Screening for haemochromatosis

This issue of the journal contains two papers by Bradley and colleagues on screening for haemochromatosis.[1 2] One interest of the authors was to conduct a meta-analysis of the published estimates of the frequency of homozygosity for haemochromatosis.[1] The authors also employed meta-analysis to evaluate the ability of blood and liver tests of iron stores to identify correctly the previously unidentified homozygous siblings of affected probands.[2] This is the first known application of meta-analysis to screening for haemochromatosis.

The authors identified five independent studies that could be used, and the combined estimate of the prevalence of homozygosity for haemochromatosis was 5.3 per 1000 individuals of European ancestry. This is similar to some previously published reports. Given a homozygote frequency of 5.3 per 1000, the gene frequency and hence the prevalence of heterozygosity for haemochromatosis (13%) can be calculated. These results indicate that in populations of European ancestry haemochromatosis is more common than is generally recognised, and that heterozygosity for haemochromatosis is very common.

Bradley and colleagues show that transferrin saturation can be used in screening. They estimated the detection rate of homozygosity for haemochromatosis according to transferrin saturation cut off values between 50 and 75%. In men, employing a transferrin saturation cut off of 75%, the detection rate was 64% and the false positive rate below 0.1%. In women, with a 65% cut off, the detection rate was 58% and the false positive rate 0.18%. The authors also examined the morbidity from undiagnosed haemochromatosis in previously unidentified homozygous siblings of affected index cases. Under the age of 40, 55% of male and 43% of female homozygote siblings had one or more clinical manifestations of morbidity with haemochromatosis (such as abdominal pain, fatigue, arthropathy). Over the age of 40, 73% of men and 44% of women had morbidity. These findings from meta-analysis suggest that screening before age 40 is important, especially for men, because more than half of unselected homozygous men had morbidity by age 40. In an earlier study, however, the morbidity from haemochromatosis among previously unidentified homozygotes was materially greater over age 40 than under age 40.[3] Haemochromatosis heterozygotes usually do not develop iron overload, and are therefore asymptomatic, unless an additional condition is also present. A description of the iron phenotype of about 1000 heterozygotes will be published in December 1996.[4] The two articles by Bradley and colleagues in this issue provide useful data that can be used in the design of future haemochromatosis screening studies.

Some siblings who are HLA-identical with an index case affected with haemochromatosis do not have iron overload. This does not necessarily mean that some homozygotes do not express the iron loading phenotype, as these siblings may be heterozygote through inheriting a recombinant chromosome from one parent. The location and the nature of the haemochromatosis gene is undergoing intense scrutiny.[5] In a study of 178 individuals who had iron overload compatible with haemochromatosis, 83% were homozygous for a mis-sense mutation at site Cys282Tyr of a new gene called HLA-H. Only 10 of the 155 control subjects (6%) possessed a copy of the Cys282Tyr mutation.

Studies are in progress in several centres around the world to determine the frequency of the HLA-H Cys282Tyr mutation in other populations of haemochromatosis homozygotes. To date, this is considered the best candidate gene for haemochromatosis. Presumably there will be some non-iron-loaded individuals with two copies of the Cys282Tyr mutation, unless HLA-H is the haemochromatosis gene, and unless Cys282Tyr is the mutation responsible for the iron loading phenotype in haemochromatosis. It is now possible to include testing for the Cys282Tyr mutation among individuals who are thought to be haemochromatosis homozygotes.

After the location and nature of the haemochromatosis gene is verified, and its abnormal protein product identified, it should be possible to determine the mechanism by which the haemochromatosis gene stimulates (or fails to turn off) excessive duodenal iron absorption. Indeed, it is probable that future study of the haemochromatosis gene will provide insight into iron absorption in normal individuals.

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5 Feder JN, Gnirke A, Thomas W, *et al.* A novel MHC class I-like gene is mutated in patients with hereditary hemochromatosis. *Nature Genetics* 1996;13:399–408.