Issues concerning feedback about genetic testing and risk of depression

Kay Wilhelm, Bettina Meiser, Philip B. Mitchell, Adam W. Finch, Jennifer E. Siegel, Gordon Parker and Peter R. Schofield

Background
Recent studies show that adverse life events have a significantly greater impact on depression onset for those with the s/s allele of the genotype for the 5-HT gene-linked promoter region. Research in genes related to risk of depression leads to the question of how this information is received by individuals.

Aims
To investigate factors related to the response to receiving one’s own serotonin transporter genotype results.

Method
Predictors of the impact of receiving individual genotype data were assessed in 128 participants in a study of gene–environment interaction in depression onset.

Results
Two-thirds decided to learn their individual genotype results (receivers) and prior to disclosure this decision was associated with a perception of greater benefit from receipt of the information (P=0.001). Receivers completing the 2-week (n=76) and 3-month follow-up (n=78) generally reported feeling pleased with the information and having had a more positive experience than distress. However, distress was related to genotype, with those with the s/s allele being most affected.

Conclusions
There was high interest in, and satisfaction with, learning about one’s serotonin transporter genotype. Participants appeared to understand that the gene conferred susceptibility to depression rather than a direct causal effect.

Declaration of interest
None.

Method
Participants
Participants were from an initial group of 170 adults (114 women and 56 men) recruited in 1978 during a 1-year postgraduate teacher training programme. In 1983, 165 of the initial sample formed a cohort for a longitudinal study investigating risk factors of depression and were followed up at 5-year intervals.16 Cohort members were of a similar age (mean 23 years in 1978) with similar career and life opportunities and ethnic backgrounds; 160 were White from European backgrounds, 2 and 3 were of Chinese and Indian descent respectively. These shared demographic characteristics reduced the likelihood of psychosocial confounders.

By 2003, 149 of the original 165 individuals remained in the study (8 had died, 2 were unable to be located, 2 were too ill to continue and 4 refused further involvement). Criteria for the Composite International Diagnostic Interview-derived17 lifetime diagnosis of major depression had been met by 62 (42%) of the remaining participants, with mean age at onset of 30.7 years (s.d. = 8.2, range 15–50). Of the 149, 128 participants provided informed consent for collection of genetic material. On recruitment for the genetic study, they were given a page of general information about serotonin, the serotonin transporter gene and a summary of the study by Caspi et al.4

After the genotype study10 was completed, participants were invited to an information evening to discuss the results of the original genetics study, but not their own genotype. The issue of individual feedback was raised and interest level was high.
Participants were also given information about the possible limitations, including the potential future obligation to provide results to insurance companies.

Following institutional ethics committee approval, cohort members were offered the opportunity to learn their own genotype and discuss any implications. Prior to divulgence of their genotype result, they were sent a ‘baseline’ self-rated questionnaire (see below), consent form and reply-paid envelope. After completion, an appointment was made, either in person or by telephone with the principal investigator (K.W.), a psychiatrist who had followed them throughout the study.

Participants were also offered the option of discussing their results with another clinician, and/or genetic counsellor, but none took up this offer.

At the interview, K.W. covered the following areas.

(a) Prior to disclosure, K.W. ascertained how much of the information provided had been accessed by the participant and each participant’s knowledge of the relationship between the serotonin transporter genotype, stress and depression, with further details provided where necessary.

(b) The results were then given, together with further information about the implications for the participant or their family.

(c) After disclosure, K.W. raised the issue of participants’ coping styles in times of stress, emphasising the need to review whether their coping styles served them well, with further time for questions.

(d) An offer of further discussion was made if indicated.

At the time of disclosure, those with the l/l allele were told that they were in the 30% of the population likely to have lower reactivity to a series of adverse life events; those with the s/l allele were told they were in the 20% who were potentially more emotionally reactive when confronted with a series of life events, with an increased risk (≈twofold) for depression. Regardless of genotype, the importance of reflecting on how they dealt with stressful events was emphasised. Participants had already been told at the information night that the genetic effect seemed more relevant for the first onset of depression; that the peak age at onset of depression was emphasised. Participants had already been told at the information night that the genetic effect seemed more relevant for the first onset of depression; that the peak age at onset of depression was

Outcome variables

**Perceived benefits and limitations of testing.** A 14-item measure that assessed perceived benefits and limitations of ‘testing for gene variations that influence the impact of stress on depression onset’ using a five-point Likert scale, ranging from ‘not at all important’ to ‘extremely important’. The items were developed on the basis of a qualitative study which explored the range of perceived benefits and limitations of genetic testing for bipolar disorder. The two subscales comprising this measure demonstrated high internal consistency in the previous study on bipolar disorder and were adapted for this study by omitting items considered unsuitable for the current sample (e.g. items related to decision-making about marriage and childbearing). Using data from the current study, an exploratory factor analysis using maximum likelihood extraction followed by oblique (promax) rotation produced a two-factor solution with each item loading on a factor (r > 0.4) and the factors matching the a priori scales for the perceived benefits and limitations of genetic testing for bipolar disorder. The benefits factor (eight items) explained 31.4%, and the limitations factor explained 25.1% (six items) of the total variance and the correlation between factors was low (r = 0.06), supporting their independence. They demonstrated good reliability, with Cronbach’s alphas of 0.88 (benefits scale) and 0.85 (limitations scale).

**Measures**

**Predictor variables**

Data already collected from the 25-year follow-up included in this analysis were age, gender, number of children, personal and family history of depression, and 5-HTT genotype status. The following measures were administered at baseline only.

**Causes of depression.** Measured on a five-point Likert scale, ranging from ‘totally owing to genetics’ to ‘totally owing to environment’, this single item assessed belief about the extent to which genetic v. environmental factors cause depression.

**Short Positive and Negative Affect Scale (Short-PANAS).** A 10-item measure of positive and negative affect was used to predict test uptake impact, with ten adjectives rated according to the extent participants described the way they felt ‘in general’.

**Statistical analysis**

Mann–Whitney U-tests were carried out using the ‘coin’ software and other analyses were conducted using SPSS (version 14) for Windows. Receivers and decliners were compared across a number of likely predictor variables using logistic regressions for categorical variables and Mann–Whitney U-tests for continuous variables as these variables were non-normal and could not be transformed into a normal distribution.

Controlling for the presence of lifetime major depression, we ran a repeated measures linear regression using mixed-effects modelling to assess whether the perceived risk of developing future depression differed between study groups (s/s, s/l, l/l
Results

Response rate and analysis of participation bias
As shown in Fig. 1, 102 (80%) participants returned their baseline questionnaire prior to receiving their genotype result. Individuals who completed baseline questionnaires were significantly more likely to subsequently choose to learn their genotype results ($\chi^2=35.5, \text{d.f.}=1, P<0.001$).

Uptake of genotyping results
Of the 128 individuals (Fig. 1) offered the opportunity to learn their results, 84 (66%) chose to receive their results (receivers). When only those 102 participants returning baseline questionnaires are included in the denominator, the percentage of receivers is higher, with 79 (78%) receivers and 23 (23%) decliners. Of the 84 receivers, 80 elected to learn their results by telephone and four face to face. Receivers learned their results between 0 and 181 days (mean=62, s.d.=52) after completion of baseline assessment.

Perceived benefits and limitations of testing
Figure 2 shows the rates of endorsement for each item pertaining to the perceived benefits and limitations of genetic testing by receiver and decliner status. Overall, the items most frequently endorsed by the total group ($n=102$) as ‘quite/ extremely’ important benefits of receiving such genotyping information were that it: (a) allowed for earlier intervention (84%); (b) provided the potential to prevent the onset of depression (83%); and (c) helped people proven to have a gene variation to avoid stressors or triggers that may lead to the onset of depression (77%). The most frequently endorsed items seen as ‘quite/extremely important’ limitations of receiving genotype information for the total group were that it could: (a) lead to insurance discrimination (73%); (b) lead to discrimination by employers (72%); and (c) make people who have a gene variation more likely to feel stressed, depressed or vulnerable (62%).

Predictors of decision to learn genotyping results
Tables 1 and 2 shows the variables assessed as predictors of the decision to learn results (for all individuals invited into the study). The only factor significantly associated with the decision to learn genotyping results was higher ‘perceived benefits of testing’ scale scores ($P=0.001$) (Table 2).

Causation of depression
The majority of receivers (59%) considered that genetics and environment were equally causative of depression, and 18% judged genetic factors and 22% judged environmental factors as more important in causing depression. No one indicated that depression was caused exclusively by either genetic or environmental factors. There were no differences by genotype ($\chi^2=1.2, \text{d.f.}=2, P=0.54$).

Impact of learning test result on perceived risk of depression
Figure 3 shows changes in perceived lifetime depression risk across time points for decliners and receivers, grouped by testing result. A general reduction in perceived depression risk from baseline to each follow-up time point is reflected by the mixed-effects analysis. Although controlling for history of major depression, there was a significant effect for time ($F(2,163) = 8.09, P<0.001$) and for the study group ($F(3,98) = 3.02, P=0.033$ but the interaction between group and time was not significant ($F(5,163) = 0.50, P=0.773$). The covariate, history of major depression, was also found to exert a significant effect on one's perceived risk of depression ($F(1,97) = 15.15, P<0.001$). Controlling for history of major depression, contrast tests showed significantly higher estimates of risk of future episodes of depression among those with s/s genotypes than each of the other study groups (s/l and l/l genotypes, and decliners) prior to disclosure of genotype results. These estimates remained significantly higher at 2 weeks post-disclosure among receivers with the s/s genotype.

![Flow chart of the group and assessment structure.](image)
Participants with the s/s genotype demonstrated significantly higher distress levels after learning their result at the 2-week ($\chi^2=11.5$, d.f.=2, $P=0.003$) and 3-month follow-up ($\chi^2=13.0$, d.f.=2, $P=0.001$) compared with the other genotypes (Fig. 4).

There were no differences between groups in terms of test-related positive experiences at either follow-up.

At both 2-week and 3-month follow-up after result disclosure, 92% of receivers reported feeling pleased that they had learnt their result, 8% were not sure and none regretted learning their result. At the 2-week and 3-month follow-ups 92% and 87% of receivers respectively correctly stated their genotyping result.

Table 1  Demographics of study participants a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decliners, n (%)</th>
<th>Receivers, n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (44)</td>
<td>24 (56)</td>
<td>1.90 (0.9–4.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>Female</td>
<td>25 (29)</td>
<td>60 (71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10 (40)</td>
<td>15 (60)</td>
<td>1.35 (0.6–3.3)</td>
<td>0.51</td>
</tr>
<tr>
<td>Yes</td>
<td>34 (33)</td>
<td>69 (67)</td>
<td>1.35 (0.6–3.3)</td>
<td>0.51</td>
</tr>
<tr>
<td>Genotype result</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s/s</td>
<td>12 (44)</td>
<td>15 (56)</td>
<td>1, Reference</td>
<td></td>
</tr>
<tr>
<td>s/l</td>
<td>23 (37)</td>
<td>40 (64)</td>
<td>1.39 (0.6–3.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>l/l</td>
<td>9 (24)</td>
<td>29 (76)</td>
<td>1.61 (0.9–2.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Prior episodes of major depression b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25 (34)</td>
<td>49 (66)</td>
<td>1, Reference</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>6 (29)</td>
<td>15 (71)</td>
<td>1.28 (0.4–3.7)</td>
<td>0.65</td>
</tr>
<tr>
<td>Two or more</td>
<td>13 (39)</td>
<td>20 (61)</td>
<td>0.89 (0.6–1.4)</td>
<td>0.58</td>
</tr>
<tr>
<td>Family history of depression b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19 (31)</td>
<td>43 (69)</td>
<td>0.88 (0.4–1.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>Yes</td>
<td>19 (33)</td>
<td>38 (67)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

reception.

a. All participants who were invited to the study were included in analysis, regardless of whether or not they completed baseline questionnaires.

b. Was assessed in 1998.
In this study, 66% of the 128 participants offered the opportunity to learn their genotype elected to do so, suggesting high acceptance of genotyping for risk of depression under stress. These results are consistent with findings from previous surveys of attitudes about (rather than uptake of) genetic testing for psychiatric disorders, which found that between 69%23 and 97%24 of respondents expressed interest in genetic testing for psychiatric disorders, including bipolar disorder,20,23–25 schizophrenia26,27 and other adult-onset disorders.28,29 These studies included psychiatrists,23,24,27 people with a diagnosis of a psychiatric disorder,20,23,25,27 as well as the general population.29

Attitudinal surveys of interest in genetic testing for other adult-onset disorders report that actual uptake of testing is lower than expressed intentions and that the decision to forego testing is associated with a greater perceived likelihood of adverse emotional effects.20 Our uptake rate exceeds the 10–20% rates among those at risk for Huntington’s disease approached by registries31 and the 40–60% rates of test uptake in families with identified mutations predisposing to hereditary cancer.1 The high uptake is likely to reflect a number of factors. Namely, participants were tertiary educated, well informed about previous study findings and had a trusting relationship with the research team. Further, participants had taken part in a genetic study of vulnerability to depression and may have been more disposed to accept a genetic explanation for mood disorders than the general population. Testing was free of charge and participants had the option of receiving their results by telephone. Finally, their mean age exceeded 50 years, well past the mean age at onset of depressive disorders.32 Additionally, interest among participants may have reflected the high lifetime incidence of major depression (42%) recorded in this cohort.33,34

### Table 2 Factors explored for association with decision to learn serotonin transporter genotype result (n = 128) a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Decliners</th>
<th>Receivers</th>
<th>Difference in means (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perceived lifetime risk a,b,c</td>
<td>n = 84</td>
<td>n = 44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived benefits of testing c</td>
<td>n = 78</td>
<td>n = 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causes of depression c</td>
<td>n = 76</td>
<td>n = 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived limitations of testing</td>
<td>n = 79</td>
<td>n = 23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Differs significantly from s/s scores (P < 0.05).

### Fig. 3 Perceived risk of future episodes of depression across time for decliners and receivers (n = 102) a

(a) Distress

<table>
<thead>
<tr>
<th>s/s</th>
<th>s/l</th>
<th>l/l</th>
<th>Decliners</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline 2-week follow-up 3-month follow-up</td>
</tr>
</tbody>
</table>

(b) Positive experiences

<table>
<thead>
<tr>
<th>s/s</th>
<th>s/l</th>
<th>l/l</th>
<th>Decliners</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Baseline 2-week follow-up 3-month follow-up</td>
</tr>
</tbody>
</table>

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#### Discussion

In this study, 66% of the 128 participants offered the opportunity to learn their genotype elected to do so, suggesting high acceptance of genotyping for risk of depression under stress. These results are consistent with findings from previous surveys of attitudes about (rather than uptake of) genetic testing for psychiatric disorders, which found that between 69%23 and 97%24 of respondents expressed interest in genetic testing for psychiatric disorders, including bipolar disorder,20,23–25 schizophrenia26,27 and psychiatric disorders in general.32 Additionally, interest among participants may have exceeded 50 years, well past the mean age at onset of depressive disorders.32

Receivers who completed baseline questionnaire after learning their results (n=5) were excluded from the analysis. Note: data is based on estimated marginal means from the mixed-model analysis.

Receivers who completed baseline questionnaire after receiving genetic testing results (n=5) are excluded from analysis.

Response options ranged from ‘very slightly or not at all’ (1) to ‘extremely’ (5). Scores for each sub-scale ranged from 5 to 25, with higher scores indicating more positive or negative affect.
To know or not to know

The most significant difference between those electing and not electing to receive information was the relative weight placed on personal benefits of testing. Those who wished to know their results emphasised the benefits of genetic testing to themselves and society. The most important perceived benefits were that genetic testing potentially allows for prevention and earlier intervention of depression, particularly for those with the s/s genotype. These findings contrast with attitudes to genetic testing for Huntington’s disease and hereditary cancer, where the most important reasons for genetic testing are ‘to be certain’ and ‘to learn one’s children’s risk’ respectively. This highlights the participants’ appreciation of the preventive potential for the current genetic testing knowledge combined with effective environmental (stress) management.

The most important perceived limitations of testing were that the genotype result could lead to discrimination by insurance companies or employers, and that those with the s/s genotype may become more stressed, depressed or vulnerable. These findings contrast with results from surveys in the hereditary cancer setting, where only a minority were concerned about discrimination. However, they are consistent with findings from a study of ethical issues related to the genetics of smoking, where nearly two-thirds of Americans stated that they would refuse a genetic test if employers or health insurers were able to access the results. Heightened concern about discrimination in our participants relate to greater perceived stigma for depression and psychiatric illness overall.

Participants’ responses indicated that they appreciated that depression is caused by both genetic and environmental factors. Although we ascertained the participants’ knowledge of the inter-relationship between genotype, stress and depression and their perception of causation of depression, we did not assess their knowledge of genetics and depression more broadly. Future research could consider whether the extent of participants’ knowledge relates to testing uptake.

Cohort-specific issues

Given the age of the sample, a first depression onset subsequent to genetic testing was thought unlikely. The s/s genotype is considered to affect risk of first onset (or early episodes) of depression and studies investigating the interaction between environmental stress and 5-HTT genotype on the onset of depressive episodes in older-aged samples have found no such effect. However, prior to genetic testing, individuals with the s/s genotype perceived a higher risk of future depression (which would include further episodes as well as new episodes) than other genotype groups and this may account for their lower uptake of test disclosure.

We have previously found that the s/s genotype is associated with a lower use of problem-solving coping strategies within the cohort from which the current study sample was drawn. Furthermore, brain imaging studies have demonstrated greater stress-induced amygdala activation in s/s carriers. We have hypothesised that deficient problem-solving coping and/or a hyper-reactivity to stressors may convey an increased risk of future depressive episodes among the s/s genotype group which could explain their perceptions of heightened depression risk. Alternatively, participants may have assessed their own future likelihood of depression based on their previous reactions following stressful events and past depression history.

Each group across the genetic risk spectrum (s/s, s/l and l/l genotypes) reported some reduction in the perceived chance of a future depressive episode following disclosure of their genotype results. We speculate that the information was provided in a manner that empowered the participants to actively address their coping styles rather than view themselves as passive recipients. However, those declining to learn their results also demonstrated a reduction in their perceived risk of depression from baseline to 3-month follow-up.

There was little indication of marked distress due to learning one’s genotype result as each genotype group reported more positive feelings than distress. However, the s/s genotype group experienced more distress associated with receipt of the test results compared with those with the s/l and l/l genotypes (who reported almost no negative emotional impact).

Study limitations

The limitations of this study should be mentioned. The sample was a highly select and homogeneous group with regard to educational levels, professional and ethnic backgrounds and age range, which considerably limits the generalisability of the findings. Also, participants were from a cohort of an existing longitudinal study on risk factors of depression and their participation may have altered interest in genetic testing for depression risk. Furthermore, they were a select group of this cohort who had consented to genetic testing. Finally, we observed participation bias in that participants who had declined information about their genotype were also less likely to participate in this study. However, the very same features of this cohort were what influenced our ethics committee to approve the study. We see this study as a first step and, clearly, further studies involving samples that are more heterogeneous with regard to age, educational level and cultural background are required to ensure the best means of providing information to participants and to assess the acceptability and psychosocial impact of genotyping for depression risk in more representative population samples.
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