HFE-Associated Hereditary Hemochromatosis (HFE-HH)

What is Hemochromatosis?

Hemochromatosis is a common adult-onset condition that causes the body to absorb and store too much iron. Without treatment, this condition may result in end-organ damage, particularly of the liver, skin, pituitary gland, pancreas, heart, joints and testes in males. Hemochromatosis can either be acquired (non-genetic) or hereditary.

Hereditary hemochromatosis (HH) is an autosomal recessive condition due to mutations in the HFE gene (HFE-HH).

Counselling for HFE-HH is not always straightforward because mutations do not always result in disease even in the homozygous state. There are gender-based differences and significant environmental factors such as dietary iron load that affect when/if an individual will show signs of HFE-HH.

Two common mutations have been described in the HFE gene and are tested for in our laboratories: C282Y (c.845G>A p.Cys282Tyr) and H63D (c.187C>G p.His63Asp) (NM000410.3). Although the C282Y mutation is an accepted predisposing factor for hemochromatosis, the H63D mutation is thought to confer a much lower predisposition. H63D homozygotes are common in the general population, but most of them are healthy.

Among individuals of European ancestry, the carrier frequency of the most significant mutation (p.Cys282Tyr or C282Y) is ~1/10.

Juvenile hereditary hemochromatosis has an earlier age of onset and more severe clinical manifestations than HFE-HH. Juvenile hereditary hemochromatosis is caused by mutations in a different gene. More information on juvenile hereditary hemochromatosis can be found at http://www.ncbi.nlm.nih.gov/books/NBK1170/.

Genetic testing for HFE-HH

Molecular testing for HFE-HH should be regarded as a test for predisposition to hemochromatosis and NOT as a diagnostic test unless the individual is already clinically and/or biochemically affected.

Genetic testing for HFE-HH is indicated in individuals where a diagnosis of HFE-HH is being considered due to abnormal biochemical indices (elevated transferrin saturation and ferritin). *Increased ferritin alone (i.e. with normal transferrin saturation) is not likely due to HFE-HH and other causes should be considered by the referring physician.*

Molecular Diagnostics Laboratory
Calgary Tel: 403-955-7397 Fax: 403-955-7624 * Edmonton Tel: 780-407-1434 Fax: 780-407-1761
www.albertahealthservices.ca/lab/page8667.aspx

Genetic testing may also be considered in adults at risk for HFE-HH due to a known family history of HFE-HH. Genetic testing of the adult offspring, siblings and parents of an affected individual is available to clarify their genetic status and risk to develop symptoms. Biochemical evidence of iron overload is not a requirement for genetic testing in this situation.

Genetic testing of asymptomatic minors is not performed.

Current testing is limited to the two most common mutations in the Northern European population. There are specific mutations confined to other ethnic groups not tested for in Alberta.

A positive genetic test result may have implications for life/disability insurance, employability, and emigration. Appropriate counselling to ensure that patients understand the implications is important. As an alternative to genetic testing, serum transferrin saturation and ferritin levels can be monitored on a yearly basis in those at risk for HFE-HH.

Follow-up and Management

Frequency of ongoing biochemical screening in biochemically/clinically asymptomatic individuals is dependent on the specific genetic results.

Therapeutic phlebotomy is indicated in patients presenting with biochemical evidence of iron overload and/or end-organ damage regardless of genetic results. **Referral of patients to the Medical Genetics Clinic is recommended.**

Referrals for genetic counselling can be made to:

University of Alberta Hospital
Medical Genetics Clinic
Edmonton, AB T6G 2H7
Fax: 780-407-6845
Phone: 780-407-7333

Dr. R. Brian Lowry Clinical Genetics Unit
Alberta Children's Hospital
Calgary, AB T3B 6A8
Fax: 403-955-2701
Phone: 403-955-7373

Management information can be obtained through the Alberta Toward Optimized Practice website (Towards Optimized Practice > CPGs {Clinical Practice Guidelines} > Other > Hemochromatosis)