GENEReviews

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Juvenile Hereditary Hemochromatosis

[*Hemochromatosis, Type 2. Includes: HAMP-Related Juvenile Hemochromatosis, HJV-Related Juvenile Hemochromatosis*]

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Summary

Disease characteristics. Juvenile hemochromatosis is characterized by onset of severe iron overload occurring typically 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 disease. If juvenile hemochromatosis is detected early enough and blood is removed regularly through the process of phlebotomy to achieve iron depletion, morbidity and mortality are greatly reduced.

Diagnosis/testing. Serum ferritin concentration ranges from 1000 to 7000 µg/L. Transferrin-iron saturation is typically very high, often reaching 100%. MRI is used as a noninvasive method of quantifying hepatic iron overload. A hepatic iron index of higher than 1.9 on liver biopsy suggests iron overload. The two genes known to be associated with juvenile hemochromatosis are *HJV (HFE2)* (locus name HFE2A) encoding hemojuvelin, accounting for more than 90% of cases, and *HAMP (HEPC)* (locus name HFE2B) encoding hepcidin, which accounts for fewer than 10% of cases.

Management. *Treatment of manifestations:* phlebotomy for treatment of iron overload is the same as for classic *HFE*-associated hemochromatosis, i.e., phlebotomy of one unit of blood (~200 mg of iron) one to two times per week for up to two to three years to reduce iron stores to desired levels (serum ferritin concentration below 50 ng/mL and normal transferrin-iron saturation), followed by phlebotomies to maintain normal serum iron studies. Conventional treatment of secondary complications, including hypogonadotrophic hypogonadism, arthropathy, cardiac failure, liver disease, diabetes mellitus. *Prevention of primary manifestations:* regular phlebotomies until excess iron stores are depleted. *Prevention of secondary complications:* hormone replacement therapy (HRT) to prevent osteoporosis. *Surveillance:* Monitor those at risk with annual measurement of serum ferritin concentration and transferrin-iron saturation starting in early childhood; for those with hepatic cirrhosis,

monitor for hepatocellular cancer with biannual abdominal ultrasound examination and serum alpha-fetoprotein concentration. *Agents/circumstances to avoid:* alcohol consumption; ingestion of iron-containing preparations and supplemental vitamin C; handling or eating uncooked shellfish or marine fish because of risk of fatal septicemia from the marine bacterium *V. vulnificus*. *Testing of relatives at risk:* biochemical testing (i.e., serum ferritin concentration and transferrin-iron saturation) or molecular genetic testing in relatives at risk before evidence of organ damage from iron overload; monitor sibs with annual measurement of serum ferritin concentration and transferrin-iron saturation starting in early childhood.

Genetic counseling. Juvenile hemochromatosis 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 unaffected 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. No laboratories offering prenatal diagnosis of juvenile hemochromatosis are listed in the GeneTests Laboratory Directory; however, custom prenatal testing may be available for families in which the disease-causing mutations have been identified.

Diagnosis

Clinical Diagnosis

Juvenile hemochromatosis should be suspected in any child, adolescent, or young adult with findings of iron overload; such findings include the following:

- Hypogonadotropic hypogonadism
- Hepatomegaly
- Hepatic cirrhosis
- Hepatocellular carcinoma
- Diabetes mellitus
- Cardiomyopathy
- Arrhythmias
- Arthritis
- Progressive increase in skin pigmentation

Many of these features are evident before age 30 years.

Presenting symptoms in the first or second decade may be less specific, including lack of appetite, fatigue, amenorrhea, or arthralgia.

Testing

Biochemical testing. Data are minimal as documented cases of juvenile hemochromatosis are rare; however, the following two biochemical measurements should be performed:

- **Serum ferritin concentration,** which ranges from 1000 to 7000 µg/L in affected individuals (normal: 20-260 µg/L for male children/adolescents; 5-140 µg/L for female children/adolescents; 25-300 µg/L for adult males; 25-200 µg/L for adult females)
- **Transferrin-iron saturation,** which is typically very high, often reaching 100% (normal: 15%-50% in children/adolescents; ~33% in adults)

Imaging

- **Magnetic resonance imaging (MRI)** has become a valuable noninvasive technique to quantify hepatic iron overload [Gandon et al 2004].
- **Superconducting quantum interference device (SQUID)** is a noninvasive method for quantifying liver iron biomagnetometry; SQUID is available on a research basis only [Fung et al 2004].

Liver biopsy. A hepatic iron index of higher than 1.9 suggests iron overload in *HFE*-associated hereditary hemochromatosis. Similarly, because iron overload is more severe in juvenile hemochromatosis, an index of higher than 1.9 also applies for juvenile hemochromatosis (normal: <1.0) [Pietrangelo 2004].

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—Genes. Two genes are currently known to be associated with juvenile hemochromatosis:

- ***HJV (HFE2)*** **(locus name HJV [HFE2A]), encoding hemojuvelin,** accounts for more than 90% of cases reported to date.
- ***HAMP (HEPC)*** **(locus name HFE2B), encoding hepcidin,** accounts for fewer than 10% of cases reported to date.

Clinical testing

- **Mutation scanning.** Mutation scanning is expected to detect mutations in more than 98% of individuals with *HJV*-related juvenile hemochromatosis. Mutation scanning would not detect an extensive deletion.

  To date, the most frequently reported mutation in *HJV* is p.Gly320Val; it accounted for two-thirds of mutations identified in the original *HJV* positional cloning report [Papanikolaou et al 2004].

  The p.Gly320Val mutation was identified in all French-Canadian individuals with juvenile hemochromatosis phenotypes from the Saguenay-Lac-Saint-Jean region [Lanzara et al 2004].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Juvenile Hereditary Hemochromatosis

Test Method	Mutations Detected	Proportion of JHH caused by Mutations in this Gene	Mutation Detection Frequency [1]	Test Availability
Mutation scanning	*HJV* sequence variants	>90%	>98%	Clinical Testing
	HAMP sequence variants	<10%	>98%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene and test method

Testing Strategy

To establish the diagnosis of juvenile hemochromatosis in a proband, the following sequence of tests is used:

1. Biochemical testing (high serum ferritin concentration; high transferrin-iron saturation)
2. Molecular testing of *HJV* and *HAMP*
3. Hepatic imaging
4. Possible liver biopsy

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.

Genetically Related (Allelic) Disorders

To date, no other phenotypes are known to be associated with mutations in *HJV* or *HAMP*.

Clinical Description

Natural History

Juvenile hemochromatosis is characterized by early onset of severe iron overload. Juvenile hemochromatosis typically presents in the first to third decades of life.

Males and females are equally affected.

In clinical practice, individuals with juvenile hemochromatosis are rarely diagnosed before significant iron overload occurs.

Prominent clinical features include hypogonadotropic hypogonadism, cardiomyopathy, arthropathy, and liver fibrosis or cirrhosis. Osteopenia and osteoporosis are common complications in individuals with prolonged hypogonadism [Vaiopoulos et al 2003]. The clinical course is severe, with the main cause of death being cardiac-related disease [De Gobbi et al 2002]. The prevalence of cardiac disease is strikingly high, and in some instances is the presenting finding [Filali et al 2004].

Individuals with juvenile hemochromatosis may develop adrenocortical insufficiency or hypothyroidism, but these complications are rare [Varkonyi et al 2000].

Despite the more severe iron overload seen in juvenile hemochromatosis as compared to *HFE*-associated hereditary hemochromatosis, hepatocellular cancer has not been reported in juvenile hemochromatosis [Camaschella et al 2002]; a possible explanation is that untreated individuals with juvenile hemochromatosis die prematurely as a result of cardiac complications [Camaschella 1998].

If juvenile hemochromatosis is detected early enough and blood is removed regularly through the process of phlebotomy to achieve iron depletion, morbidity and mortality are greatly reduced.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported with *HJV*-related juvenile hemochromatosis or *HAMP*-related juvenile hemochromatosis; the clinical and biochemical phenotypes reported for all mutations identified so far appear similar.

Koyama et al (2005) reported three Japanese individuals (two from the same family) presenting around age 50 years with typical clinical signs of JHH and hepatic histologic damage compatible with hemochromatosis. All three were homozygous for *HJV* mutations.

- One was homozygous for the novel missense mutation 745G>C (p.Asp249His), suggesting that the mutation, which results in a relatively mild late-onset phenotype, may not be highly detrimental to hemojuvelin functioning.
- The two from the same family were homozygous for another novel mutation, 934C>T (p.Gln312X), which induced a premature stop codon, suggesting that unidentified factor(s) in this family may modify the clinical phenotype, as other truncating mutations typically have a more severe clinical presentation.

This adult presentation in three individuals with *HJV* mutations [Koyama et al 2005] highlights the wide spectrum of iron overload disease phenotypes related to *HJV* mutations, from classic juvenile hemochromatosis to the late-onset adult form, and further underscores the importance of multiple genetic and environmental factors in determining the final phenotype.

Thus, in a given individual, the degree of iron loading and the resultant clinical severity ultimately depends on the combination of genetic and enviromental load.

Nomenclature

Despite use of the terms HFE2A and HFE2B for the two loci for juvenile hemochromatosis, and use of *HFE2* for the gene symbol for one of the two juvenile hemochromatosis-related genes, juvenile hemochromatosis is **not** associated with mutations in the *HFE* gene that cause *HFE*-associated hereditary hemochromatosis, an adult-onset disorder of iron storage. As this is highly confusing, all researchers/physicians now refer to the common juvenile hemochromatosis gene as hemojuvelin *(HJV)* and the corresponding 1q locus as the HJV locus.

Prevalence

Juvenile hemochromatosis is rare.

Affected individuals have been reported worldwide.

Mutations in *HJV* represent the majority of worldwide cases of juvenile hemochromatosis. To date, *HJV*-related juvenile hemochromatosis has been reported in individuals of Northern European (including Canadian, American, and Australian) ethnicities; Italian, Greek, Dutch, Albanian, Romanian, Japanese, and Chinese descent; and in the French-Canadian region of Saguenay-Lac-Saint-Jean. No particular ethnic background appears to have a higher frequency; however, a clustering of *HJV* mutations occurs in Italy and Greece.

A much smaller number of individuals of Italian, Greek, Arab, and Portuguese descent with *HAMP*-related juvenile hemochromatosis have been reported.

Differential Diagnosis

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

Iron overload phenotypes can be primary or secondary.

Primary iron overload phenotypes include the following:

- ***HFE*-associated hereditary hemochromatosis (adult-onset classic hemochromatosis; type 1 hemochromatosis, HFE1).** At the milder end of the

spectrum, classic hereditary hemochromatosis is known to be caused by homozygous mutations in *HFE*, with clinical features typically presenting in the 40s to 50s in contrast to juvenile hemochromatosis, which typically presents before age 30 years. *HFE*-associated hereditary hemochromatosis, considered the classic and most common form, has many features in common with juvenile hemochromatosis, including hypogonadotrophic hypogonadism, cardiomyopathy, diabetes mellitus, hepatic cirrhosis, and skin hyperpigmentation; however, the clinical findings of juvenile hemochromatosis are much more severe than those seen in classic hereditary hemochromatosis because of the much higher rate of iron accumulation in the former. In particular, in juvenile hemochromatosis the clinical features of hypogonadotrophic hypogonadism and cardiomyopathy are more prominent than those in classic hereditary hemochromatosis [Camaschella et al 2002]. Classic hereditary hemochromatosis is caused by increased intestinal iron absorption as a result of a defect in the HFE protein. DNA diagnostic testing is available. Controversy exists as to the exact penetrance of hereditary hemochromatosis, although it is widely accepted that classic hereditary hemochromatosis, in contrast to juvenile hemochromatosis, is a low-penetrant disorder. In both juvenile hemochromatosis and classic hereditary hemochromatosis, macrophages are iron depleted despite total body iron excess.

An intermediate iron overload phenotype has been described in individuals with digenic inheritance of heterozygous mutations in *HAMP* and *HFE* or heterozygous mutations in *HJV* and *HFE*. The reports suggest that an explanation for the low penetrance rate in classic hereditary hemochromatosis is the need for genetic modifiers, such as mutations in *HJV* and *HAMP*, in addition to mutations in *HFE* to produce the classic hereditary hemochromatosis disease phenotype. However, because digenic inheritance accounts for a small proportion of individuals with *HFE*-associated classic hereditary hemochromatosis reported to date, other mechanisms are likely to modify penetrance. Further investigation of the importance of *HJV*, *HAMP*, *HFE*, and other iron metabolism-related alleles in the clinical expression of iron overload is warranted [Lee et al 2002; Merryweather-Clarke et al 2003; Lanzara et al 2004; Lee, Barton et al 2004; Lee, Beutler et al 2004; Le Gac et al 2004; Majore et al 2004; Pietrangelo 2004].

- ***TFR2* (transferrin receptor 2)-related hemochromatosis (type 3 hemochromatosis, HFE3).** The iron overload phenotype is variable: in some families, adult onset (similar to that seen in *HFE*-associated classic hereditary hemochromatosis) is observed; in others, the onset occurs before adulthood but later than in juvenile-onset hemochromatosis [Camaschella et al 2000, Le Gac et al 2004].
- **HFE (p.Cys282Tyr/p.His63Asp compound heterozygosity) and transferrin receptor 2 (p.Gln317X homozygosity).** A few individuals clinically diagnosed with juvenile hemochromatosis have not had mutations in either *HJV* or *HAMP*. In a family with typical clinical findings of JH in adolescence, no mutations were identified in either *HJV* or *HAMP*; affected individuals were compound heterozygous for the *HFE* mutations p.Cys282Tyr/p.His63Asp and homozygous for the *TFR2* mutation p.Gln317X [Pietrangelo et al 2005].
- **Ferroportin *(SLC40A1)*-related iron overload (ferroportin disease; type 4 hemochromatosis, HFE4).** Individuals with mutations in the gene encoding ferroportin also have iron overload, but unlike juvenile hemochromatosis and *HFE*-associated classic hereditary hemochromatosis, they show macrophages that are iron laden. Affected individuals have high serum ferritin concentration despite normal/low transferrin-iron saturation at early stages of the disease. Mild anemia can accompany the disease. Anemia may occur early in therapeutic phlebotomy.

Ferroportin-related iron overload presents in adulthood and is transmitted in an autosomal dominant manner [Montosi et al 2001, Njajou et al 2001].

It is now apparent that different *SLC40A1* mutations can culminate in different iron overload phenotypes [De Domenico et al 2006]. Ferroportin mutant proteins can be divided into the following two main classes:

- Proteins that fail to localize to the cell surface and are thus unable to export iron. Affected individuals have typical ferroportin disease with low transferrin saturation and early Küpffer cell iron loading.
- Proteins that localize to the cell surface but are not responsive to the hepcidin (hepcidin resistance). Affected individuals have high transferrin saturation and early hepatocyte iron loading similar to classic *HFE*-associated hereditary hemochromatosis [De Domenico et al 2006].

- **Neonatal hemochromatosis.** Iron overload occurs in utero. This severe, often fatal iron overload syndrome usually presents at birth. Inheritance is unknown, but autosomal recessive and mitochondrial inheritance have been postulated. No locus has been identified.
- **Atransferrinemia.** Atransferrinemia is characterized by absent transferrin and therefore an inability to deliver iron to the red cell precursors in the bone marrow. This lack of iron for the red cell precursors sets up a powerful erythroid drive with massive intestinal hyperabsorption of iron. Affected individuals are iron overloaded, yet have a microcytic anemia. This condition is an exceedingly rare autosomal recessive disorder, with only a few individuals reported worldwide. **Hypotransferrinemia** is a milder phenotype that is allelic with atransferrinemia.

Secondary disorders of iron overload include the following:

- **African iron overload.** African iron overload occurs in individuals with a predisposition to iron overload that is exacerbated by excessive intake of dietary iron. It is particularly prevalent among Africans who drink a traditional beer brewed in non-galvanized steel drums. In the past, African iron overload was mainly attributed to dietary excess alone. However, serious iron overload does not develop in all beer drinkers, and not all individuals with iron overload consume excessive amounts of the beer, suggesting that other yet-to-be-defined iron-related genes predispose to the condition. A specific mutation (p.Gln248His) in *SCL40A1*, the gene encoding ferroportin 1, has been associated with tendency to iron overload in Africans and African Americans [Beutler et al 2003, Gordeuk et al 2003].
- **Transfusional iron overload.** Individuals receiving red blood cell transfusions or any products containing red blood cells on a regular basis develop iron overload as a result of the transfused iron.
- **Nontransfusional iron overload.** Nontransfusional iron overload can occur in conditions in which ongoing erythroid destruction generates an erythroid drive signaling intestinal iron hyperabsorption. For example, iron overload is a feature in beta-thalassemia intermedia, for which most affected individuals are not transfused. Other examples include congenital dyserythropoetic anemia and sideroblastic anemia.

Disorders of excess ferritin without iron overload include the following:

- **Hyperferritinemia cataract syndrome (HCS).** Individuals with HCS do not have iron overload. They have very high serum ferritin concentration caused by a mutation in the iron-responsive element in the 5' untranslated region of the gene encoding the

ferritin light chain that leads to inappropriate excessive production of ferritin. Transferrin-iron saturation is normal. Individuals with HCS have early-onset bilateral (often congenital) cataracts. Phlebotomy is contraindicated in these individuals [Girelli et al 1995, Aguilar-Martinez et al 1996].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with juvenile hemochromatosis, the following evaluations are recommended:

- **Serum iron status.** Measurements of serum iron concentration, total iron binding capacity, transferrin saturation, and serum ferritin concentration
- **Pituitary-gonadal axis.** Recording of signs and symptoms of hypogonadotrophic hypogonadism and measurement of serum concentration of gonadotropins (i.e., FSH, LH) (pituitary gland) and testosterone (testes) or estradiol (ovaries). In several clinical situations, a dynamic evaluation of the pituitary-gonadal axis is required, consisting mainly of a GnRH (gonadotropic releasing hormone) stimulation test. Pituitary MRI may be considered in some cases.
- **Affected joints.** Radiographic evaluation
- **Bone mineral density.** Dual photon absorptiometry of the lumbar spine
- **Cardiac manifestations.** ECG, transthoracic echocardiogram. In individuals without overt clinical manifestations of cardiac failure or arrhythmias, findings suggestive of left ventricular diastolic dysfunction (reduced left ventricular compliance) often precede evidence of ventricular dilatation and compromised ejection fraction.
- **Liver function.** Liver function histology to determine the extent of liver damage. Documentation of the presence or absence of cirrhosis is of prognostic significance. Current recommendations for *HFE*-associated classic hereditary hemochromatosis are that *HFE* p.Cys282Tyr homozygotes with serum ferritin concentration lower than 1000 ng/mL and/or normal liver function enzymes need not be biopsied. Liver biopsy should be considered for individuals with higher serum ferritin concentrations and/or raised liver function enzymes in order to establish prognosis [Morrison et al 2003]. Because of the rarity of juvenile hemochromatosis, a specific protocol for individuals with juvenile hemochromatosis is not available, but the adaptation of the *HFE*-associated classic hereditary hemochromatosis recommendation is a reasonable approach.
- **Diabetes mellitus.** Screening for diabetes mellitus by overnight fasting plasma glucose measurement and, when indicated, by oral glucose tolerance test

Treatment of Manifestations

Management and treatment recommendations for juvenile hemochromatosis stated here are based on the established *HFE*-associated hemochromatosis recommendations when specific juvenile hemochromatosis information may not exist.

Treatment of iron overload. Phlebotomy is the therapy of choice in juvenile hemochromatosis and follows the same principles as the treatment of classic *HFE*-associated hemochromatosis. It is simple, safe, and effective. Affected individuals should be encouraged to follow a regimen of phlebotomy of one unit of blood once or twice weekly [Tavill 2001]. Approximately 200 mg of iron are removed per unit of blood depending on the individual's hematocrit. Because individuals with juvenile hemochromatosis are usually severely iron

overloaded, a therapeutic regimen of one to two weekly phlebotomies may take up to two to three years to reduce iron stores to desired levels.

The hematocrit should be monitored prior to phlebotomy; phlebotomy should be postponed if the hematocrit drops more than 20% of its initial value [Tavill 2001]. Systematic administration of erythropoietin has been successful in maintaining the hematocrit in individuals who failed to mount an adequate bone marrow response to the phlebotomy regimen [De Gobbi et al 2000].

Serum ferritin concentration reflects body iron stores and is used to monitor the progress of therapy; it is expected to fall progressively, along with iron mobilization. Measuring serum ferritin concentration every ten to 12 phlebotomies is reasonable; however, once serum ferritin concentration is below 100 ng/mL, it should be measured more often, ideally prior to each phlebotomy. Achievement of serum ferritin concentration below 50 ng/mL and restoration of normal transferrin-iron saturation indicates the end point of the intensive phlebotomy treatment.

Maintenance therapy. The frequency of phlebotomies is adjusted to maintain normal serum ferritin concentration and transferrin-iron saturation. When iron removal is not urgent, phlebotomies could be spaced further apart according to the responsiveness of the bone marrow to restore adequate hematocrit. Usually four to six phlebotomies annually are sufficient. The individual should permanently continue on this schedule of plebotomy maintenance therapy.

Iron chelators such as parenteral deferoxamine (Desferal®) are used to treat individuals with secondary iron overload. They are not recommended in the treatment of juvenile hemochromatosis unless the disease is complicated by concomitant anemia or severe cardiac failure. In the latter situation, administration of deferoxamine alone or in combination with deferiprone can reduce mortality by improving left ventricular ejection fraction [Kelly et al 1998, Fabio et al 2007].

Treatment of secondary complications does not essentially differ from the conventional treatment applied in other situations:

- **Hypogonadotrophic hypogonadism** is generally considered irreversible, despite adequate iron removal. However, reversal of hypogonadism has been observed in some young individuals who have been successfully treated with phlebotomy or iron chelation [Angelopoulos et al 2005]. For the majority of individuals with hypogonadism, testosterone or HRT is required to improve symptoms and prevent the development of secondary osteopenia or osteoporosis [Angelopoulos et al 2006]. (See Hypogonadotrophic Hypogonadism Overview.) Transdermal preparations (i.e., patches) deliver testosterone or estradiol at a controlled rate into the systemic circulation, avoiding first-pass hepatic metabolism; therefore, this approach may be useful for individuals with juvenile hemochromatosis, eliminating the risk of potential liver complications.

  Administration of gonadotropins has restored fertility and has led to a twin pregnancy in a woman with juvenile hemochromatosis.

- **Arthropathy** is not modified by treatment. Individuals with juvenile hemochromatosis have to cope with persistent arthralgia presenting at a young age. Painful joints may require treatment with salicylates or nonsteroidal anti-inflammatory drugs (NSAIDS) [Vaiopoulos et al 2003].

- **Severe cardiac failure** is treated with ACE inhibitors, diuretics, cardiac glycosides, and possibly deferoxamine. If left untreated, cardiac disease progresses rapidly and

becomes refractory to treatment, leading to death in most cases. Orthotopic heart transplantation has been used on occasion [Caines et al 2005].

- **Liver steatosis and fibrosis** are treated with appropriately early phlebotomy [Camaschella et al 2002]; however, it is uncertain whether these features are reversible. Reversibility of liver fibrosis has been reported in individuals treated for *HFE*-associated hemochromatosis [Falize et al 2006].

  Cirrhosis is thought to be irreversible despite iron removal. Individuals with cirrhosis should undergo endoscopic evaluation to document the presence of varices and should be treated with propranolol or nadolol, as indicated. In advanced disease, orthotopic liver transplantation (OLT) could be considered. Of note, individuals with hereditary hemochromatosis undergoing OLT display an overall lower survival than individuals undergoing OLTs for other causes of liver disease. Because most post-transplantation deaths occur in the perioperative period from cardiac disease or infection, it is advisable to remove as much of excess iron stores as possible before OLT even though the effect of excess tissue iron on survival post-OLT is not known [Tavill 2001].

- **Diabetes mellitus** may require insulin administration; successful iron removal may improve its course [Angelopoulos et al 2007].

Prevention of Primary Manifestations

Individuals with biochemical evidence of iron overload but without evidence of organ dysfunction or failure should be encouraged to undergo regular phlebotomies until excess iron stores are depleted to prevent the development of complications associated with excess iron stores.

Treatment by phlebotomy in presymptomatic stages can prevent organ damage.

Prevention of Secondary Complications

HRT prevents the development of osteoporosis.

Surveillance

Whenever hepatic cirrhosis is identified, monitoring for hepatocellular cancer is recommended. Most hepatologists propose twice-yearly screening with abdominal ultrasound examination and serum alpha-fetoprotein concentration [Tavill 2001].

Agents/Circumstances to Avoid

- Alcohol consumption, which has a synergistic effect with iron-induced liver damage in individuals with liver damage
- Iron-containing preparations and supplemental vitamin C
- Handling or eating uncooked shellfish or marine fish, because of susceptibility to fatal septicemia from the marine bacterium *V. vulnificus*

Testing of Relatives at Risk

Each sib of an affected individual should be monitored with measurement of serum ferritin concentration and transferrin-iron saturation annually starting in early childhood. Homozygotes for *HJV* or *HAMP* mutations, identified through family screening, should be monitored similarly. Children with presymptomatic juvenile hemochromatosis and heavy parenchymal iron deposition have been described.

If juvenile hemochromatosis is detected, either by biochemical testing (i.e., serum ferritin concentration and transferrin-iron saturation) or by molecular genetic testing in relatives at risk before evidence of organ damage, treatment via phlebotomy can reverse or prevent many of the secondary complications resulting from organ damage.

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, staffed by genetics professionals, provide 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 may include disease-specific and/or umbrella support organizations.

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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

Juvenile hemochromatosis is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.

Offspring of a proband. The offspring of an individual with juvenile hemochromatosis are obligate heterozygotes (carriers) for a disease-causing mutation.

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 techniques is available to family members at risk if both disease-causing mutations have been identified in the family.

Related Genetic Counseling Issues

See Testing of Relatives at Risk 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 and clarification of carrier status 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 at risk.

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.

Use of samples that have been banked should be explicitly approved in a written, revocable consent by each person from whom the sample is obtained. Such consents should detail all known potential biologic, ethical, social, and legal risks and their implications.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of juvenile hemochromatosis are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in the family. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for conditions such as juvenile hemochromatosis that do not affect intellect and have 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 regarding prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

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

Molecular Genetics

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

Table A. Molecular Genetics of Juvenile Hereditary Hemochromatosis

Locus Name	Gene Symbol	Chromosomal Locus	Protein Name
HFE2B	*HAMP*	19q13	Hepcidin
HJV	*HJV*	1q21	Hemojuvelin

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 Juvenile Hereditary Hemochromatosis

602390	HEMOCHROMATOSIS, JUVENILE; JH
606464	HEPCIDIN ANTIMICROBIAL PEPTIDE; HAMP
608374	HEMOJUVELIN

Table C. Genomic Databases for Juvenile Hereditary Hemochromatosis

Gene Symbol	Entrez Gene	HGMD
HAMP	57817 (MIM No. 606464)	HAMP
HJV	148738 (MIM No. 608374)	

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

Note: HGMD requires registration.

HJV (HFE2)

Normal allelic variants: *HJV* comprises four exons. The first exon is not translated. Multiple alternate splicing has been observed with five potential transcripts defined. The mRNA is 2.2 kb in size and is highly expressed in liver, skeletal, and cardiac muscle.

Pathologic allelic variants: Over 30 different *HJV* mutations, all in the coding region, have been identified so far in either homozygous or compound heterozygous form. The majority of mutations appear to be private; however, the *HJV* mutation p.Gly320Val is the most prevalent mutation reported to date, representing more than 50% of all detected mutations in affected individuals worldwide.

Normal gene product: The full-length hemojuvelin protein comprising 426 amino acids is predicted to be approximately 41 kd in size. Bioinformatic analyses revealed that a 35-amino acid hydrophobic signal peptide is at the N-terminal. At the C-terminal, a transmembrane domain and a glycophosphatidyl inositol (GPI) addition signal sequence exist. The GPI anchor is functional in vitro [Zhang et al 2005]. At position 98, a tri-amino acid RGD (Arg-Gly-Asp) domain is thought to be important in cell adhesion. A partial vWF-like domain spans the central portion of the protein (aa 167-253). Several cleavage sites are predicted in hemojuvelin, including furin and repulsive guidance molecule (RGM) autocatalytic sites. Overall, the hemojuvelin protein is about 91% homologous to RGM type C in the mouse.

Two isoforms of hemojuvelin have been identified: the full-length protein and the disulphide bonded N- and C-terminal chains of hemojuvelin cleaved at the Asp-Pro RGM autocatalytic cleavage site. A soluble form of hemojuvelin is released or secreted and competes with the membrane-bound form of hemojuvelin [Lin et al 2005]. Iron modulates the release of soluble hemojuvelin [Lin et al 2005, Silvestri et al 2007, Zhang et al 2007], and in primary hepatocytes,

increasing amounts of soluble hemojuvelin reduced hepcidin mRNA expression [Lin et al 2005].

Hemojuvelin is a key upstream regulator of hepcidin expression. Hemojuvelin acts as a coreceptor for bone morphogenetic protein (BMP) signaling in the hepatocyte [Babitt et al 2006], signaling via BMP receptors and SMADs. SMAD4 is the terminal transcriptional effector critical for mediating hemojuvelin/BMP induction of hepcidin [Wang et al 2005]. In addition, hemojuvelin positively modulates hepcidin expression via the multifunctional membrane receptor neogenin [Zhang et al 2007].

Abnormal gene product: Individuals with mutations in hemojuvelin have extremely low levels of hepcidin in urine, suggesting that hemojuvelin normally regulates hepcidin expression [Papanikolaou et al 2004]. Similarly, hepcidin levels are depressed in hemojuvelin knockout mice [Huang et al 2005, Niederkofler et al 2005]. Furthermore, siRNA knockdown of hemojuvelin resulted in decreased hepcidin mRNA expression in primary hepatocytes, underscoring hemojuvelin's critical role in modulating hepcidin. Loss of hemojuvelin function results in decreased BMP signaling in the liver, with associated decreased hepcidin expression.

HAMP (HEPC)

Normal allelic variants: *HAMP* comprises three exons. Exon 3 encodes the active 25-amino acid peptide. The hepcidin mRNA is 0.4 kb in size.

Pathologic allelic variants: Six different mutations in *HAMP* causing juvenile hemochromatosis in six independent families have been reported to date [Roetto et al 2003, Delatycki et al 2004, Matthes et al 2004, Roetto et al 2004, Rideau et al 2007]. Mutations have been reported in both coding and non-coding regions of the gene.

Normal gene product: The 84-amino acid pre-protein contains an N-terminal signal sequence (24 amino acid) and a penta arginyl proteolysis site, which is used to produce the active C-terminal 25-amino acid peptide. The active peptide comprises eight cysteines forming four disulfide bridges. As hepcidin is a small peptide, it is filtered by the kidney and detectable in the urine. Hepcidin is predominantly expressed in liver, and detected in much lower amounts in heart, brain, lung, and other tissues. Hepcidin functions as a key liver-produced hormone regulating intestinal iron absorption and macrophage iron release. Hepcidin interacts with ferroportin to mediate ferroportin internalization and subsequent degradation. When iron overload occurs, hepcidin is secreted and serves to limit plasma iron concentration by preventing iron uptake in the intestine and preventing iron release from macrophages. In contrast, in the clinical setting of iron deficiency, hepcidin is suppressed to allow intestinal iron absorption.

Abnormal gene product: Individuals with mutant hepcidin fail to prevent iron uptake in the intestine, resulting in iron overload. Macrophages are iron-depleted as a result of failure of hepcidin action.

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.

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Richmond V6Y 3Z5
Canada
Phone: 877-223-4766 (toll-free in Canada only); 604-279-7135
Email: office@toomuchiron.ca
www.toomuchiron.ca

Iron Disorders Institute, Inc
2722 Wade Hampton Blvd Suite A
Greenville SC 29615
Phone: 864-292-1175
Fax: 864-292-1878
Email: PatientServices@irondisorders.org
www.irondisorders.org

National Library of Medicine Genetics Home Reference
Hemochromatosis

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

Author Notes

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