

Population genetic screening for hereditary haemochromatosis: are we a step closer?

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Now that we can predict risk accurately, we need to reconsider screening strategies

The recent completion of the Human Genome Project offered great promise that medical genetics would have a population-based impact on the prevention and treatment of inherited conditions. A common inherited condition, hereditary haemochromatosis, was initially touted as a “poster child” for population genetic screening. Most cases are due to homozygosity for a single mutation of the *HFE* gene, leading to iron overload. Hereditary haemochromatosis is considered an ideal candidate for population genetic screening as genetic susceptibility is common, testing is inexpensive, and iron studies can detect early stages of the disease.¹ Most importantly, venesection is a simple and effective way to both prevent and manage the potential sequelae of iron overload,² which include severe fatigue, arthritis, impotence, cirrhosis, diabetes, and cardiomyopathy.³ However, even for an inherited condition as apparently straightforward as haemochromatosis, justifying population genetic screening has proven more complicated than initially expected.⁴

After the gene linked with hereditary haemochromatosis was identified in 1996,⁵ a flurry of publications called for the consideration of population genetic screening, as it was thought that most people who were homozygous for the C282Y mutation would eventually develop the disease. Although more than 90% of cases are due to C282Y homozygosity,³ there is now good evidence that not all those who are homozygous will progress through all stages of the disease. These stages comprise genetic predisposition without abnormality; iron overload (raised serum ferritin in the presence of a raised fasting transferrin saturation) without symptoms; iron overload with haemochromatosis-associated symptoms, such as arthritis and fatigue; and iron overload with organ damage, particularly cirrhosis.⁶ Although most of those who are homozygous appear to develop raised serum ferritin and raised transferrin saturation by the fifth decade of life,⁷ until now there have been few reliable data on the number of homozygous individuals who develop disease as a result of iron overload.

Population estimates of the prevalence of non-specific signs and symptoms of haemochromatosis (eg, arthritis and fatigue) and disease due to documented iron overload (eg, cirrhosis) in C282Y homozygous individuals have been hindered by either the failure to clinically assess individuals before knowledge of their genetic status or an inability to account for the long lead time of preclinical iron-overload status. A cross-sectional population study of participants aged 20–80 years suggested that disease attributable to haemochromatosis occurs in fewer than 1% of those who are homozygous, regardless of sex.⁸ However, this study did not conduct clinical examinations or liver biopsies, and a quarter of the homozygous patients were excluded on the basis that they had been previously diagnosed. This exclusion would be expected to reduce the estimate of clinical penetrance of C282Y homozygosity. Furthermore, the study included homozygous patients of ages at

which disease would not be expected to have developed. Until recently, there had been only two longitudinal studies of hereditary haemochromatosis designed to accurately estimate the proportion of homozygous patients who will develop disease secondary to iron overload.^{9,10} However, with a combined total of 23 patients, they were substantially underpowered to assess disease prevalence.

In the largest longitudinal prospective study to date, my colleagues and I assessed 203 homozygous individuals among a healthy population of 31 192, followed up over 12 years.¹¹ Data were collected by physicians who were blinded to genotype, and liver biopsies were performed as clinically indicated (serum ferritin > 1000 µg/L, unexplained hepatomegaly or raised serum aminotransferase levels).¹² We found that homozygous individuals with a serum ferritin level higher than 1000 µg/L were at increased risk of haemochromatosis-associated signs and symptoms, when compared with either those who were homozygous with a serum ferritin level of 1000 µg/L or less, or individuals with other *HFE* genotypes. In particular, homozygous men with a serum ferritin level higher than 1000 µg/L reported greater fatigue, use of arthritis medication and history of liver disease than men without the C282Y mutation.

We also assessed the proportion of homozygous individuals with disease that was directly attributable to iron overload using the combined definition of documented iron overload¹³ and one or more of the following: cirrhosis, liver fibrosis, hepatocellular carcinoma, raised aminotransferase concentration, physician-diagnosed symptomatic hereditary haemochromatosis, and arthropathy of the second and third metacarpophalangeal joints. Iron overload-related disease developed in 28% of homozygous men, but only 1% of homozygous women.¹¹

Our study is important because it enables us, for the first time, to make accurate predictions about the proportion of those at genetic risk of haemochromatosis who will develop symptoms that could otherwise be prevented. Furthermore, we confirmed that homozygous individuals with a serum ferritin level higher than 1000 µg/L were not only at increased risk of cirrhosis, but also of non-specific signs and symptoms of haemochromatosis. This has implications for a cost-effectiveness analysis of population genetic screening for hereditary haemochromatosis. Other criticisms of such screening,¹⁴ including concerns over insurance implications and creating a cohort of “worried well” among those at genetic risk of haemochromatosis, have proved unfounded.^{15,16} It appears that cost is the last barrier to screening. The questions that remain regarding population screening include: Would it be more cost-effective to simply offer screening to men? What is the most cost-effective age to screen at? What is the most pragmatic way to access a population before an age at which disease is likely to develop? Hereditary haemochromatosis may yet offer a prototype for population genetic screening programs, but the journey of justification has offered unexpected challenges.

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