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Molecular genetic testing for hereditary haemochromatosis

Introduction

Hereditary haemochromatosis is an inherited disorder of iron metabolism and affects approximately 1 in 200 people in the UK. It is characterised by over-absorption of iron by the gastrointestinal mucosa. This leads to excessive storage of iron especially in the liver, skin, pancreas, heart, joints and testes, where it can impair tissue structure and function. If left untreated over decades, progressive iron-loading can result in serious illnesses including cirrhosis, hepatomas, diabetes, cardiomyopathy, arthritis and hypogonadotrophic hypogonadism. Treatment of haemochromatosis by removal of excess iron by therapeutic phlebotomy decreases the morbidity due to haemochromatosis if implemented before irreversible tissue damage has occurred.

Classical or type 1 hereditary haemochromatosis (OMIM 235200) is the most common form and is due to mutations in the *HFE* gene (OMIM 613609). Amongst individuals of Northern European ethnic origin, 80-93% of patients with *HFE*-related hereditary haemochromatosis are homozygous for the *HFE* c.845G>A p.(Cys282Tyr) mutation, commonly referred to as C282Y. Most of the remainder are compound heterozygous for c.845G>A with a second mutation c.187C>G p.(His63Asp), also referred to as H63D. A rare third mutation c.193A>T p.(Ser65Cys), also called S65C, has a minor effect on iron homeostasis and may underlie hereditary haemochromatosis when found in compound heterozygotes with C282Y. Individuals homozygous for H63D or S65C are unlikely to have increased risk of iron over-load. These mutations show low penetrance which means that a significant proportion of individuals with these genotypes remain asymptomatic lifelong.

Reasons for referral

Early symptoms of hereditary haemochromatosis, which include abdominal pain, weakness, lethargy and weight loss, are non-specific. However, if left untreated patients may develop hepatic fibrosis or cirrhosis and 25% of patients with established cirrhosis develop hepatocellular carcinoma. Furthermore, untreated individuals may also develop hyperpigmentation of the skin, diabetes mellitus, cardiomyopathy, arthritis and hypogonadism. Therefore, rapid molecular genetic testing for haemochromatosis is a valuable tool to aid in the management of patients with these non-specific symptoms and biochemical evidence of iron-overload.

Service offered

Confirmatory diagnostic testing: molecular testing for the three common *HFE* gene mutations, c.845G>A p.(Cys282Tyr), c.187C>G p.(His63Asp) and c.193A>T p.(Ser65Cys). Genetic testing for other *HFE* mutations and non-HFE-related haemochromatosis is not currently available.

Target reporting time

5 working days

Sample type

3ml blood in EDTA anti-coagulant