

Population genetic screening for hereditary haemochromatosis

Even for a simple genetic condition, screening the general population is not straightforward

HEREDITARY HAEMOCHROMATOSIS has been touted as the “poster child” for public health genetics. Most cases of haemochromatosis are due to homozygosity for a single mutation leading to iron overload. It is considered to be an ideal candidate for population genetic screening because genetic susceptibility is common, testing is inexpensive, and iron studies can detect early stages of disease. Most importantly, venesection is a simple and effective way to both prevent and manage the potential sequelae of iron overload, which include severe fatigue, arthritis, impotence, cirrhosis, diabetes, and cardiomyopathy. However, even though most cases of haemochromatosis are due to a single mutation, it is still unclear how many people homozygous for this mutation will develop serious disease. Consequently, there is uncertainty as to the benefit of screening.

Following characterisation of the *HFE* gene in 1996,¹ genetic testing for hereditary haemochromatosis has become available. In Australia, Medicare claims for testing for genetic susceptibility to hereditary haemochromatosis have risen from 14 414 in 1999 to almost 30 000 in 2002.² It is predicted that about one in 200 Australians are homozygous for the C282Y mutation, which accounts for about 90% of cases of hereditary haemochromatosis identified to date in high-risk families.³

A person carrying two copies of the C282Y mutation is at risk of developing iron overload and subsequent disease. However, like all diseases, haemochromatosis is defined by

pathology, and a person does not have hereditary haemochromatosis unless body iron stores, as reflected by abnormal iron indices (serum ferritin and fasting transferrin saturation), are elevated. There is a wide spectrum of potential consequences of iron overload, and while about 60% of C282Y homozygotes will eventually develop iron overload,^{3,4} it is not known what proportion will progress to serious clinical disease. The answer is complicated by the long latency for development of disease (probably many years) and the possible modifying effects of sex, diet, environment and other genes.

Recent population-based studies have shed light on disease expression in people genetically susceptible to hereditary haemochromatosis. In the Busselton study, 16 homozygotes were identified from a sample of 3011 adults (1 in 188) with a median age of 52.7 years (range, 20–79 years).³ Twelve were not previously aware of their genetic risk, and of these, seven had elevated serum ferritin levels and the four with normal iron studies were premenopausal women. Half of the original 16 had clinical features consistent with hereditary haemochromatosis, although the prevalence of symptoms in non-homozygotes of the same age was not presented for comparison.³

A recent study in California identified 152 homozygotes from a sample of 41 038 individuals (1 in 270) with mean age 57 years (SD, 14).⁴ Among these homozygotes, 76% of men and 54% of women had raised serum ferritin levels.

Homozygotes were twice as likely as controls to report liver problems (8.1% versus 4.1%), but there was no evidence for a higher prevalence in homozygotes for any other symptom associated with hereditary haemochromatosis. The authors estimated only a small percentage of homozygotes would develop frank clinical haemochromatosis.⁴ However, exclusion of people with pre-existing disease may have biased this estimate downwards.⁵ Although it is possible that disease expression is greater in Australia, owing to our relatively higher meat and alcohol intake,⁶ the results of the Californian study indicate that further population-based studies are necessary.

The key factors in considering population screening of asymptomatic people are whether it will do more benefit than harm and whether it is cost-effective.⁷ International expert opinion has been cautious about population genetic screening for hereditary haemochromatosis,^{8,9} given the limited population data and possible adverse effects of screening, such as the potential for insurance discrimination in the United States. In Australia, health insurance is population-rated and discrimination is illegal. For life insurance, an agreement has been reached with the insurance industry that considerably reduces the risk of discrimination.¹⁰

Because cost-benefit analyses depend upon the number of people for whom disease can be prevented, enthusiasm for population screening for hereditary haemochromatosis has been dampened by the Californian findings. Even if these results are confirmed in whole or in part, it could be argued that, in Australia, there is minimal "cost" to genetically susceptible individuals in becoming blood donors, which virtually eliminates their risk of disease.¹¹ However, until it can be demonstrated that benefits or savings outweigh any potential harm or costs, population genetic screening programs — paid for by the public purse — are on the backburner.

The current standard of care remains cascade screening (ie, testing the *HFE* mutation status of first-degree relatives of individuals who have developed iron-related disease), because it is reasonable to assume that familial homozygous individuals are more likely to express disease.¹² Genetic testing for *HFE* mutations is also appropriate as a follow-up in people with abnormal iron studies (ie, elevated serum transferrin saturation and serum ferritin). Iron studies should be considered for patients with unexplained symptoms or conditions consistent with hereditary haemochromatosis, such as severe fatigue, liver disease and diabetes, although the predictive value of such testing is likely to be low.

C282Y homozygotes found to have high serum ferritin levels, with or without increased transferrin saturation, should have regular therapeutic venesection. Those with normal iron studies should be monitored expectantly, but do not require venesection unless they develop persistent abnormalities in serum ferritin levels.

The Human Genome Project has made a great step forward in mapping tens of thousands of genes, but it may be decades before we can predict which individuals are most likely to develop serious disease. Even for a condition as

apparently straightforward as hereditary haemochromatosis, the path to general population genetic screening has proven more complicated than initially expected.

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