Hereditary Haemochromatosis (HH) - General Information

- HH, an autosomal recessive adult onset disorder, is marked by increased plasma transferrin saturation associated with defective synthesis and / or regulation of hepcidin. Genes involved include *HFE*, *HFE2*, *TFR2* and *HAMP*. ***HFE*-related HH is by far the most common form of the disorder**.

- Patients with suspected iron overload should have fasting transferrin saturation and serum ferritin measurements. **Normal serum ferritin essentially rules out iron overload, except in *very rare* cases of non HFE related HH**. Raised serum ferritin levels have low specificity. ***HFE* genotyping is indicated only if transferrin saturation is increased.**

- About 80% of Europeans with clinical iron overload are homozygous for the HFE C282Y variant (p.Cys282Tyr). **When iron stores are elevated, with or without clinical symptoms, C282Y homozygosity is required for a diagnosis of HFE-HH.** Any other HFE genotype should be interpreted with caution. **Homozygosity alone for C282Y is not sufficient to diagnose HH - about 1 in 250 Caucasians in the general population have this genotype.**

- **C282Y homozygotes** are likely to develop increased serum ferritin and transferrin saturation, **however only about 15 to 20% of individuals with this genotype go on to show clinical symptoms of iron overload.** HH penetrance in C282Y homozygotes is higher in men than in women. Environmental factors such as alcohol misuse, steatosis and viral infections play key roles in the development of clinical symptoms.

- The risk to develop iron overload in the future is increased in asymptomatic adult first degree relatives of C282Y homozygous index cases. Genotyping for C282Y, in association with genetic counselling, is recommended in such relatives in order to inform their future risk to develop iron overload.

- The predicted heterozygous carrier rate for C282Y in the general population is approximately 10%. **C282Y heterozygotes, including those in families where a diagnosis of iron overload has been made, are at very low risk of developing HH and genotyping of their first degree relatives is not recommended.**

- In Europe, the HFE H63D (p.His63Asp) polymorphism is found in 20 to 25% of the general population. C282Y / H63D compound heterozygosity is a risk factor for mildly elevated serum iron and hepatic iron stores but is considered to be insufficient independently to cause haemochromatosis. C282Y / H63D compound heterozygotes with iron overload should be investigated for additional contributory causes of hyperferritinaemia.

- Homozygosity for H63D may be associated with increased transferrin saturation and serum ferritin, **however this genotype is considered unlikely independently to be sufficient cause for iron overload.** H63D homozygotes with iron overload should be investigated for additional contributory causes of hyperferritinaemia. Heterozygosity for H63D is not a risk factor to develop haemochromatosis.

- About 1 to 3% of individuals in northern European populations carry the HFE S65C (p.Ser65Cys) polymorphism. There is no evidence that S65C has a role in clinically manifest iron overload and testing for S65C is not recommended for diagnostic purposes.

- About 5% of patients with haemochromatosis lack the above variants in the *HFE* gene. Other rare genetic factors may be involved in some of these cases. If there is evidence of iron accumulation in the presence of a normal *HFE* genotype, such as persistently raised transferrin saturation, then further investigation may be justified after exclusion of secondary iron overload.

Reference:

EMQN best practice guidelines for the molecular genetic diagnosis of Hereditary Hemochromatosis (HH). G Porto, P Brissot, D Swinkels, H Zoller, O Kamarainen, S Patton, I Alonso, M Morris, and S Keeney [European Journal of Human Genetics: http://www.nature.com/ejhg/journal/vaop/ncurrent/full/ejhg2015128a.html]

Testing method: Genomic DNA from whole blood subjected to an Agena iPLEX ® assay (MALDI-TOF MS based analysis). Method developed in house and validated on a panel of known genotype controls and by confirmation using an alternative assay method.
