

## W Use of community genetic screening to prevent HFE-associated hereditary haemochromatosis

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HFE-associated hereditary haemochromatosis is a recessive, iron-overload disorder that affects about one in 200 north Europeans and that can be easily prevented. However, genetic screening for this disease is controversial, and so we assessed whether such screening was suitable for communities. Cheek-brush screening for the Cys282Tyr HFE mutation was offered to individuals in the workplace. Outcomes were assessed by questionnaires before and after testing. 11 307 individuals were screened. We recorded no increase in anxiety in individuals who were homozygous for the Cys282Tyr mutation or non-homozygous. Self-reported tiredness before testing was significantly higher in homozygous participants than in non-homozygous participants ( $\chi^2$  test,  $p=0.029$ ). Of the 47 homozygous individuals identified, 46 have taken steps to treat or prevent iron accumulation. Population genetic screening for HFE-associated hereditary haemochromatosis can be practicable and acceptable.

HFE-associated hereditary haemochromatosis is an autosomal recessive disorder of iron overload, with about one in 200 north Europeans being homozygous for the Cys282Tyr mutation.<sup>1</sup> If untreated, the disease can result in hepatic cirrhosis, cardiomyopathy, diabetes mellitus, arthritis, impotence, and chronic fatigue. Importantly, although genetic homozygotes are at risk of developing disease, if iron is prevented from accumulating above healthy concentrations (eg, through phlebotomy), disease onset can be prevented.<sup>1</sup>

Whether the use of community screening for hereditary haemochromatosis is appropriate is still debatable.<sup>1</sup> Genetic screening can potentially prevent disease related to hereditary haemochromatosis. However, difficulties include incomplete knowledge of disease penetrance, potential for insurance and employment discrimination, and possible anxiety caused by screening. We aimed to assess whether genetic screening—by painless cheek-brush sampling of asymptomatic individuals in the workplace setting—is practicable and acceptable to communities. Methods of recruitment and data collection have been described

previously.<sup>2</sup> The study was approved by the Ethics in Human Research Committee of the Department of Human Services, Melbourne, Australia. Informed consent was obtained from all participants.

All attendees completed questionnaires before testing.<sup>2</sup> A follow-up questionnaire was sent 1 month after receipt of test results to all individuals homozygous for the Cys282Tyr mutation, and to age-matched and sex-matched non-homozygous controls. The questionnaires included: (1) sociodemographic details, (2) self-report of symptoms and medical conditions possibly related to hereditary haemochromatosis, (3) the general health perception subscale of the Medical Outcomes Survey (SF-36), (4) the state component of the short form of the Spielberger State-Trait Anxiety Inventory (STAI), and (5) the intrusion subscale of the impact of event scale (IES). Items (1) and (2) were measured at baseline only, (3) and (4) at baseline and follow-up, and (5) only at follow-up. Statistical analysis was by descriptive statistics, independent sample *t* tests, paired *t* tests,  $\chi^2$  tests, and Fisher's exact test as appropriate. Total numbers within

	Wild-type (n=9821)		Heterozygous Cys282Tyr (n=1325)		Homozygous Cys282Tyr (n=51)	
	Men	Women	Men	Women	Men	Women
Number of individuals	4609	5212	642	683	25	26
<b>Age (years)</b>						
Median (IQR)	38.0 (29.3–47.0)	33.0 (26.0–44.0)	40.0 (31.0–49.0)	34.0 (26.0–43.0)	41.0 (35.0–47.0)	36.0 (29.0–49.3)
Ethnic origin (north European)	2986 (69%)	2991 (61%)	541 (90%)	567 (88%)	22 (92%)	23 (92%)
<b>Symptoms*</b>						
Tiredness	1438 (34%)	2352 (48%)	196 (33%)	322 (50%)	11 (50%)	15 (65%)
Abdominal pain	488 (12%)	1057 (22%)	66 (11%)	147 (23%)	2 (9%)	6 (26%)
Joint pain	1028 (24%)	1245 (26%)	142 (24%)	173 (27%)	5 (23%)	6 (26%)
<b>Previous diagnosis*</b>						
Diabetes	91 (2%)	87 (2%)	11 (2%)	10 (2%)	0	2 (9%)
Arthritis	275 (6%)	361 (7%)	46 (8%)	51 (8%)	1 (5%)	3 (14%)
Liver disease	80 (2%)	62 (1%)	7 (1%)	9 (1%)	0	0

Data are number (% of total) unless otherwise indicated. Total numbers for every variable differ slightly due to missing data. \*Data exclude three women and one man homozygous for Cys282Tyr with previous diagnosis of hereditary haemochromatosis. †Homozygous patients had a significantly higher rate of tiredness than that of non-homozygous patients ( $\chi^2$  test,  $p=0.029$ ).

Table 1: Characteristics, symptoms, and clinical diagnoses for 11 197 participants who completed questionnaires at baseline

categories differed slightly because of missing data for some questions.

11 307 (96%) of 11 841 individuals attending screening sessions chose to have cheek-brush testing for the *HFE* Cys282Tyr mutation. Table 1 shows demographic data for the 11 197 individuals who completed questionnaires at baseline. 51 participants (one in 221) were identified as homozygous for the Cys282Tyr mutation and 1338 heterozygous (one in 8.4). Age or proportion of female individuals did not differ significantly between homozygous and non-homozygous groups. We excluded four individuals who were homozygous for the mutation and who were previously aware of their status from further analysis. Rate of tiredness was significantly higher in homozygous than in non-homozygous individuals ( $\chi^2$  test,  $p=0.029$ ; table 1). Frequency of other symptoms and diagnoses did not change significantly between the homozygous group and the other groups.

46 of the 47 individuals newly identified to be homozygous for the Cys282Tyr mutation agreed both to having iron indices measured and to entering into an appropriate programme of medical management. Follow-up questionnaires were completed by 42 (89%) homozygous individuals and by 158 (43%) of 369 controls (table 2). At least three age-matched and sex-matched controls were used per homozygous participant. These controls had mean scores at baseline for state anxiety and general health perceptions that were similar to those in the overall non-homozygous cohort (data not shown).

1 month after participants were informed of their results, anxiety and health perception scores in homozygous individuals did not change compared with scores at the time of testing (table 2). The mean score for the intrusion subscale of the IES was significantly higher in homozygous participants than in controls. However, only three homozygous individuals had IES scores of nine or higher (regarded as clinically significant), compared with only one control who had an IES score of nine. Almost all individuals in both Cys282Tyr homozygous and control groups were pleased they had the test (table 2).

19 (83%) of 23 homozygous men and 11 (48%) of 23 homozygous women had raised fasting transferrin saturation. Six men met the criteria for a liver biopsy.<sup>3</sup> Biopsies were done on four individuals. Two had advanced pre-cirrhotic liver fibrosis and two had moderate haemosiderosis with mild portal fibrosis, which represents a minimum frequency for advanced hepatic fibrosis of at least 4% (two of 47) in individuals homozygous for the Cys282Tyr mutation who are identified in the workplace. All individuals newly identified as homozygous with raised concentrations of serum ferritin have entered a phlebotomy programme to reduce their ferritin to within the normal range.

Our results show that those individuals who participated in genetic screening for hereditary

	Homozygous Cys282Tyr (n=42)	Control (n=158)	p*
<b>STAI state anxiety†</b>			
Before testing	34.2 (12.9)	32.7 (12.6)	0.51
After testing	34.8 (10.3)	34.0 (11.1)	0.67
p‡	0.75	0.33	..
<b>General health perception subscale of SF-36§</b>			
Before testing	73.9 (16.0)	68.8 (18.9)	0.12
After testing	73.8 (16.8)	69.3 (17.3)	0.11
p‡	0.93	0.97	..
Impact event scale¶	2.5 (4.3)	0.47 (1.4)	0.005
Remembered result correctly	41 (98%)	125 (80%)	0.005
Interpreted result correctly	41 (98%)	148 (94%)	0.47
Pleased to have had test	41 (98%)	150 (95%)	0.69

Data are mean (SD) or number of individuals (%) unless otherwise indicated. \*Comparison of mean score for homozygous individuals versus controls—independent sample t test. †Scores ranging from 20 to 80; high scores indicate greater anxiety. ‡Paired t test comparing scores before and after testing. §Scores ranging from 0 to 100; high scores indicate better-perceived health status. ¶Scores ranging from 0 to 35; high scores indicate higher stress response. A score of nine or higher has been suggested to be clinically significant.

**Table 2: Measures before testing and 1 month after receipt of test results for individuals homozygous for Cys282Tyr and controls**

haemochromatosis were not made anxious by testing and, importantly, most of those identified to be at risk took steps to prevent disease. We believe this action to seek treatment is because the disorder can be prevented by simple measures. Our results showing compliance with preventative therapy are of major importance if screening programmes are to achieve their aim of preventing disease. Individuals identified by our programme to be homozygous for the Cys282Tyr mutation were well informed about disease prevention<sup>2</sup> and were clearly motivated, since all but one such participant in our study underwent appropriate clinical follow-up. Additionally, all homozygous individuals who sought insurance had their policies underwritten at standard rates on the basis of an agreement we achieved with the Australian insurance industry to ensure asymptomatic people homozygous for the mutation were not discriminated against.<sup>4</sup>

Much discussion has been made regarding the penetrance of Cys282Tyr homozygosity. One study concluded that clinical penetrance is less than 1%,<sup>5</sup> although the methods have been criticised.<sup>6</sup> Furthermore, a study based on clinical investigation and liver biopsy showed that of asymptomatic individuals homozygous for the mutation detected by health checks or by family screening, 8% of men and 2% of women had hepatic cirrhosis.<sup>7</sup> Our study was not designed to examine penetrance in hereditary haemochromatosis. We chose to undertake screening in the work-place setting where individuals are less likely to be ill than in a health-care setting. Moreover, the average age of our participants was 37 years, which is below the average age of symptom onset in the disorder of 41 years.<sup>8</sup> Nevertheless, we identified two (more than 4%) individuals with severe hepatic fibrosis who, if untreated, were at substantial risk of

progressing to cirrhosis and of developing hepatocellular carcinoma. Tiredness was increased in individuals homozygous for the Cys282Tyr mutation that could have important repercussions in the workplace setting.

Health economic considerations are vital to decisions regarding screening programmes. An economic analysis of this programme is currently ongoing. If genetic screening is shown to be cost effective, it should be implemented since hereditary haemochromatosis can be prevented by simple measures and, as shown in our study, the risks of such screening are very low and genetic discrimination need not occur.

#### Contributors

All authors participated in the design, implementation, analysis, and interpretation of the study. M B Delatycki, K J Allen, A E Nisselle, V Collins, and R Williamson participated in all phases of the study. S Metcalfe, M A Aitken, and A A Gason had specific responsibilities for educational aspects of the study. D du Sart, A Wakefield, and A Ritchie were responsible for the design and implementation of the molecular genetic aspects of the study. J Halliday had specific responsibilities in questionnaire design and data analysis and interpretation. I Macciocca and V Hill had specific responsibilities in genetic counselling. A J Nicoll undertook follow-up of homozygous individuals needing liver biopsy. L W Powell provided input to study design and data interpretation. M B Delatycki, K J Allen, A E Nisselle, V Collins, and R Williamson wrote the report with input from all other investigators.

#### Conflict of interest statement

We declare that we have no conflict of interest.

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## Safer injection facility use and syringe sharing in injection drug users

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Safer injection facilities provide medical supervision for illicit drug injections. We aimed to examine factors associated with syringe sharing in a community-recruited cohort of illicit injection drug users in a setting where such a facility had recently opened. Between Dec 1, 2003, and June 1, 2004, of 431 active injection drug users 49 (11.4%, 95% CI 8.5–14.3) reported syringe sharing in the past 6 months. In logistic regression analyses, use of the facility was independently associated with reduced syringe sharing (adjusted odds ratio 0.30, 0.11–0.82,  $p=0.02$ ) after adjustment for relevant sociodemographic and drug-use characteristics. These findings could help inform discussions about the merits of such facilities.

Vancouver, Canada, like many urban centres, has been the site of continuing HIV and overdose epidemics in illicit injection drug users.<sup>1</sup> In response to these public health problems, health officials in Vancouver opened North America's first medically supervised safer injection facility in September, 2003.<sup>1,2</sup> As previously described,<sup>1</sup> injection drug users in the facility can access sterile injecting equipment, inject preobtained illicit drugs under the supervision of nurses, and access nursing care and addictions counselling. Although such facilities exist in several European settings and in Sydney, Australia, few formal epidemiological analyses have been done of their effects on reported HIV risk behaviours,

such as syringe sharing.<sup>1,3,4</sup> In Vancouver, a continuing prospective cohort study of injection drug users allowed us to examine factors associated with syringe sharing in local users after the opening of the safer injection facility.

We obtained data for these analyses from the Vancouver Injection Drug Users Study,<sup>5</sup> a prospective cohort that has been described previously. The study has been approved by the University of British Columbia and Providence Health Care ethics review boards, and all study participants provided written consent before enrolment. To be consistent with earlier analyses,<sup>6</sup> and to provide sufficient statistical power, syringe sharing was defined as borrowing or lending a used syringe in the