LETTER

The geography of *HFE* mutations: molecular diagnosis of haemochromatosis and the globalization of genetic testing

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We read with great interest the comprehensive review by Godard *et al* in *Eur J Human Genet*¹ on population-screening programmes. The review highlights hereditary haemochromatosis (HH) as a potential disease for genetic screening (p S58), as well as the difficult matter of genetic testing commercialization (S67–S68). Hereby, we would like to draw the reader's attention to another important issue, to a certain extent related to commercialization, namely how the patent for genetic testing influences genetic diagnosis and may indeed have important implications for population-based studies. We would like to illustrate this point by reporting our experience with the HH molecular diagnostic testing in Singapore. HH is an inherited iron absorption abnormality due to mutations in the *HFE* gene.^{2,3} In particular, homozygous mutations C282Y and H63D are responsible for about 62–100% of HH worldwide.⁴ The low frequency of these mutations in Asian populations is presumed to be the cause of the very low incidence of HH in that part of the world.⁴ Hence, it could be presumed that HH genetic analysis in a South-east Asian molecular diagnostic laboratory would be a low-volume test with a minuscule number of positive results.

Our laboratory validated the HH molecular test for the analysis of the *HFE* C282Y and H63D mutations according to published protocols,⁵ and in the context of full accreditation by the College of American Pathologists. In 4 years, a total of 56 tests have been ordered by local clinicians. Of these, 10 (18%) were homozygous for the C282Y mutation, while none exhibited H63D homozygosity. Heterozygosities for C282Y or H63D were 6 (11%) and 14 (25%), respectively, while compound C282Y/H63D heterozygosity was noted in three cases (5%). This number of detected mutations (including a 18% of C282Y homozygosity) is quite remarkable, particularly when in some European countries the frequency of *HFE* C282Y mutations in clinically proven HH patients can be as low as 33 or 67%.⁴ And, yet, the frequency of HH in Singaporeans is remarkably low, as is heterozygosity for these mutations in the general population (~0.5%, Koay, unpublished data). How do we explain this apparent contradiction?

Singapore is a highly developed society with a significant number of Caucasian expatriates. This is a highly educated, health-conscious group. In some instances, it was the patient who learnt that our laboratory was performing the test and called us directly, with us putting them in contact with the appropriate clinician who would evaluate the clinical implications of the test, request the test itself and offer or arrange genetic counselling prior to and after the test result.

Thus, it is not surprising that 33 (59%) of the patients tested were Caucasian. This is the group in which all the homozygosity and most of the heterozygosity (except for six H63D heterozygous patients) were detected. In other words, 10 out of 33 (30%) of our Caucasian patients were homozygous for C282Y.

We would like to suggest that the phenomenon of a highly educated, migrating population seeking genetic testing may be an important factor in understanding the distribution of diseases worldwide, and may influence the choice of test availability and test validation. In general, this tendency may quickly modify the prevalence of certain genetic diseases in countries where their prevalence was very low if the migrants are from a country of high prevalence. Furthermore, it could be that the racial profile of patient mix presenting to us may be modulated by the *globalization of genetic testing*. In the February 2002 issue of *Nature*, Merz *et al*⁶ illustrated how the patenting and licensing of genes is becoming an integral part of contemporary medical care, and US genetic laboratories are refraining to offer the *HFE* mutation test because of the patent. This may be the case in Europe soon⁶ while in other places, due to the relative paucity of tests for a given disease, patents are not so vigorously enforced. We feel that a significant percentage of the Caucasian patients we diagnose may be taking advantage of a patent-free environment (albeit for the HH testing, and just for the moment). Interestingly, these patients will have a 'genetic diagnosis' that does not necessarily feature in their home healthcare records. As a whole, this represents a clear example of the economy of genetics and globalization of health care economics, a tendency that may indeed modulate the routine diagnostic practice of many molecular

diagnosticians, and eventually dictate genetic screening programmes worldwide.

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