Scheme 5B – Interpretative HFE Genotyping and Hereditary Haemochromatosis

General Comments Scenarios 3 and 4/2018 **Distributed September 2018**

The presenting symptoms of haemochromatosis can often be vague and so patients often are referred from one specialist to another. One key finding that may help speed up diagnosis is the specific finding of a particular ankle arthropathy associated that is linked to haemochromatosis. This specific bony extension is only seen in patients with haemochromatosis. The references are below.

Clinical reference

Richardson A, Prideaux A, Kiely PDW. Haemochromatosis: unexplained MCP or ankle arthropathy should prompt diagnostic tests; findings from two UK observational cohort studies. Scand J Rheumatol 2017; 46: 69-74. DOI: 10.3109/03009742.2016.1155645

MRI reference

Elstob A, Ejindu V, Heron C, Kiely PDW. Haemochromatosis arthropathy: MRI hindfoot characteristics; a case-control study. Clin Rad 2017 doi:10.1016/j.crad.2017.10.002

General thoughts about the arthropathy reference

Kiely PDW. Haemochromatosis arthropathy – a conundrum of the celtic curse. J R Coll Physicians Edinb 2018; 48: 233-8. doi 10.4997/JRCPE.2018.307

About 80% of haemochromatosis patients in the UK are homozygous for the p.C282Y mutation. A proportion of the remainder show digenic inheritance. Many of these have one copy of the p.C282Y HFE mutation and one copy of a mutation in one of the other genes in the iron handling pathway. The first such case of digenic inheritance in haemochromatosis was identified over 10 years ago. The phenotype in some cases may be mild so the serum iron indices will not be exceptionally high especially in women. Such patients respond well to treatment. If the serum iron indices lie outside the normal range then fasting measurements need to be taken and if still raised further investigations made. In this case there was mention of a family history. Haemochromatosis is not just a case of two copies of the p.C282Y mutation. The p.C282Y mutation can often occur in conjunction with a ferroportin mutation and this muddies the water and can change the phenotype. Further genetic studies are justified.

One of the reasons for penalties was making the decision that as Mhairi was heterozygous for p.C282Y with mild iron overload no further action was required. The clues to the fact that she had haemochromatosis were the raised iron indices, the bony ankle and the family history. These weren't always picked up on.

Scenario 4

In this scenario the Robert has been identified as being a C282Y heterozygote. His half-brother has been identified as a p.C282Y homozygote who has haemochromatosis. The p.C282Y allele frequency in the UK population is anywhere from 1 in 10 to 1 in 15 depending upon the ethnic mix. Screening of the parent not shared by the two brothers would quickly identify the risks of other family members. If this parent had the wildtype genotype, then any other half siblings would either be heterozygotes or wildtype. Advice should have been about screening siblings, parents and the partner of the heterozygote. If the partner has the wildtype genotype any children will be carriers of the p.C282Y mutation. A statement should have been made about no further action being needed if serum iron indices were normal. Penalties were given for not including these points. Where a proband has been identified, this provides the opportunity to identify other affected individuals who may not be symptomatic. Many of the reports were too brief and did not provide useful information.