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Juvenile Hemochromatosis

Synonyms: Hemochromatosis Type 2, Juvenile Hereditary Hemochromatosis

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Summary

Clinical 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, glucose intolerance and diabetes, arthropathy, and liver fibrosis or cirrhosis. Hepatocellular cancer has been reported occasionally. The main cause of death is cardiac disease. If juvenile hemochromatosis is detected early enough and if blood is removed regularly through the process of phlebotomy to achieve iron depletion, morbidity and mortality are greatly reduced.

Diagnosis/testing

The diagnosis of juvenile hemochromatosis is established in a proband with clinical and laboratory features of iron overload by identification of biallelic pathogenic variants in *HAMP* or *HJV* on molecular genetic testing. Individuals with suggestive features of juvenile hemochromatosis who do not have biallelic *HAMP* or *HJV* pathogenic variants identified on molecular genetic testing should have further evaluation by imaging and/or liver biopsy.

Management

Treatment of manifestations: Phlebotomy for treatment of iron overload as for *HFE* hemochromatosis: phlebotomy of 1 unit of blood (~200 mg of iron) 1x/week for up to 2-3 years to reduce iron stores to desired levels (serum ferritin concentration ~50 ng/mL), followed by phlebotomies to maintain normal serum iron levels. Conventional treatment of secondary complications including hypogonadotropic hypogonadism, arthropathy, cardiac failure, liver disease, and diabetes mellitus as indicated. Hypogonadism is treated with testosterone replacement in males and cyclical estrogen and progesterone therapy in fertile females. Arthropathy

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is treated with analgesics and NSAIDs. Cardiac failure and arrhythmias require treatment as per cardiologist. Glucose intolerance or diabetes may require oral agents or insulin administration.

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.

Prevention of secondary complications: Hormone replacement therapy may prevent osteoporosis.

Surveillance: Monitor those at risk with annual measurement of serum ferritin concentration and transferrin saturation starting in early childhood. For individuals with iron overload: serum ferritin every 4-8 phlebotomies during the induction phase; every 1-2 phlebotomies as ferritin levels approach the target of 50 ng/mL; liver function tests and fibroelastography every 6-24 months according to severity of liver dysfunction; abdominal ultrasound and serum alpha-fetoprotein concentration every 6 months in those with severe fibrosis or cirrhosis to monitor for hepatocellular cancer; cardiac ultrasound and MR-based quantitation of iron according to the severity of cardiac dysfunction; Holter ECG as needed to evaluate for arrhythmias; serum FSH, LH, and testosterone or estradiol every 12 months or as needed; fasting and postprandial serum glucose and Hgb A1c every 6-12 months according to needs; vitamin D, PTH, serum and urinary calcium and phosphorus, C-terminal telopeptide every 12 months according to needs; DEXA every 24 months or as needed.

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*.

Evaluation of relatives at risk: It is appropriate to clarify the clinical/genetic status of all at-risk family members (i.e., sibs) of an affected individual in order to identify as early as possible those who would benefit from early monitoring for the development of iron overload. If juvenile hemochromatosis is detected before evidence of organ damage, treatment via phlebotomy can reverse or prevent many of the secondary complications resulting from organ damage. Evaluation can include serum iron indices (i.e., serum iron, transferrin saturation, and serum ferritin), serum transaminases, C-reactive protein, and molecular genetic testing in relatives at risk before evidence of organ damage from iron overload.

Genetic counseling

Juvenile hemochromatosis is inherited in an autosomal recessive manner. If each parent is known to be heterozygous for a *HAMP* or *HJV* pathogenic variant, each sib of an affected individual has at conception 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. Carrier testing for at-risk relatives and prenatal testing are possible if both pathogenic variants in the family have been identified.

Diagnosis

Suggestive Findings

Juvenile hemochromatosis **should be suspected** in individuals with the following findings:

- Less specific symptoms in the first decade (e.g., fatigue, arthralgia, lack of appetite), which are often erroneously attributed to iron deficiency anemia
- Decreased libido, impotence (males), and amenorrhea (females) in adolescents and/or young adults suggesting hypogonadotropic hypogonadism
- Hepatomegaly, slight alterations of serum transaminases suggesting liver disease or severe fibrosis/cirrhosis

- Fasting hyperglycemia, glucose intolerance, or frank diabetes
- Arrhythmias, dyspnea on exertion, heart failure suggesting cardiomyopathy
- Arthropathy and osteoporosis
- Hyperpigmentation

Note: Many of these features are evident before age 30 years, although they may appear at a later age in some individuals [Kong et al 2019].

Laboratory features

- **Transferrin saturation**, which is typically high, often reaching 100% (normal values 16%-45%). Normal transferrin saturation excludes the diagnosis of juvenile hemochromatosis.
- **Serum ferritin concentration**, which is increased relative to the normal values for age and gender according to data published by World Health Organization:
  - Upper normal value in male and female children and young adolescents: 100-125 ng/mL
  - Upper normal value in premenopausal adult women: 150 ng/mL, and in postmenopausal women: 250 ng/mL [Milman et al 2003]
  - Upper normal value in healthy adult men: 400 ng/mL [Milman et al 2002]
  - In the earlier stages of juvenile hemochromatosis, serum ferritin can be slightly increased, but can rapidly increase over 1000 ng/mL and even much higher.

Establishing the Diagnosis

The diagnosis of juvenile hemochromatosis **is established** in a proband by identification of biallelic pathogenic variants in *HAMP* or *HJV* on molecular genetic testing (see Table 1) [Piperno 2013, Porto et al 2016, Brissot et al 2018].

Molecular genetic testing approaches can include use of a **multigene panel** or **single-gene testing**:

- **An iron overload multigene panel** that includes *HAMP*, *HJV*, *HFE*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost, including digenic forms of hemochromatosis and genetic variants in modifier genes [Badar et al 2016, Faria et al 2016, Wallace & Subramaniam 2016]. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Single-gene testing** can be considered in individuals with early-onset iron overload. Sequence analysis of *HJV* can be performed first to detect small indels and missense, nonsense, and splice site variants. If no or only one pathogenic variant is found, perform sequence analysis of *HAMP*. If no or only one pathogenic variant is identified, consider other genes of interest (see Differential Diagnosis). If no or only one pathogenic variant is identified, perform gene-targeted deletion/duplication analysis of *HAMP*, *HJV,* and other genes of interest (see Differential Diagnosis) to detect intragenic deletions or duplications.

Table 1. Molecular Genetic Testing Used in Juvenile Hemochromatosis

Gene [1, 2]	Proportion of Juvenile Hemochromatosis Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
HAMP	<10%	100% [6]	None reported [6]
HJV	>90%	>98% [7]	1 individual 8

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. 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.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used 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. Data derived from Human Gene Mutation Database [Stenson et al 2017]
7. Includes identification of the most common *HJV* pathogenic variant p.Gly320Val, which accounts for more than 50% of *HJV* pathogenic variants identified in individuals of northern European ancestry [Kong et al 2019].
8. Lanktree et al [2017]

Imaging

Magnetic resonance imaging (MRI) has become a valuable noninvasive technique to quantify hepatic iron overload, provided it is performed in a properly controlled and validated manner. MRI also allows assessment of iron load in the pancreas, heart, spleen, and pituitary gland. Two advanced methods that can measure liver iron concentration (LIC) quantitatively:

- Relaxometry is the quantitative evaluation of the MRI signal loss due to the predominant shortening of the T_2-weighted as well as the T_2*-weighted relaxation times. It can be based on the calculation of the T_2-weighted time constant, based on spin-echo sequences, and on the T_2*-weighted time constants, based on gradient echo sequences (or their mathematical inverses, R_2 and R_2*, respectively). R_2* relaxometry has emerged as a reliable method providing a linear correlation with the LIC. Although some biases exist, studies have shown that the technique provides a clinically acceptable estimation of the LIC with reproducible results in different centers [Kirk et al 2010, Galimberti et al 2015, Henninger et al 2020]. R_2* relaxometry has further emerged as a very quick technique, acquired in only one breath-hold,although there remains an inaccuracy in very high iron values (>20-25 mg/g dry weight).
- The signal intensity ratio (SIR) method (imagemed.univ-rennes1.fr) is based on measuring the signal intensity ratio between the liver and the paraspinal muscles [Gandon et al 2004]. Subsequent studies showed a tendency to overestimate overload in the range of normal or moderately increased iron storage [Castiella et al 2011]. Another limitation of SIR is that the technique does not correct for fat.

Superconducting quantum interference device (SQUID) is a noninvasive method for quantifying liver iron biomagnetometry [Fung et al 2004]. The main limitations are the low availability (only 2 or 3 devices available worldwide) and low versatility (can measure only liver iron).

Liver Biopsy

Liver biopsy is currently limited to prognostic purposes (assessment of liver damage) in individuals with serum ferritin higher than 1000 ng/mL or high amount of iron at quantitative MRI, whereas its use for diagnostic purposes is limited to selected situations [Bassett et al 2011]. Noninvasive estimation of liver fibrosis (fibroelastography) will further reduce the need for liver biopsies in the future [Fu et al 2019].

Clinical Characteristics

Clinical Description

To date, approximately 120 individuals have been identified with juvenile hemochromatosis [De Gobbi et al 2002, Merryweather-Clarke et al 2003, Roetto et al 2003, Delatycki et al 2004, Jacolot et al 2004, Matthes et al 2004, Roetto et al 2004, Island et al 2009, Lok et al 2009, Hattori et al 2012, Kong et al 2019]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Features of Juvenile Hemochromatosis

Feature	*HJV* Hemochromatosis: % of Persons w/ Feature	*HAMP* Hemochromatosis: Proportion of Persons w/Feature [1]
Cardiomyopathy	35%-37%	4/7
Hypogonadotropic hypogonadism	67%-91%	See footnote 2.
Reduced glucose intolerance / diabetes	30%-57%	7/8
Liver fibrosis	44%-58% [3]	6/7 [4]
Liver cirrhosis	27%-42%	
Hyperpigmentation	24.5%	See footnote 2.

1. In *HAMP* hemochromatosis data are limited and clinical descriptions have been incomplete although similar to *HJV* hemochromatosis.
2. Not enough information is available to determine the proportion of individuals with this feature.
3. Not all individuals in reported studies underwent liver biopsy.
4. Proportion of persons with *HAMP* hemochromatosis with either liver fibrosis or cirrhosis

Juvenile hemochromatosis is characterized by early-onset severe iron overload. Individuals with juvenile hemochromatosis typically present in the first to third decade of life; however, adult presentation has been described in individuals with *HJV* hemochromatosis [Koyama et al 2005, Ravasi et al 2018, Kong et al 2019], expanding the spectrum of disease phenotypes related to *HJV* pathogenic variants from classic juvenile hemochromatosis at one extreme to a late-onset adult form at the other extreme. Males and females are equally affected.

Individuals with juvenile hemochromatosis are rarely diagnosed before significant iron overload occurs. Prominent clinical features include hypogonadotropic hypogonadism, cardiomyopathy, diabetes and glucose intolerance, arthropathy, and liver fibrosis or cirrhosis.

Cardiac. The prevalence of cardiac disease is strikingly high [De Gobbi et al 2002, Kong et al 2019] and in some individuals is the presenting finding [Filali et al 2004]. Myocardial iron accumulation induces the development of restrictive cardiomyopathy with early diastolic dysfunction that may progress towards dilated cardiomyopathy. Heart failure is the main cause of death in untreated individuals with juvenile hemochromatosis [Murphy & Oudit 2010]. A variety of arrhythmias and sudden death can also occur in individuals with severe iron overload although further investigations to clarify the etiology and clinical relevance of iron overload-induced arrhythmias are needed [Shizukuda & Rosing 2019]. Iron removal can significantly improve and/or normalize cardiac function [Murphy & Oudit 2010].

Hypogonadotropic hypogonadism characterized by low levels of gonadotropins (FSH and LH) and testosterone is the most frequent endocrinologic complication in individuals with iron overload due to juvenile hemochromatosis [De Gobbi et al 2002, Borgna-Pignatti et al 2004]. It causes decreased libido and infertility, amenorrhea in females, and impotence in males, and contributes to the development of osteoporosis. Iron removal in early stages can lead to symptomatic improvement or resolution and normalization of hormonal indices [Angelopoulos et al 2006, Pelusi et al 2016].

Diabetes mellitus. Most of the information on diabetes development has been obtained in individuals with *HFE* hemochromatosis, where the pathogenesis of glucose intolerance and diabetes is likely multifactorial. Autopsy findings in individuals with hemochromatosis showed variable iron deposition in the exocrine pancreas and in beta cells together with loss of endocrine granules. It can be hypothesized that a severe and rapid iron overload in the exocrine pancreas could induce an initial beta-cell oxidative stress followed by iron accumulation and decreased insulin secretory capacity secondary to beta-cell apoptosis and desensitization of glucose-induced insulin secretion [Backe et al 2016]. Glucose intolerance or diabetes may require oral agents or insulin administration. Phlebotomy has a variable impact on diabetes control. In general, it may prevent progression if started in the earlier stages of disease, although the majority of individuals with diabetes will experience no significant change or worsening in their glucose metabolism control [Angelopoulos et al 2007, Pelusi et al 2016].

Liver. Although hepatomegaly is usually included among the earlier manifestations of juvenile hemochromatosis there is no information on its frequency as it is often poorly noted in clinical evaluations. Because the liver can compensate for iron toxicity, cirrhosis takes decades to develop. While in individuals with *HFE* hemochromatosis a serum ferritin value above 1000 ng/mL is a validated marker of increased risk of severe hepatic fibrosis/cirrhosis [Allen et al 2010], there are no data available for juvenile hemochromatosis. Therefore, assessment by liver fibroelastography and/or liver biopsy is mandatory. Environmental (e.g., alcohol consumption, steatosis, coexistent viral infection) and possibly genetic factors can modify the risk for cirrhosis [Brissot et al 2018]. Based on data related to other liver disease and *HFE* hemochromatosis [Falize et al 2006] it can be assumed that iron depletion can improve fibrosis unless cirrhosis is fully established. Hepatocellular carcinoma is rarely reported in individuals with juvenile hemochromatosis [Ramzan et al 2017]. A possible explanation is that untreated individuals with juvenile hemochromatosis die prematurely as a result of cardiac complications.

Skeletal. Articular symptoms, arthralgias, and/or arthritis was reported in seven of eight individuals with *HJV* hemochromatosis [Vaiopoulos et al 2003]. The age at onset of arthropathy ranged from 20 to 45 years. In two individuals arthropathy preceded other symptoms of juvenile hemochromatosis. The involved joints were most frequently metacarpophalangeal joints; knees, lumbar spine, and shoulder and metatarsophalangeal joints were variably involved. Four of the six individuals evaluated had osteopenia or osteoporosis, common complications in individuals with prolonged hypogonadism. However, a more recent study of 73 individuals with *HJV* hemochromatosis reported a very low frequency of osteopathy (7%) [Kong et al 2019] – a finding to be taken with caution because osteopenia and osteoporosis can be underestimated if not sought with appropriate investigations through bone densitometry (DEXA). Iron removal, in contrast with the visceral manifestations, often did not mitigate orthopedic complications [Sahinbegovic et al 2010].

Skin. A recent review reported hyperpigmentation in approximately 25% of individuals with *HJV* hemochromatosis [Kong et al 2019] – a finding that contrasts with older reports of skin hyperpigmentation at diagnosis in about 90% of individuals with hemochromatosis. Hyperpigmentation developed very gradually. This may suggest that iron-induced skin changes take too long to manifest in the majority of individuals with juvenile hemochromatosis.

If juvenile hemochromatosis is detected early and treated with phlebotomy to achieve iron depletion, morbidity and mortality are greatly reduced.

Other. Although individuals with juvenile hemochromatosis may develop adrenocortical insufficiency or hypothyroidism, these complications are rare [Varkonyi et al 2000, Pelusi et al 2016].

Heterozygotes and digenic inheritance. Heterozygous pathogenic variants in *HAMP*, *HJV*, and/or *TFR2* have been shown to increase the risk for iron overload in *HFE* p.Cys282Tyr heterozygotes [Merryweather-Clarke et al 2003] and to increase iron burden in *HFE* p.Cys282Tyr homozygotes [Jacolot et al 2004, Majore et al 2004,

Pietrangelo et al 2005]. However, only a very small proportion of individuals with *HFE* hemochromatosis are reported to have polygenic inheritance due to pathogenic variants in *HAMP* and *HJV*.

Genotype-Phenotype Correlations

No genotype-phenotype correlations can be provided for *HAMP* juvenile hemochromatosis due to the small number of reported individuals.

***HJV*.** More than 90% of homozygotes with *HJV* pathogenic variants in exons 2 and/or 3 developed hemochromatosis before age 30, compared with only 66% of homozygotes with *HJV* pathogenic variants in exon 4 [Kong et al 2019], indicating that the genetic defects in exons 2 and 3 may have a more deleterious effect on HJV function.

Nomenclature

Despite use of the locus names HFE2A and HFE2B for the two juvenile hemochromatosis genes (*HJV* and *HAMP*, respectively), juvenile hemochromatosis is not associated with pathogenic variants in *HFE* – mutation of which causes *HFE* hemochromatosis, an adult-onset disorder of iron storage.

Prevalence

Juvenile hemochromatosis is rare; global *HJV* pathogenic allele frequency has been estimated at 0.000316-0.00074 [Wallace & Subramaniam 2016]. Affected individuals have been reported worldwide. The variant p.Gly320Val is the most prevalent pathogenic variant (>50%) reported to date; p.Cys321Ter is the most frequent pathogenic variant in individuals of Chinese ancestry; p.Gln312Ter (also reported in individuals of Chinese ancestry) and p.Asp249His are the predominant pathogenic variants in Japan [Ikuta et al 2017]; p.Arg385Ter recurs in North Africa and Italy [Lanzara et al 2004, Kong et al 2019]. The variant p.Ala310Gly is common in African Americans and Brazilians, but its role is still undefined [Lee et al 2004, Santos et al 2011]. Table 7 reports the most frequent pathogenic variants according to ethnicity.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *HAMP* or *HJV*.

Differential Diagnosis

Iron overload phenotypes can be primary or secondary.

Note: Iron overload disorders presenting with hyperferritinemia with normal or reduced transferrin saturation (e.g., aceruloplasminemia and ferroportin disease) and disorders with hyperferritinemia without iron overload (e.g., hyperferritinemia-cataract syndrome and benign hyperferritinemia) should not be considered in a differential diagnosis with juvenile hemochromatosis because juvenile hemochromatosis is strongly characterized by high or very high transferrin saturation, high serum ferritin, and prevalent iron accumulation in parenchymal cells [Camaschella & Poggiali 2009, Pietrangelo 2017].

Primary Iron Overload Disorders

Table 3. Primary Iron Overload-Related Disorders with High Transferrin Saturation and Serum Ferritin to Consider in the Differential Diagnosis of Juvenile Hemochromatosis

Gene	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/JH	Distinguishing from JH
HFE	*HFE* hemochromatosis	AR	• Iron overload distribution mainly involving parenchymal cell; sparing reticuloendothelial macrophages • Hepatic fibrosis/cirrhosis • Diabetes mellitus • Skin hyperpigmentation • Cardiomyopathy • Hypogonadotropic hypogonadism	• Transferrin saturation less ↑ (variably ranges >45%) • Low penetrance w/variable expression • Later onset (40s-50s) • Hepatic fibrosis/cirrhosis more common • Hepatocellular carcinoma most frequent cause of death • Cardiomyopathy & hypogonadism less common
TFR2	*TFR2* hereditary hemochromatosis	AR	• Transferrin saturation in *TFR2*-HHC often as ↑ as in JH [1] • Iron overload distribution mainly involving parenchymal cells; sparing reticuloendothelial macrophages • Hepatic fibrosis/cirrhosis • Diabetes mellitus • Skin hyperpigmentation • Cardiomyopathy • Hypogonadotropic hypogonadism	• Cardiomyopathy & hypogonadism less common • Phenotype (age of onset & complications) intermediate between *HFE*-HHC & *HJV*-JH related to age of presentation & clinical complications [2]
SLC40A1	Type 4 hemochromatosis [3, 4] (OMIM 606069)	AD	• Iron overload distribution mainly involving parenchymal cells; sparing reticuloendothelial macrophages • Hepatic fibrosis/cirrhosis • Diabetes mellitus • Skin hyperpigmentation • Cardiomyopathy (less than in JH) • Hypogonadotropic hypogonadism (less than in JH)	• Typically presents in 40s & 50s (vs <30 yrs in JH) • Because of lower rate of iron accumulation, clinical findings (esp hypogonadism & cardiomyopathy) less common than in JH • Note: It is generally assumed that type 4 HHC is similar to *HFE*-HHC in age of presentation & clinical complications

Table 3. continued from previous page.

Gene	Differential Diagnosis Disorder	MOI	Features of Differential Diagnosis Disorder	
			Overlapping w/JH	Distinguishing from JH
TF	Atransferrinemia [5] (OMIM 209300)	AR	Iron overload distribution mainly involving parenchymal cells; sparing reticuloendothelial macrophages	• Ultra-rare; <15 individuals • Age of presentation: 1-2 yrs • Severe microcytic anemia that may require blood transfusion • Undetectable serum transferrin & very ↓ serum iron levels • If untreated, growth deficiency, severe iron-related complications & death may occur.
SLC11A2	DMT1 deficiency [6] (OMIM 206100)	AR	Variably ↑ serum ferritin that is disproportionally ↓ compared to liver iron concentration	• Ultra-rare, <10 individuals • Age of presentation: postnatal to young adult • Severe microcytic anemia that may require blood transfusion • If untreated, growth deficiency may occur.

AD = autosomal dominant; AR = autosomal recessive; DMT1 = divalent metal transporter; HHC = hemochromatosis; JH = juvenile hemochromatosis; MOI = mode of inheritance

1. Some *TFR2* pathogenic variants can cause juvenile-like hemochromatosis and increased iron indices in childhood [Le Gac et al 2004, Ravasi et al 2015].

2. De Gobbi et al [2002]

3. Mutation of *SLC40A1* can lead to two different disorders of iron metabolism, previously classified as hemochromatosis type-4A and -4B. The former and most frequent, type-4A, is characterized by atypical manifestations that do not correspond to hemochromatosis. Owing to this, it should be considered a distinct disorder characterized by hyperferritinemia with normal transferrin saturation and prevalent iron accumulation in macrophages (ferroportin disease). Type-4B shows typical serum iron index alterations and pattern of iron overload and should be now referred to as type 4 hemochromatosis [Pietrangelo 2017, Brissot et al 2018, Viveiros et al 2019]. Type 4 hemochromatosis is caused by gain-of-function variants that affect amino acids interacting with hepcidin, resulting in complete or partial resistance to hepcidin (see Molecular Pathogenesis).

4. Because of the rarity of type 4 hemochromatosis, data should be interpreted with caution.

5. In atransferrinemia, the lack of serum transferrin causes the loss of its iron scavenger and transport functions leading to severe iron deficiency anemia, non-transferrin-bound iron formation and severe iron overload in non-hematopoietic tissues.

6. DMT1 deficiency is also referred to as hypochromic microcytic anemia with iron overload-1. DMT1 transmembrane protein is involved in dietary non-heme iron uptake and plays a crucial role in iron utilization at the endosomal membrane of the erythroid precursors. In humans, DMT1 has a prevalent role in erythroid cells, and the reduction of DMT1 causes a more complex phenotype characterized by congenital microcytic anemia (due to defective iron transport and utilization in erythroid precursors) and biochemical and histologic features of iron overload [Iolascon & De Falco 2009].

Secondary Iron Overload Disorders

Transfusional iron overload. One unit of packed red blood cells contains approximately 200–250 mg of iron. Individuals requiring frequent transfusions due to inherited anemias (e.g., thalassemia major, Diamond-Blackfan anemia) will develop severe iron overload and iron-related complications at an early age if untreated. Other transfusion-dependent iron overload conditions include survivors of bone marrow transplant, myelodysplastic disorders, myeloproliferative syndromes, and aplastic anemia. Iron accumulation occurs initially in the reticuloendothelial macrophages. After iron excess overwhelms homeostatic mechanisms in macrophages, transferrin becomes fully saturated leading to elevated non-transferrin-bound iron and parenchymal iron overload [Porter et al 2014].

Iron loading anemias. This group of disorders includes: non-transfusion-dependent thalassemia (thalassemia intermedia), congenital and acquired sideroblastic anemias, congenital dyserythropoietic anemias, pyruvate kinase deficiency, and other anemias, all characterized by ineffective erythropoiesis. Chronic anemia, hypoxia, and ineffective erythropoiesis activate erythroid signaling, suppressing liver hepcidin synthesis and leading to increased intestinal iron absorption and iron release from macrophages [Muckenthaler et al 2017]. High transferrin saturation and ferritin, and parenchymal iron overload are typical manifestations of this group of disorders.

African iron overload (OMIM 601195) occurs in individuals with a predisposition to iron overload that is exacerbated by excessive intake of dietary iron. Iron accumulation primarily involves reticuloendothelial macrophages and later hepatocytes. It is particularly prevalent among Africans who drink a traditional beer brewed in non-galvanized steel drums. 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. *SCL40A1* pathogenic variant p.Gln284His appeared to be unique to African populations and associated with a mild iron-loading tendency [Gordeuk et al 2003]. However, a subsequent study failed to show that p.Gln284His was responsible for iron overload, while it could influence the inflammatory response in African populations [McNamara et al 2005].

Neonatal hemochromatosis (NH) is a severe liver disorder associated with extrahepatic siderosis with the same distribution seen in juvenile hemochromatosis (sparing the reticulo-endothelial system). NH is characterized by high mortality. Recurrence is approximately 80% in the offspring of affected women. Because it was observed in sibs, NH was classified as a familial hemochromatosis (OMIM 231100). However, clinical evidence now suggests that NH is the consequence of fetal liver injury due to a variety of causes. Most NH is ascribed to gestational alloimmune liver disease (GALD; NH-GALD). GALD can also produce liver disease without extrahepatic siderosis and the absence of siderosis in the newborn liver does not exclude the diagnosis of GALD.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with juvenile hemochromatosis, the evaluations summarized Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Juvenile Hemochromatosis

System	Evaluation	Comment
Liver	• Biochemical tests: serum transaminases, gammaglutamyl transferase, albumin, INR, bilirubin • Instrumental tests: abdominal ultrasound, fibroelastography • MR-based quantification of liver iron overload • CT & MR as needed (e.g., if focal lesions on ultrasound) • Liver biopsy for prognostic evaluation (severe fibrosis/cirrhosis) in those w/severe iron overload [1]	To determine the extent of liver damage & establish prognosis

Table 4. continued from previous page.

System	Evaluation	Comment
Cardiac	• ECG & Holter ECG • Transthoracic echocardiogram • MR-based quantification of myocardial iron overload	• Myocardial iron accumulation often precedes cardiac dysfunction. • Findings of left ventricular diastolic dysfunction (↓ left ventricular compliance) often precede ventricular dilatation & compromised ejection fraction in those w/out manifestations of cardiac failure or arrhythmias.
Skeletal	DEXA of femur & lumbar spine	To evaluate bone mineral density
	Radiologic evaluation of painful joints	To evaluate joints for arthropathy
Endocrine	• Overnight fasting serum glucose & insulin measurement • Oral glucose tolerance test w/baseline & 120-min serum glucose & insulin measurement	To evaluate for diabetes mellitus, glucose intolerance, & insulin resistance
	• Measurement of serum FSH & LH, & testosterone or estradiol • GnRH stimulation test as needed • Pituitary MRI as needed	To evaluate for hypogonadotropic hypogonadism

1. Current recommendations for *HFE* 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. Specific recommendations for individuals with juvenile hemochromatosis are not available; adaptation of the *HFE* hemochromatosis recommendation is a reasonable approach.

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 *HFE* hemochromatosis. It is simple, safe, and effective. Affected individuals should be encouraged to follow a regimen of phlebotomy of one unit of blood once weekly [Adams & Barton 2010]. 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, phlebotomy therapy may take more than one year and may require combined treatment with iron chelating agents in some individuals with very severe iron overload. See **Iron chelators** (following).

Hemoglobin should be monitored prior to phlebotomy; if the value is less than 11 g/dL, the treatment schedule is modified to every other week [Adams & Barton 2010, Brissot et al 2018]. 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 4-8 phlebotomies according to the amount of iron overload is reasonable; however, once serum ferritin concentration is below 100 ng/mL, it should be measured more often.

Individuals are treated until the serum ferritin is approximately 50 ng/mL, a value in the lower reference range that signifies that there is little or no storage iron [Adams & Barton 2010]. Experimental studies demonstrated that nonheme iron absorption is markedly increased and hepcidin is markedly decreased by phlebotomy

inducing very low serum ferritin. This could lead to unnecessary induction and maintenance phlebotomy [Lynch et al 1989, Piperno et al 2007].

Transferrin saturation usually decreases much less rapidly in response to phlebotomy therapy than the serum ferritin level. It may remain increased when body iron stores and serum ferritin values have already reached target levels. Despite successful iron depletion, transferrin saturation often remains increased in individuals with juvenile hemochromatosis, and reducing transferrin saturation to low-normal values may result in iron deficiency. Thus, experts recommend that serum ferritin, not transferrin saturation, be used as the indicator for cessation of phlebotomy induction therapy [Adams & Barton 2010, Brissot et al 2018].

Erythrocytoapheresis can be a rapid and safe alternative treatment, but it requires special apparatus and facilities and has limited availability. Although this treatment is excellent in selected individuals, erythropoietin stimulation may be required to maintain adequate hemoglobin level. This treatment may be preferred for individuals with severe iron overload and individuals whose clinical condition requires maintaining the isovolemic status or sparing of plasma proteins as in severe cardiomyopathy or advanced liver disease [Rombout-Sestrienkova et al 2016, Brissot et al 2018].

Iron chelators can be used when phlebotomies are contraindicated or in combined therapy in individuals with severe iron overload. There are few reports using iron chelators in individuals with hemochromatosis. Deferoxamine therapy is cumbersome, requiring daily parenteral administration (subcutaneous infusions), and can lead to poor compliance over the long term [Adams & Barton 2010]. Deferasirox is an oral iron chelator whose efficiency has been reported in individuals with juvenile hemochromatosis [Maeda et al 2011, Masera et al 2013]. It can be used as an off-label therapy in individuals with hemochromatosis.

Maintenance therapy. The frequency of phlebotomies is adjusted to maintain normal serum ferritin concentration and transferrin 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 phlebotomy maintenance therapy.

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

- Hypogonadism is treated with testosterone replacement in males and cyclical estrogen and progesterone therapy in fertile females. Although iron-induced pituitary hypogonadism is generally considered irreversible, it has been shown that gonadotropin cell dysfunction can be reversed when specific treatment is introduced early in the progression of the disease [Angelopoulos et al 2006, Pelusi et al 2016]. Therefore, hormonal substitution treatment should be withdrawn to reassess gonadotropin secretion when body iron stores have been normalized.
- Limited data regarding treatment of the joint involvement of hemochromatosis exist. Treatment relies on symptomatic measures with the use of analgesics and NSAIDs. Colchicine can be useful during flares most probably due to calcium pyrophosphate deposition. Intra-articular corticosteroid injections can be used but no relevant published data is available. Some data suggest the possible efficacy of phlebotomy but its effects, if any, are unpredictable. Joint prosthetic replacement (mainly hip and knee) is an option [Guggenbuhl et al 2011].
- Cardiac failure and arrhythmias require treatment as per cardiologist. Iron removal is mandatory because of the evidence of its significant effect in improving cardiac function [Murphy & Oudit 2010]. If left untreated, cardiac disease progresses rapidly and becomes refractory to treatment, leading to death in most affected individuals. Orthotopic heart transplantation has been used on occasion [Caines et al 2005].
- Based on data related to other liver disease and *HFE* hemochromatosis [Falize et al 2006] it can be assumed that iron depletion can improve fibrosis unless cirrhosis is fully established. Nevertheless,

individuals with liver cirrhosis require endoscopic evaluation to document the presence of varices and ultrasounds every six months to monitor (nodular evolution, portal hypertension, gallstones). In general, hemochromatosis remains an uncommon indication for liver transplantation usually limited to individuals with hemochromatosis and hepatocellular carcinoma. Pretransplant iron depletion is recommended if tolerated as it reduces the risk of cardiac and infectious complications postoperatively [Dar et al 2009, Brissot et al 2018].

- Glucose intolerance or diabetes may require oral agents or insulin administration. Phlebotomy has a variable impact on diabetes control. In general, it may prevent progression if started in the earlier stages of disease, although the majority of individuals with diabetes will experience no significant change or worsening in their glucose metabolism control [Angelopoulos et al 2007, Pelusi et al 2016].

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

Hormone replacement therapy may prevent the development of osteoporosis.

Surveillance

If hepatic cirrhosis is identified, monitoring for hepatocellular cancer (HCC) is recommended. The imaging test most widely used for surveillance is ultrasonography (US), and a 6-month interval represents a reasonable choice. The performance of US in early detection of HCC is highly dependent on the expertise of the operator and the quality of the equipment. Thus, special training for ultrasonographers is recommended. AFP is the most widely tested biomarker in HCC, but it has a suboptimal performance as a serologic test for surveillance [European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer 2012].

Table 5. Recommended Surveillance for Individuals with Juvenile Hemochromatosis

Manifestation/ System	Evaluation	Frequency
Iron overload	Serum ferritin concentration; transferrin saturation	In those at risk annually starting in early childhood; every 6-12 mos in maintenance phase
	Serum ferritin	Every 4-8 phlebotomies during induction phase; every 1-2 phlebotomies as ferritin levels approach the target of 50 ng/mL
Liver	Liver function tests	Every 6-12 mos according to severity of liver dysfunction
	Abdomen ultrasound + serum alpha-fetoprotein	Every 6 mos in individuals w/severe fibrosis/cirrhosis to monitor for hepatocellular cancer
	Abdomen ultrasound	Every 12-24 mos in non-cirrhotics in maintenance therapy
	Fibroelastography	Every 12-24 mos to monitor for fibrosis evolution
Heart	Cardiac ultrasound & MR for evaluating morphology & function	According to severity of cardiac dysfunction; MR every 6-12 mos if myocardial iron overload is present
	Holter ECG for evaluating arrhythmias	According to symptoms & history of arrhythmias
Pituitary-gonadal axis	Testosterone; estradiol	Every 12 mos or as needed

Table 5. continued from previous page.

Manifestation/ System	Evaluation	Frequency
Endocrine pancreas	Fasting & postprandial serum glucose; glycosylated hemoglobin (Hgb A1c)	Every 6-12 mos as needed
Bone & joints	Vitamin D, PTH, serum & urinary calcium & phosphorus, C-terminal telopeptide	Every 12 mos as needed
	DEXA	Every 24 mos or more often according to presence of osteoporosis

Agents/Circumstances to Avoid

Avoid the following [Adams & Barton 2010, Brissot et al 2018]:

- 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*

Evaluation of Relatives at Risk

Once a diagnosis of juvenile hemochromatosis has been made in a family, it is appropriate to clarify the clinical/genetic status of all at-risk family members (i.e., sibs) of an affected individual in order to identify as early as possible those who would benefit from early monitoring for the development of iron overload. If juvenile hemochromatosis is detected before evidence of organ damage, treatment via phlebotomy can reverse or prevent many of the secondary complications resulting from organ damage.

Evaluation of at-risk family members can include:

- Serum iron indices (serum iron, transferrin saturation, and serum ferritin) and serum transaminases as first evaluation of coexistent liver damage and C-reactive protein to exclude inflammatory conditions that can influence serum iron indices;
- Molecular genetic testing (if the *HAMP* or *HJV* pathogenic variants have been identified in an affected family member).

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

Pregnancy Management

All pregnant women with juvenile hemochromatosis should be under the care of a maternal-fetal medicine specialist, an endocrinologist, and a cardiologist. Preferably women with juvenile hemochromatosis should be seen by these specialists prior to becoming pregnant.

Pregnancy in women with untreated juvenile hemochromatosis is high risk because the increased hemodynamic burden of pregnancy can precipitate cardiac failure in women with an underlying cardiomyopathy. Of note, it is critically important for specialists in endocrinology and infertility to be aware of juvenile hemochromatosis as a cause of infertility and to evaluate individuals for iron overload prior to correcting the underlying hormonal imbalance [Filali et al 2004].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for 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

Juvenile hemochromatosis 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., presumed to be carriers of one *HAMP* or *HJV* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that each parent is heterozygous for a pathogenic variant in either *HAMP* or *HJV* and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are not at risk of developing juvenile hemochromatosis. Middle-age-onset hemochromatosis has been reported in some *HJV* heterozygotes [Kong et al 2019]. However, it is possible that undetected pathogenic variants or rearrangements in *HJV* or other iron genes are present in these individuals.

Sibs of a proband

- If both parents are known to be heterozygous for a pathogenic variant in either *HAMP* or *HJV*, each sib of an affected individual has at conception 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 not at risk of developing juvenile hemochromatosis. Middle-age-onset hemochromatosis has been reported in some *HJV* heterozygotes [Kong et al 2019]. However, it is possible that undetected pathogenic variants or rearrangements in *HJV* or other iron genes are present in these individuals.

Offspring of a proband. Unless an individual with juvenile hemochromatosis has children with an affected individual or a carrier, his/her offspring will be heterozygotes (carriers) for a pathogenic variant in *HAMP* or *HJV*.

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

Carrier (Heterozygote) Detection

Carrier testing for at-risk relatives requires prior identification of the *HAMP* or *HJV* pathogenic variants in the family.

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 Testing

Once the juvenile hemochromatosis-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for juvenile hemochromatosis 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.**
  P.O. Box 950871
  Lake Mary FL 32795-0871
  Phone: 407-829-4488; 888-655-IRON (4766)
  Fax: 407-333-1284
  Email: mail@americanhs.org
  www.americanhs.org
- **EFAPH: European Federation of Associations of Patients with Haemochromatosis**
  4 rue Paul Demange
  Croissy-sur-Seine F-78290
  France
  Phone: 00 33 (0)6 08 25 94 04
  Email: fcourtois.dom@wanadoo.fr; efaph@gmx.eu
  www.efaph.eu

- **Haemochromatosis Society**
  Haemochromatosis UK Office
  Henrith Business Centre, 3 Enterprise Way
  Pinchbeck, Spalding Lincolnshire PE11 3YR
  United Kingdom
  Phone: 03030 401 101; 03030 401 102
  Email: office@huk.org.uk; helpline@huk.org.uk
  www.haemochromatosis.org.uk
- **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
  Fax: 604-279-7138
  Email: office@toomuchiron.ca
  www.toomuchiron.ca
- **Iron Disorders Institute (IDI)**
  Phone: 888-565-4766 (Toll-free Information Request Line); 864-292-1175
  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. Juvenile Hemochromatosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HAMP	19q13.12	Hepcidin	HAMP @ LOVD	HAMP	HAMP
HJV	1q21.1	Hemojuvelin	HFE2 @ LOVD	HJV	HJV

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 Juvenile Hemochromatosis (View All in OMIM)

602390	HEMOCHROMATOSIS, TYPE 2A; HFE2A
606464	HEPCIDIN ANTIMICROBIAL PEPTIDE; HAMP
608374	HEMOJUVELIN; HJV

Table B. continued from previous page.

613313	HEMOCHROMATOSIS, TYPE 2B; HFE2B

Molecular Pathogenesis

Diferric transferrin (Tf-Fe2) provides iron to most cells of the body. The control of systemic iron levels occurs through the regulation of:

- **Acquisition and delivery according to need**
  - Enterocytes. Absorption through duodenal and upper jejunum
  - Macrophages. Senescent erythrocytes
  - Hepatocytes. Tf-Fe2
  - Placental cells. Maternal transferrin
- **Recycling.** Unidirectional from senescent erythrocytes to the erythroid bone marrow through macrophages
- **Storage.** Liver and spleen are the main storage organs.

There is no known regulated form of iron excretion; however, 1-2 mg iron are lost daily through cellular exfoliation.

The iron saturation of serum transferrin is both a major indicator and a determinant of systemic iron homeostasis [Anderson & Frazer 2017, Muckenthaler et al 2017]. Cellular iron release occurs through the iron exporter ferroportin, encoded by *SLC40A1* (see Differential Diagnosis). Ferroportin activity on cell membranes is predominantly governed post-translationally by hepcidin.

HAMP encodes the liver peptide hepcidin, the master regulator of iron homeostasis. Hepcidin regulates intestinal iron absorption and iron release from storage cells by binding and blocking ferroportin [Aschemeyer et al 2018], thus increased hepcidin expression limits iron absorption via repression of ferroportin while its reduction allows greater iron absorption and macrophage iron release via release of ferroportin.

HJV encodes hemojuvelin (HJV), a main regulator of hepcidin, is a GPI-linked protein that activates hepcidin as a co-receptor for BMP cytokines [Silvestri et al 2019]. Hence, HJV-deficient individuals and mice have undetectable levels of hepcidin, thus explaining the more severe phenotype of individuals with *HJV* juvenile hemochromatosis. In addition, other hemochromatosis-associated proteins (HFE and transferrin receptor 2 [TFR2]) are iron-dependent positive regulators of *HAMP* expression [Brissot & Loréal 2016]. Hemochromatosis caused by mutation of *HFE*, *TFR2* (see Differential Diagnosis), as well as *HJV* involves defective synthesis of hepcidin, and is possibly involved in the same regulatory pathway of hepcidin. Defective HFE or TFR2 prevents the formation of a functional iron sensor and signal transduction effector complex leading to reduced or inadequate hepcidin expression.

Mechanism of disease causation. Autosomal recessive juvenile hemochromatosis occurs through a loss-of-function mechanism.

Table 6. Juvenile Hemochromatosis: Gene-Specific Laboratory Technical Considerations

Gene [1]	Considerations
HAMP	None
HJV	First exon is not translated. Most pathogenic variants occur in exons 3 and 4.

1. Genes from Table 1 in alphabetic order

Table 7. Juvenile Hemochromatosis: Notable Pathogenic Variants by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [2])	Comment [Reference]
HAMP	NM_021175.4 NP_066998.1	c.166C>T	p.Arg56Ter	Pathogenic variants that occur in known functional domains [Roetto et al 2003; Delatycki et al 2004; Jacolot et al 2004; Roetto et al 2004; Badar et al 2016; Author, unpublished data]
		c.175C>G	p.Arg59Gly	
		c.175C>T	p.Arg59Ter	
		c.176G>C	p.Arg59Pro	
		c.208T>C	p.Cys70Arg	
		c.233G>A	p.Cys78Tyr	
HJV	NM_213653.3 NP_998818.1	c.959G>T	p.Gly320Val	Most prevalent pathogenic variant reported to date [Kong et al 2019]
		c.295G>A	p.Gly99Arg	Recurrent pathogenic variants in northern European individuals [Lanzara et al 2004, Hamdi-Rozé et al 2019]
		c.302T>C	p.Leu101Pro	
		c.445delG	p.Asp149fs (p.Asp149ThrfsTer97)	Recurrent pathogenic variant in Italian individuals [Lanzara et al 2004]
		c.526C>T	p.Arg176Cys	Pathogenic variant recurrent in French individuals [Hamdi-Rozé et al 2019]
		c.745G>C	p.Asp249His	Most common pathogenic variant in Japanese individuals [Ikuta et al 2017]
		c.934C>T	p.Gln312Ter	Predominant pathogenic variant in Japanese; recurrent in Chinese individuals [Ikuta et al 2017]
		c.962_963delGCinsAA	p.Cys321Ter	Most common pathogenic variant in Chinese population [Lv et al 2018]
		c.1006G>T	p.Gly336Ter	Pathogenic variant recurrent in Indian population [Dhillon et al 2018]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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

1. Genes from Table 1 in alphabetic order

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

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