

Genetic testing for hereditary haemochromatosis

Background:

Hereditary haemochromatosis (HH) is a recessive inherited autosomal disorder of iron metabolism, characterized by continuous absorption of iron in the upper intestinal tract despite fully saturated iron stores. Progressive accumulation of iron in various organs causes progressive development of clinical symptoms with increasing age, finally leading to irreversible tissue damage. The main target organs are the liver (cirrhosis, hepatocellular carcinoma), pancreas (diabetes), joints (arthralgia, arthritis), heart (cardiomyopathy) and hypophysis (hypogonadism). The disease is fairly common in the Caucasian population (1 in 300), with a carrier frequency between 1 in 8 to 1 in 10. The gene encoding the HFE protein that is responsible for the disorder harbours two mutations that are associated with HH: C282Y and H63D. 85% of patients are homozygous for the C282Y mutation, while the H63D mutation can be considered as a predisposing factor when combined with other genetic (C282Y heterozygosity) or environmental factors. Early detection of the disease and treatment by regular phlebotomy offer a normal life expectancy for the patient. HH is the most common genetic disease in Europe and its treatment is simple and efficient.

Indications for testing:

- increased transferrin saturation (>50%) or serum ferritin concentration (>400 g/l in men, >200 g/l in women)
- the clinical diagnosis of haemochromatosis
- clinically diagnosed haemochromatosis or family history of verified C282Y mutation (combined with genetic counselling)

Method:

PCR, restriction digestion and agarose gel electrophoresis

Diagnostic predictive value:

Homozygosity for the C282Y or compound heterozygosity is equivalent with the diagnosis of HH. The lack of both mutations does not rule out the possibility that a causative mutation is present in another location of the HFE gene or in another gene. The lack of the C282Y mutation in a family member of a patient with a verified C282Y mutation virtually rules out the presence of HH.

Sample requirement:

- buccal swab at room temperature *or*
- 2 ml blood in an EDTA (lavender top) tube, transported at +4 °C

*Feder JN et al., A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nature Genet.* 13: 399-408, 1996.