To tell or not to tell – what to do about p.C282Y heterozygotes identified by HFE screening


Hereditary hemochromatosis (HH) is a common preventable disorder of iron overload that can result in liver cirrhosis and reduced lifespan. Most HH is due to homozygosity for the HFE p.C282Y substitution. We conducted a study of screening for p.C282Y in high schools where p.C282Y heterozygotes (CY) individuals were informed of their genotype by letter. We studied whether these individuals understood the implications of their genotype, whether this resulted in anxiety or reduced health perception and whether cascade testing was higher in families of CY than wild-type homozygous (CC) individuals. We found 586 of 5757 (1 in 10) screened individuals were CY. One month after receiving their result, 83% correctly answered that they have one copy of p.C282Y. There was no adverse change in anxiety or health perception from prior to screening to 1 month after receiving results. Significantly more family members of CY individuals than CC individuals were informed about HH and had testing for HH. In conclusion, we found that informing CY individuals of their genotype does not increase anxiety and the implications are generally well understood. This leads to cascade testing in a minority of families. CY individuals should be informed of their genetic status when identified by population screening.

Conflict of interest
The authors have no conflict of interest.

Population screening for the HFE c.845G→A transition that results in the HFE p.C282Y substitution will identify homozygotes for the mutation (henceforth termed YY), heterozygotes (CY) and those homozygous for the wild-type allele (CC). YY individuals are at high risk of iron overload which, untreated, can result in symptomatic hereditary hemochromatosis (HH) including liver cirrhosis, cardiomyopathy and diabetes mellitus (1). CY individuals are at negligible risk of iron overload related disease (1). Our team has undertaken two large studies of population screening for p.C282Y. The first, HaemScreen, was conducted in workplaces (2, 3) whereas the second, ironXS, recruited subjects in high schools (4, 5). In HaemScreen, the workplace study, the decision was made to send the same letter to CY and CC individuals were informed about HH and had testing for HH. In conclusion, we found that informing CY individuals of their genotype does not increase anxiety and the implications are generally well understood. This leads to cascade testing in a minority of families. CY individuals should be informed of their genetic status when identified by population screening.
the decision was made to inform p.C282Y heterozygotes about their genotype and to study the outcomes of this. The study questions were:

(1) Are CY students made anxious by learning their genotype?
(2) Do students inappropriately believe they are at high risk of disease as a result of being informed of the CY result despite being informed to the contrary?
(3) Is the rate of cascade testing higher among families of CY than CC individuals?

Materials and methods

The overall methods of the ironXS study have been presented in detail previously (4, 5). Screening results were provided to parents and students via their home contact details. In addition, those found to be CY or CC received a letter that informed them of their genotype and stated that the student is at very low risk of developing iron overload related disease (Fig. S2).

At the time of screening, students completed a baseline questionnaire (Q1) which can be accessed at http://www.ironxs.com.au/questionnaire/. A follow-up questionnaire (Q2) was sent 1 month after receipt of test results to all YY and CY individuals, and to approximately one in seven randomly selected CC individuals. The questionnaires included: (i) demographic details (Q1), (ii) the general health perception sub-scale of the Medical Outcomes Survey, SF-36 (6), (iii) the state component of the short form of the Spielberger state-trait anxiety inventory (7, 8), (iv) the positive and negative affect subscales of the PANAS scale (10 items each), (v) the intrusion sub-scale of the impact of event scale (11). Item (v) was only measured in Q2.

Statistical analysis

Data were analyzed using STATA IC/11.0 (Texas). Statistical significance of differences in mean levels of continuous variables between CY and CC individuals was assessed by independent sample t-tests. The statistical significance of group differences in categorical variables was assessed using $\chi^2$ tests of association with Yates correction. Statistical significance of mean differences between baseline and follow-up scores for anxiety and general health perception were assessed using paired t-tests.

Results

Five hundred and eighty-six CY individuals were identified out of 5757 students who were screened in the ironXS program (1 in 10). Completed questionnaires (Q2) were received from 462 of 570 (81.1%) CY individuals and 643 of 807 (79.7%) CC individuals.

There was no difference in any measure of anxiety, affect or health perception between CY and CC individuals 1 month after receiving results (Table 1).

There was no significant deterioration in any of these measures between Q1 and Q2 – in fact health perception improved significantly in both CY and CC individuals.

Eighty-three percent of CY individuals correctly answered the question asking the number of copies of the p.C282Y substitution they have, 1 month after receiving their results letter (Table 2). This was a significantly higher percentage than for CC individuals (65%; $\chi^2 = 40.3$; $p < 0.001$). Eighty-six percent of CY individuals were pleased that they had the test, with 2% being unhappy and the remainder being unsure. The proportion of CY individuals who were happy to have been tested was significantly lower than for CC individuals (91%; $\chi^2 = 8.1$; $p = 0.005$).
Importantly, significantly more family members of CY individuals than CC individuals were informed about HH (39% vs 22%; \( \chi^2 = 34.6; p < 0.001 \)) and had testing for HH (10% vs 3%; \( \chi^2 = 19.0; p < 0.001 \)) indicating that the CY result triggered some cascade testing albeit in the minority (Table 2). We are aware that in one family, this resulted the father of a CY individual being identified as YY with raised serum ferritin.

Questionnaire comments were made by 241 of 462 (52.2%) CY individuals, and categories of these comments based on interview findings are only shown here relating to their perceptions of the program and understanding of their result. Categories of these 241 comments were: (i) 217 (90.9%) perceived the program as beneficial, (ii) 1 (0.4%) perceived the program as harmful, (iii) 10 (4.1%) indicated there was some confusion understanding their result, and (iv) 13 (5.4%) were neutral. The one comment that was categorized as the CY individual perceiving harm from the program was “If I had hemochromatosis then I would be unable to get life insurance therefore regretted taking the test, yet it is good to know if you have it so I am unsure”. No CY individual commented on being stigmatized or discriminated against as a result of being identified with this genotype.

Discussion

In this study, we have shown that in general, CY students have good understanding of the implications of this genotype and are pleased to have this knowledge. This knowledge is used by some families to test at-risk individuals for their risk of HH.

The Hemochromatosis and Iron Overload Screening study (HEIRS) studied screening for HH in the primary care setting and examined satisfaction of CY individuals with receiving their result by mail (13). The HEIRS study differed in a number of important ways from our two studies. Firstly, all subjects in HEIRS were tested for HFE p.H63D as well as p.C282Y and had iron indices measured. There were different approaches used for different subsets of CY individuals depending on iron indices. Letters were sent to CY individuals with normal or marginally abnormal iron indices whereas those with iron indices beyond a particular threshold, irrespective of their genotype, were invited to a face-to-face meeting where clinical and genetic information was provided (14). The letter sent to CY individuals with normal iron indices ‘encouraged’ them to share this information with their family doctor and to talk to a genetic counselor about the risk to family members. If the serum ferritin or transferrin saturation levels were marginally raised, the individual was ‘recommended’ to share the information with their family doctor (13). CY individuals were less satisfied with being notified by letter and the information provided than CC individuals. CY individuals had significantly worse recall of genotype (13) and were more likely to have at least one negative emotion (15) than CC individuals. The complexity of testing for more than one genotype as well as testing iron indices was recognized to be an important factor in the difficulty of communicating results in HEIRS (16).

In a German HH screening study where subjects were recruited through a health insurance company, there was significantly higher anxiety among CY than CC individuals (17). A possible reason for this difference compared with our study, is the method of pre-test education, which in the German study was largely in the form of written material, and the post-test information, which was given by the individual’s general practitioner. Knowledge questions, which were derived from those in our HaemScreen study, were answered correctly less often in the German study than in ours (data not shown) (18) suggesting that one factor resulting in the increased anxiety levels may have been related to poorer understanding of the clinical implications of p.C282Y heterozygosity.

The major benefit from informing p.C282Y heterozygotes of their genotype is that relatives are at increased risk of being p.C282Y homozygous and thus cascade testing can take place. We found that more relatives of CY individuals were informed of and had testing for HFE mutations than relatives of CC individuals. This indicates that this strategy was successful to some extent in achieving its goal. We are aware of one family where the father of a CY individual identified in the study was subsequently tested and found to be YY, with elevation of serum ferritin reinforcing the benefit of cascade testing following the diagnosis of an individual as CY. The precise number of relatives tested as a result of individuals being identified as CY by the screening program cannot be accurately calculated because there are many laboratories that perform HFE...
testing and because we relied on the reports of the students and their parents who would not necessarily be aware of all cascade testing in their family. The rate of cascade testing in our study is similar to that found for carrier testing for disorders such as cystic fibrosis (19) and fragile X syndrome (20). This outcome shows that cascade testing following identification of CY individuals identified in screening programs occurs but the low number of relatives reported to have been tested as a result of the program highlights the need for more intense education of CY individuals in future HH screening programs.

Another potential benefit of informing CY individuals of their genotype is that they can have testing for the p.H63D substitution. We made a considered decision, however, not to test for p.H63D in our two studies because the risk of morbidity from p.C282Y/H63D compound heterozygosity is low (21).

In conclusion, our studies of community screening for HFE p.C282Y did not identify major negative consequences of informing CY individuals of their genotype and there was evidence of benefit through cascade testing. Comparing our results to other studies, it is likely that pre-test education is important in minimizing negative consequences from the notification of CY individuals. Highlighting the potential for cascade testing and the minimal risk for morbidity for the CY individual are very important strategies for future screening programs. CY individuals should be informed of their genetic status when identified by population screening.

Supporting Information
The following Supporting information is available for this article:

Fig. S1. The letter sent to CY and CC individuals in the HaemScreen study.

Fig. S2. Letters sent to CY individuals identified by the ironXS program.

Additional Supporting information may be found in the online version of this article.

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References