CP	AR	<ul style="list-style-type: none"> • Hyperferritinemia • Diabetes mellitus 	<ul style="list-style-type: none"> • Anemia • Iron deposition in hepatic reticuloendothelial (not parenchymal) cells • Brain iron accumulation manifesting as retinal degeneration & neurologic disease (movement disorders & ataxia)
African iron overload (OMIM 601195)	Unknown		<ul style="list-style-type: none"> • Liver iron accumulation in reticuloendothelial & parenchymal cells • Cirrhosis 	<ul style="list-style-type: none"> • In drinkers of beer brewed in non-galvanized steel drums • Lower frequency of cardiomyopathy & diabetes • Susceptibility to tuberculosis & other infections
Neonatal hemochromatosis (congenital alloimmune hepatitis) (OMIM 231100)	Unknown		Iron deposition in multiple organs (liver, pancreas, heart, endocrine glands)	<ul style="list-style-type: none"> • Alloimmune pathogenesis • Iron overload in fetus • Severe liver failure at birth, often fatal without liver transplant
Bmp6-related iron overload (OMIM 112266)	BMP6	AD	<ul style="list-style-type: none"> • Biochemical features of iron overload • Liver iron accumulation 	<ul style="list-style-type: none"> • Normal transferrin saturation in some • Mild-to-moderate late onset of iron overload

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. Primary overload disorders are characterized by increased absorption of iron from a normal diet.
2. Pietrangelo [2017]

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).

See Hemochromatosis: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with TFR2-related hereditary hemochromatosis (TFR2-HHC), the following are recommended (based on recommendations for HFE-associated hereditary hemochromatosis) if they have not already been completed:

- Liver biopsy for evaluation of abnormal liver function tests and establishing prognosis when serum ferritin concentration is greater than 1,000 ng/mL, especially if there is an underlying liver disease (e.g., alcohol abuse, viral hepatitis)
- Liver elastography for detecting hepatic fibrosis
- Serum concentration of gonadotropins (FSH and LH) to assess pituitary function at time of diagnosis of iron overload. Depending on the results, a GnRH stimulation test may be necessary.
- Serum concentration of testosterone to assess testicular function and serum concentration of estradiol to assess ovarian function at time of diagnosis of iron overload
- 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 (ferritin >1,000 ng/mL)
- Screening for diabetes mellitus by fasting serum glucose concentration and oral glucose tolerance test at time of diagnosis of iron overload
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Since individuals with increased serum ferritin concentration should be treated by the same protocol as for HFE-associated hereditary hemochromatosis, the following recommendations are mainly based on guidelines proposed for HFE-associated hereditary hemochromatosis in Europe [European Association for the Study of the Liver 2010] (full text) and North America [Bacon et al 2011] (full text). However, it should be emphasized that since TFR2-HHC is rare and may progress differently from HFE-associated hemochromatosis, individual treatment is important.

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 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 checked 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 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 remains high in TFR2-related hereditary hemochromatosis when serum ferritin concentration is low (<50 ng/mL), even after intensive phlebotomy [Girelli et al 2011; Camaschella, Roetto, & De Gobbi, unpublished 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 frequency of maintenance therapy 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].

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 and is barely influenced by phlebotomy. In some individuals, joint replacement has been performed.

Cardiac failure is treated with diuretics, ACE inhibitors, cardiac glycosides, and iron chelation by intravenous or subcutaneous desferrioxamine.

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

As with treatment, the surveillance of TFR2-HHC is based on guidelines proposed for HFE-associated hereditary hemochromatosis in Europe [European Association for the Study of the Liver 2010] (full text) and North America

[[Bacon et al 2011](#)] ([full text](#)).

Once the serum ferritin concentration is around 50 ng/mL, monitoring serum ferritin concentration every three to four months is adequate while continuing phlebotomies at intervals to keep ferritin at this level.

Although hepatocellular carcinoma has not been reported in individuals with 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

Avoid the following:

- Medicinal iron and nutritional supplements containing iron
- Excessive alcohol intake because it increases iron absorption and is toxic to the hepatocytes
- Vitamin C supplements because they may enhance iron absorption
- Uncooked seafood because of the risk of infection from microorganisms thriving under conditions of excess iron (e.g., *Yersinia enterocolitica*, *Vibrio vulnificus*)

Evaluation of Relatives at Risk

In order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures, 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.

See [Genetic Counseling](#) for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Women with hemochromatosis do not need treatment during pregnancy 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, 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. —ED.

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 (i.e., carriers of one TFR2 pathogenic variant).
- Heterozygotes (carriers) are asymptomatic, do not have abnormalities of iron parameters, and are not at risk of developing the disorder [Roetto et al 2001].

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and do not have abnormalities of iron parameters.

Offspring of a proband. The offspring of an individual with TFR2-HHC are obligate heterozygotes (carriers) for the given 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 (Heterozygote) Detection

Carrier detection using molecular genetic testing for at-risk family members is possible once the pathogenic variants have been identified in an affected family member.

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, clarification of carrier status, and discussion of the availability of prenatal 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.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the TRF2 pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

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. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

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

- **American Hemochromatosis Society, Inc.**
4044 West Lake Mary Boulevard
#104, PMB 416
Lake Mary FL 32746-2012
Phone: 1-888-655-IRON; 1-888-655-4766; 407-829-4488
Fax: 407-333-1284
Email: mail@americanhs.org
www.americanhs.org
- **Canadian Hemochromatosis Society**
7000 Minoru Boulevard
Suite 285
Richmond British Columbia V6Y 3Z5
Canada
Phone: 877-BAD-IRON (1-877-223-4766); 604-279-7135
Email: office@toomuchiron.ca
www.toomuchiron.ca
- **Haemochromatosis Society**
PO Box 6356
Rugby Warwickshire CV21 9PA
United Kingdom
Phone: 03030 401 102; 03030 401 101
Email: helpline@ironoverload.org.uk; office@ironoverload.org.uk
www.haemochromatosis.org.uk
- **National Digestive Diseases Information Clearinghouse (NDDIC)**
2 Information Way
Bethesda MD 20892-3570
Phone: 800-891-5389 (toll-free); 866-569-1162 (TTY)
Fax: 703-738-4929
Email: nddic@info.niddk.nih.gov
Hemochromatosis
- **National Human Genome Research Institute (NHGRI)**
Learning About Hereditary Hemochromatosis
- **NCBI Genes and Disease**
Hereditary hemochromatosis
- **Iron Disorders Institute (IDI)**
PO Box 675
Taylors SC 29687
Phone: 888-565-4766 (Toll-free Information Request Line); 864-292-1175
Fax: 864-292-1878
Email: info@irondisorders.org
www.irondisorders.org
- **National Library of Medicine Genetics Home Reference**
Hereditary hemochromatosis

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 Hereditary 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 Hereditary 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 hereditary hemochromatosis and is abnormally increased in the anemia of chronic diseases. 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 [[Hentze et al 2010](#)]. Low/absent levels of urinary hepcidin have been reported in TFR2-related hereditary hemochromatosis [[Nemeth et al 2005](#)], suggesting a mechanism for TFR2-HHC.

Gene structure. TFR2 is 2,471 bp long and consists of 18 exons. There are two main alternatively spliced variants (see [Figure 2](#)):

- 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 [[Glöckner 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 (NM_001206855.1) lacks exons 1-3 and has 142 additional bases at its 5' end. Beta-TFR2 is expressed ubiquitously at very low levels. Based on animal models, it has been proposed that the beta form (NP_001193784.1) has a role in regulating iron export in the spleen [[Roetto et al 2010](#)] (see **Normal gene product**).

Pathogenic variants. Nearly 50 TFR2 pathogenic variants have been reported; most are rare or private [[Radio et al 2014](#)].

Table 3.

TFR2 Pathogenic Variants Discussed in This GeneReview

DNA Nucleotide Change (Alias ¹)	Predicted Protein Change (Alias ¹)	Reference Sequences
c.88_89dupC (ins88C)	p.Arg30ProfsTer31 (E60Ter)	
c.515T>A	p.Met172Lys	NM_003227.3
c.949C>T	p.Gln317Ter	NP_003218.2
c.1861_1872del12	p.Ala621_Gln624del (AVAQ621-624del)	

Note on variant classification: Variants listed in the table have been provided by the authors. GeneReviews staff have not independently verified the classification of variants.

Note on nomenclature: GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

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

Normal gene product. Tfr2 is an 801-amino-acid type II transmembrane glycoprotein characterized by short intracellular and transmembrane domains and a large extracellular domain. Domains include:

- Cytoplasmic domain (1-80aa)
- Transmembrane domain (81-104aa)
- Extracellular domain (105-801aa)

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 may be an internalization signal.

Tfr2 is expressed in the liver, especially in the hepatocytes. Recently it has been shown that Tfr2 protein is expressed in erythroid cells in mice and humans and that Tfr2 protein interacts with the erythropoietin receptor [Forejtníková et al 2010]. Furthermore, Tfr2 alpha protein is expressed in the hippocampal region of mouse brain and seems to be involved in iron accumulation in SNC [Pellegrino et al 2016], whereas beta-Tfr2 isoform is expressed in mouse heart and is involved in cardio-protection against ischemia/reperfusion damage [Boero et al 2015].

Alpha-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 (TFRC). Alpha-Tfr2 protein shows significant amino acid homology with TFRC and the prostate-specific membrane antigen, especially in the extracellular portion [Kawabata et al 1999].

Alpha-TFR2 is not transcriptionally regulated by iron. According to the most recent in vitro models Tfr2 is able to bind Hfe and Hju proteins on the cell surface [Hentze et al 2010, D'Alessio et al 2012] to regulate hepcidin production.

Beta-Tfr2 lacks the cytoplasmic and transmembrane domains and is an intracellular protein.

Animal models of the disease have been developed. Tfr2-deficient mouse models show iron overload [Roetto et al 2010, Fleming et al 2011].

Abnormal gene product. Loss of protein function is associated with disease. The pathogenic variant p.Met172Lys is of interest because it causes a missense in the alpha form but alters methionine, which is the putative initiation codon of beta-TFR2 [Roetto et al 2001, Majore et al 2006].

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Chapter Notes

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Revision History

- 15 February 2018 (sw) Comprehensive update posted live
- 9 June 2011 (me) Comprehensive update posted live
- 5 August 2008 (cd) Revision: prenatal diagnosis available clinically
- 15 May 2008 (me) Comprehensive update posted live
- 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 live
- 1 February 2005 (ar) Original submission

Figures

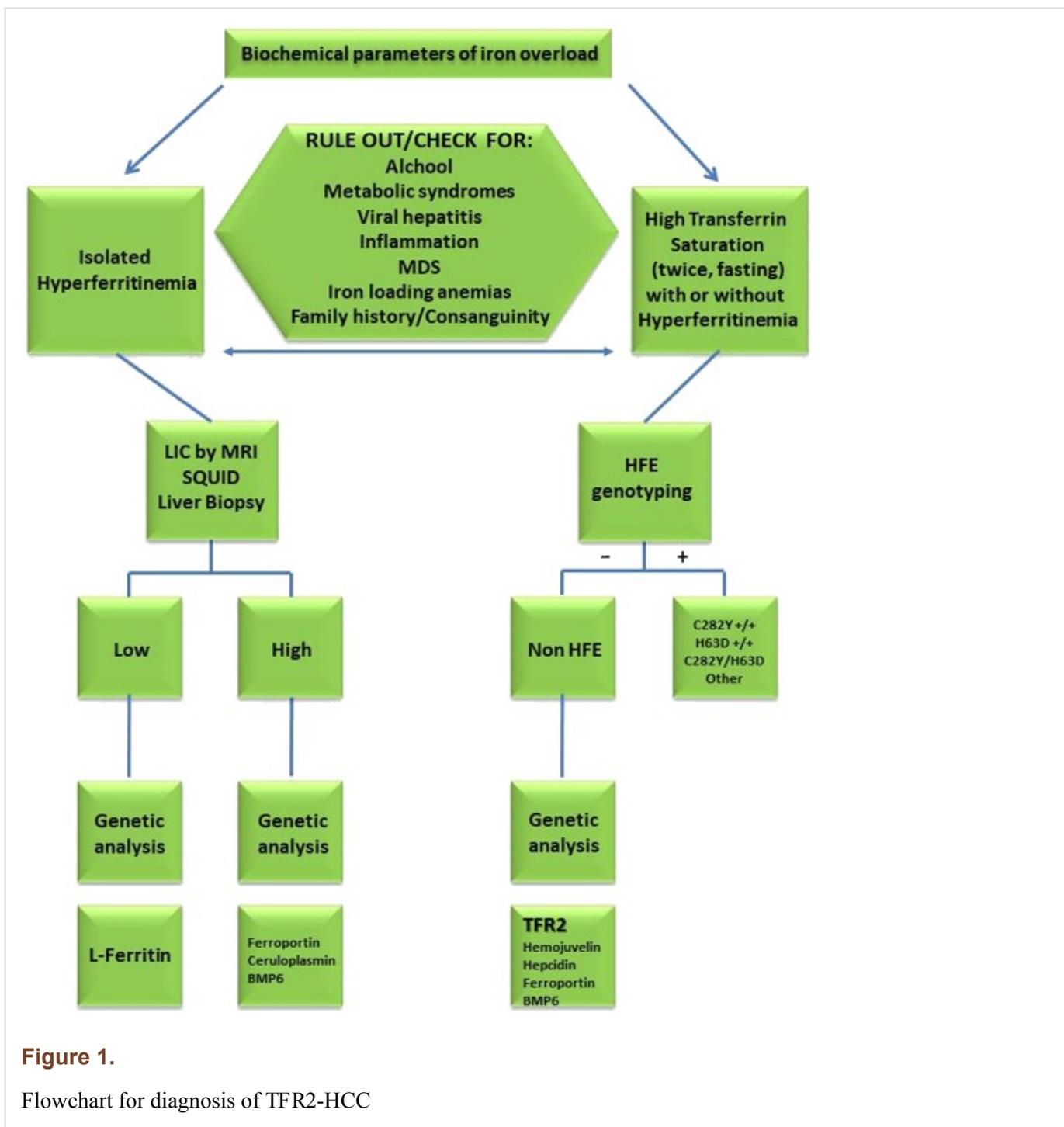
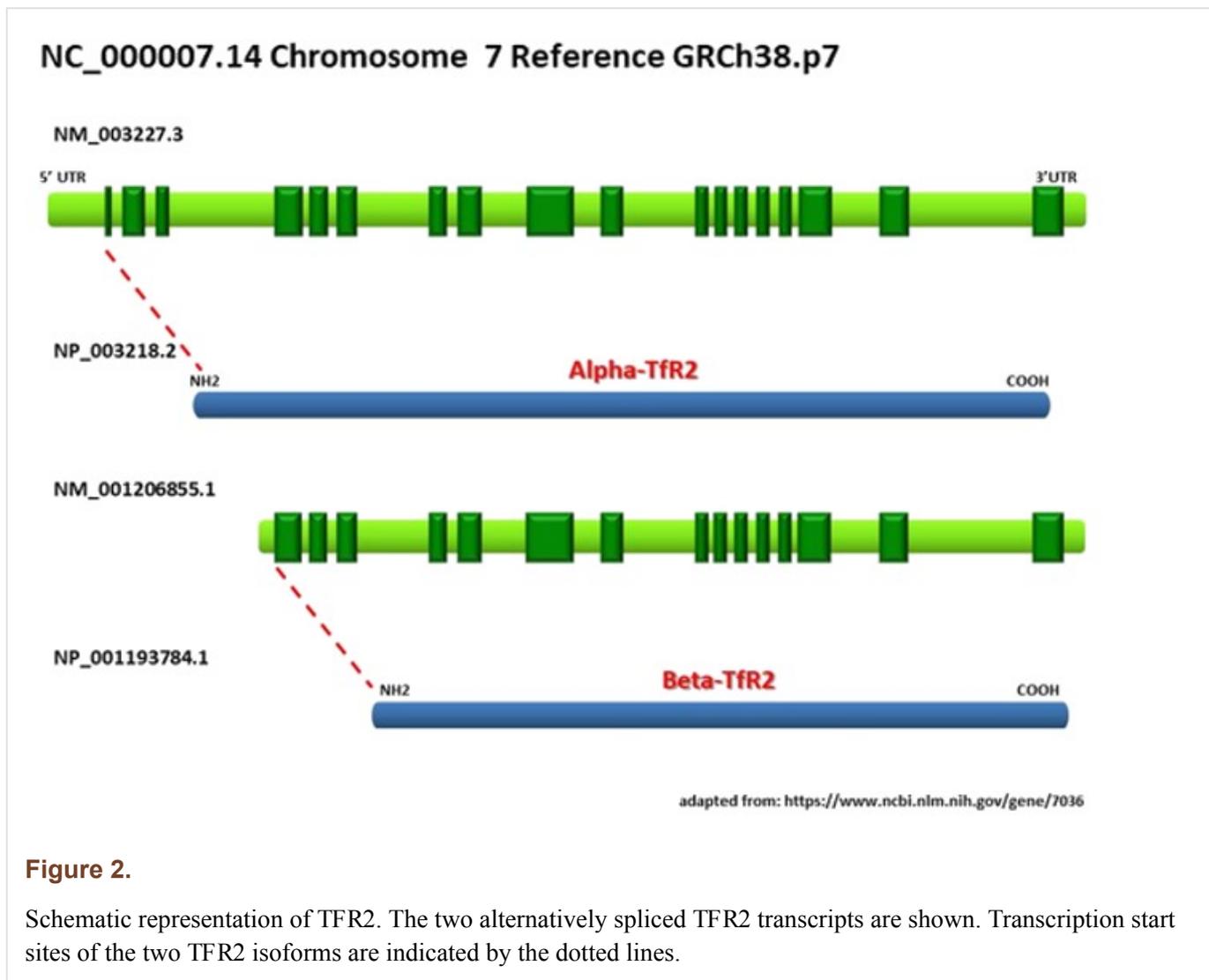


Figure 1.

Flowchart for diagnosis of TFR2-HCC



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