Title

Psychological Impact of Predictive Genetic Testing in VCP Inclusion Body Myopathy, Paget Disease of Bone and Frontotemporal Dementia

Journal

Journal of Genetic Counseling, 24(5)

ISSN

1059-7700

Authors

Surampalli, Abhilasha
Khare, Manaswitha
Kubrussi, Georgette
et al.

Publication Date

2015-10-01

DOI

10.1007/s10897-015-9819-7

HHS Public Access

Author manuscript

J Genet Couns. Author manuscript; available in PMC 2017 August 21.

Published in final edited form as:

J Genet Couns. 2015 October ; 24(5): 842–850. doi:10.1007/s10897-015-9819-7.

Psychological Impact of Predictive Genetic Testing in VCP Inclusion Body Myopathy, Paget Disease of Bone and Frontotemporal Dementia

Abhilasha Surampalli[1,*], **Manaswitha Khare**[1,*], **Georgette Kubrussi**[1,*], **Marie Wencel**[1], **Jasmin Tanaja**[1], **Sandra Donkervoort**[1], **Kathryn Osann**[2], **Mariella Simon**[3], **Douglas Wallace**[3,#], **Charles Smith**[4], **Aideen McInerney-Leo**[5], and **Virginia Kimonis**[1]

[1]Department of Pediatrics, Division of Genetics and Metabolism, University of California, Irvine, CA 92697, USA

[2]Division of Hematology/Oncology, Department of Medicine, University of California, Irvine, CA 92697, USA

[3]Department of Biological Chemistry, University of California, Irvine, CA 92697, USA

[4]Department of Neurology and Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, USA

[5]The University of Queensland Diamantina Institute, Translational Research Institute, Princess Alexandra Hospital, Woolloongabba, Brisbane, Australia

Abstract

Inclusion Body Myopathy associated with Paget's disease of Bone and Fronto-temporal Dementia, also known as multisystem proteinopathy is an autosomal dominant, late onset neurodegenerative disorder caused by mutations in *Valosin containing protein (VCP)* gene. This study aimed to assess uptake and decision making for predictive genetic testing and the impact on psychological well-being. Individuals who had participated in the gene discovery study with a 50% *a priori* risk of inheriting VCP disease were sent a letter of invitation offering genetic counseling and testing and were also invited to participate in this psychosocial study. A total of 102 individuals received an invitation and 33 individuals participated in genetic counseling and testing (32.3%) with 29 completing baseline questionnaires. Twenty completed the follow-up post-test Hospital Anxiety and Depression Scale questionnaire including 13 who had tested positive. Mean risk perception at

Corresponding Author: Virginia E. Kimonis, MD, MRCP, Div. of Genetics and Genomic Medicine, Dept. of Pediatrics, Univ. of California Irvine, 101 The City Drive South, ZC4482, Orange CA 92868, Tel: (714) 456-5791, Fax: (714) 456-5330, Pager (714) 506 2063, vkimonis@uci.edu.

*These individuals contributed equally to this work.

#Current address: Center for Mitochondrial and Epigenomic Medicine, Children's Hospital of Philadelphia and Department of Pathology and Laboratory Medicine, University of Pennsylvania, Pennsylvania, PA

Conflict of Interest Statement

Abhilasha Surampalli, Manaswitha Khare, Georgette Kubrussi, Marie Wencel, Jasmin Tanaja, Sandra Donkervoort, Kathryn Osann, Mariella Simon, Douglas Wallace, Charles Smith, Aideen McInerney-Leo and Virginia Kimonis declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

baseline was 50.1%. Reasons for testing included planning for the future, relieving uncertainty, informing children and satisfying curiosity. At baseline, one quarter of the participants had high levels of anxiety. However, scores were normal one year following testing. In this small cohort, one third of individuals at 50% risk chose pre-symptomatic testing. Although one quarter of those choosing testing had high anxiety at baseline, this was not evident at follow-up.

Keywords

Presymptomatic genetic testing; Huntington's disease; Neurodegenerative; Paget's disease Hospital Anxiety and Depression Scale

INTRODUCTION

Inclusion Body Myopathy associated with Paget's disease of the bone and Frontotemporal Dementia, IBMPFD [OMIM#(167320)], is an autosomal dominant, progressive, ultimately lethal neuromuscular disorder caused by mutations in the *Valosin Containing Protein (VCP)* gene (Kimonis et al., 2000). This is an underdiagnosed disease that has been reported in >60 families worldwide, mainly from the United States and Europe. Approximately 90% of the mutation positive individuals develop myopathy in their 30s–40s; 50% develop Paget disease of bone (PDB) typically in their 30s (Kimonis et al., 2000; Watts, Thorne, Kovach, Pestronk, & Kimonis, 2003) and 30% develop frontotemporal dementia (FTD) in their mid-50s. Individuals typically die from cardiac or respiratory failure in their 40s–60s (Kimonis et al., 2000; Watts et al., 2003). Less common phenotypic features include cardiomyopathy, hepatic stenosis, cataracts, sensory motor axonal neuropathy, pyramidal tract dysfunction, sphincter disturbance, sensorineural hearing loss and amyotrophic lateral sclerosis (ALS) like features (Djamshidian et al., 2009; Guyant-Marechal et al., 2006; Haubenberger et al., 2005; Kumar et al., 2010; Miller et al., 2009).

The diagnosis is typically made based on the presence of proximal myopathy, rimmed vacuoles, ubiquitin and TDP-43 positive inclusions in the affected tissues and typically the co-existence of PDB, FTD and/or ALS (Forman et al., 2006; Kimonis et al., 2000; Neumann et al., 2007; Watts et al., 2003; Weihl et al., 2008). PDB is responsive to treatment with bisphosphonates (Langston & Ralston, 2004; Siris, 1996), but there are currently no curative treatments for myopathy, FTD or other features.

The *VCP* gene is associated with many basic cellular functions including cell division, apoptosis, biogenesis of organelles, membrane integrity, phosphorylation, cell signaling and ubiquitin-proteasome system mediated, autophagy-associated protein degradation pathways. There is a considerable intra and inter familial phenotypic variability in a kindred with VCP disease. The R155C mutation is associated with an earlier onset of disease when compared to the R155H mutation (Mehta et al., 2007). Interestingly, mutations in *VCP* gene have also been associated with non-syndromic familial FTD (Rohrer et al., 2011) and 1–2% of familial ALS (Johnson et al., 2010).

Clinicians have long been concerned about the psychological impact of presymptomatic genetic testing for adult onset disorders, particularly in neurodegenerative disorders (Durr,

Gargiulo, & Feingold, 2005) (Schneider & Klein, 2011). One of the best studied neurodegenerative diseases to date is Huntington's disease (HD), a movement disorder associated with dementia and affective symptoms. The mean age of symptom onset is 40 years and the death occurs approximately 15–20 years later (Beighton & Hayden, 1981). In a review by Tibben (2007), the author found that the uptake rates for genetic testing for HD ranged from 4–24%. Reasons for choosing to pursue genetic testing included the desire to end uncertainty, preparing for the future, possible utility in making reproductive decisions and informing children about risk (Tibben, 2007). Reasons given for declining testing included the desire to maintain hope, the concerns about their ability to cope with adverse results and to limit insurance and employment discrimination (Babul et al., 1993; Dufrasne, Roy, Galvez, & Rosenblatt, 2011; Evers-Kiebooms, Swerts, Cassiman, & Van den Berghe, 1989; Hagberg, Bui, & Winnberg, 2011; Quaid et al., 2008). There was some evidence to suggest that those who proceeded with testing were self-selected and mentally resourceful (Codori, Hanson, & Brandt, 1994; Decruyenaere et al., 1995; Kessler, 1994; Tyler, Ball, & Craufurd, 1992).

In the previous studies, depression and anxiety scores were typically in the normal range at baseline (Tibben, 2007). A few studies found that though depression and anxiety increased in the short term (2 months) in those who tested positive on genetic testing, this reverted to baseline levels by one year (Bloch, Adam, Wiggins, Huggins, & Hayden, 1992; Hayden, Bloch, & Wiggins, 1995; Tibben et al., 1993; Wahlin et al., 1997). However, other studies revealed that the mean levels of depression in mutation positive participants were not significantly increased but there was an increase in the incidence of major depression amongst the mutation positive from 6% at baseline to 20% at one year (Codori, Slavney, Rosenblatt, & Brandt, 2004). Longer term studies reported higher levels of depression and suicidal ideation in mutation positive participants at 2 years (Lawson et al., 1996); and just an overall increase in depression and anxiety at 5 years (Decruyenaere et al., 2003). At 7–10 years post genetic testing, anxiety and depression (as measured by the General Health Questionnaire [GHQ-60]) had increased in mutation positive participants and their partners. There was also evidence that those who were lost to follow up were those who had higher levels of depression and anxiety prior to the genetic testing (Timman, Roos, Maat-Kievit, & Tibben, 2004).

Although HD and VCP disease are both neurodegenerative disorders associated with cognitive changes, the clinical phenotype and disease progression is significantly different particularly in regards to the psychiatric changes which occur in HD. The goals of this study, therefore, included assessing whether at-risk family members would be interested in genetic testing and determining what motivates their decisions and also whether learning one's genetic status was associated with a change in levels of depression and/or anxiety. Assessing whether these individuals might be at risk for psychological sequelae is imperative as presymptomatic genetic testing is increasingly being adopted in clinical settings.

MATERIALS AND METHODS

Study Population

The study was approved by the Institutional Review Board of the University of California, Irvine (UC Irvine IRB Number #2008-6279). Individuals recruited for this study were previously consented to the ongoing genetic and natural history study (UC Irvine IRB Number #2007-5832) in families with IBMPFD which had resulted in the identification of the causative *VCP* gene (Kimonis et al., 2000).

From our database of 496 individuals, who have been followed for up to 10 years, we identified individuals who were over 18 years and had a 50% *a priori* chance of inheriting the familial disease. Symptomatic individuals were excluded from the study. A total of 144 individuals unaware of their VCP familial mutation status were eligible for the disclosure study.

Questionnaire Items

Sociodemographics—All those eligible to participate in the study received a baseline questionnaire which included five questions on sociodemographic data assessing age, ethnicity, marital status and whether they have children.

Risk Perception—One item was used to assess empiric risk perception “What do you think is the chance that you have this genetic change? __%”. A five point Likert scale (Not at all, a little, Somewhat, Very and Extremely) was used to assess participants’ level of concern about each of the three primary features of the disease (i.e. myopathy, PDB and FTD). Participants were asked about concern level for themselves and for family (e.g. How concerned are you about developing the following for yourself? How concerned are you about the following in your family?).

Perceived Risks and Benefits of Testing—After being asked if they would like to pursue or decline testing, participants were asked to rate the importance (on a five point Likert scale) of each of ten items for those interested in pursuing testing or nine items for those declining testing (see Supplementary data). Reasons for and against the genetic testing were selected after reviewing the literature to identify the cited reasons in the Huntington’s disease population (Demyttenaere, Evers-Kiebooms, & Decruyenaere, 1992; Evers-Kiebooms & Decruyenaere, 1998; Quaid & Morris, 1993).

Hospital Anxiety and Depression Scale (HADS)—Zigmond and Snaith created the HADS in 1983 as a self-assessment scale for detecting states of anxiety and depression (Zigmond & Snaith, 1983). This instrument consists of 14 self-administered questions, seven of which measure anxiety and seven that reflect depression. The sum of each subscale’s scores ranges from a minimum of 0 to a maximum of 21. A score of 8–10 on either subscale suggests borderline anxiety or depression, and a score of 10 or higher is a clear indication of each condition. The sensitivity, specificity and reliability of the HADS survey has been validated in numerous populations and settings (Bjelland, Dahl, Haug, & Neckelmann, 2002; Cosco, Doyle, Ward, & McGee, 2012; Hinz & Brahler, 2011; Norton, Cosco, Doyle,

Done, & Sacker, 2013). When this instrument was administered to general control population, approximately 21%–30% of the individuals were anxious and 11–24% were depressed (Crawford, Henry, Crombie, & Taylor, 2001; Hinz & Brahler, 2011). The HADS scale has also been used in populations affected by and at increased risk of developing neurodegenerative illnesses (De Souza, Jones, & Rickards, 2010; Leentjens et al., 2011).

Study Protocol

Participants were sent the "packet" comprising of IRB-approved letter informing them of the VCP gene mutation testing, the consent form and a pre-test questionnaire assessing risk perception, reasoning for opting or declining testing along with the HADS Survey. Genetic counseling was offered to all of those who expressed an interest in knowing their mutation status. Pre-test counseling was performed by a clinical geneticist or genetic counselor in person where possible or by telephone when participants were geographically isolated. Those who elected to proceed with testing submitted a blood sample or saliva sample for DNA diagnostic testing. Results were disclosed by a clinical geneticist or genetic counselor in person or over the phone one month later. One year following the receipt of results participants were asked to complete the HADS Survey.

In the initial information packet, participants were informed that the cost of the molecular testing would be covered by the study. Testing was performed at the "Clinical Laboratory Improvement Amendments (CLIA) certified" DNA diagnostic laboratory at Boston Children's Hospital, Boston, MA or Mitomed Laboratory, University of California, Irvine, CA.

Data Analysis

The results of all the questionnaires were entered into the statistical software package SPSS 21.0 (IBM SPSS; International Business Machines, IBM Corporation, Chicago, IL, USA). Items for each of the HADS subscales were summed. Means for each scale at both time-points were calculated. Pearson's correlation calculation was used to evaluate any correlations between age and baseline risk perception and also between baseline risk perception and anxiety. Fisher's exact chi-square tests were used to ascertain whether there were any difference in the incidence of depression and anxiety at either time-point compared with normal population frequency. Where an individual had completed the HADS at both time points, Wilcoxon signed rank test was used to detect any significant change over time.

RESULTS

Participants

Of the 144 invited to participate in the study, 42 packets (29%) were returned as the intended recipient no longer resided there. Of the remaining 102 individuals, 33 (32.4%) indicated that they wished to proceed with testing but only 29 of these completed a baseline questionnaire. No questionnaires were returned from individuals declining testing and there are therefore no data on this population. The sociodemographics of the 29 individuals who completed the baseline questionnaire can be seen in Table 1.

Risk Perception and concern about specific symptoms

The mean risk perception of the participants was 50.1% (range 0–100%, SD=27.37). The level of concern for self and other family members regarding myopathy, PDB and FTD can be seen in Table 2. Pearson's correlation *r* for age and risk perception was −0.244 and for anxiety and risk perception was 0.037. Neither of these correlations was statistically significant. -.

Reasons for testing

For those that indicated the desire to be tested for VCP mutations, each reason was given a score from 0–4 (Not at all important, A little, Somewhat, Very and extremely important) and the means of these scores are reported. The reasons include being able to make arrangements for future care (mean=2.77) and general planning for the future (mean=2.75) followed by relieving uncertainty (men=2.43) and being able to inform children about their risks (mean=2.62). Other reasons include curiosity (mean=2.04); relieve anxiety (mean=1.68); planning a family (mean=1.00); planning for suicide (mean=0.46). The participants scored zero for "To alter the medical care I currently receive" and "To confirm the feeling that I already have the disease."

Pre-test HADS analysis and mutation status—The baseline data and analysis of HADS scores in 29 participants who opted for pre-symptomatic genetic testing is shown in Table 3. Mean score at baseline for the Anxiety scale was 6.17 and for the Depression scale was 2.59 both of which are in the normal range. Twenty of the 29 had a normal score for anxiety and 28 had a normal score in the depression subscale. Chi-square analysis demonstrated that the frequency of depression in this population was significantly lower (p=0.05) than the 23% seen in the general population (Hinz & Brahler, 2011) Seven of the nine individuals with a higher than normal anxiety score were in the pathological range and were counseled to consult with their primary care physician and obtain a referral to a psychologist or psychiatrist to ensure they received appropriate care. There was no significant difference in the mean pre-test and post-test anxiety scores in our study population (p=0.55 and p=0.10, respectively) when compared to the 21% with elevated anxiety in the general population (Hinz & Brahler, 2011).

Genetic test results—Eighteen of the 29 individuals tested positive for the familial VCP gene mutation. Of those 18 individuals who tested positive, six carried the R155C mutation; five the R159C; two each the R191Q, R155H, and L198W respectively and one the R155P.

One year post-test HADS analysis—One year after receipt of the results, HADS survey was posted to the 29 individuals who had pursued genetic testing and 20 returned the completed questionnaires. Thirteen tested positive and seven tested negative for the gene mutation. Mean score at follow up for the Anxiety scale was 5.65 and for the Depression scale was 2.40. In subjects with anxiety scores of >8 at any visit (n = 8), there was a significant decrease in anxiety and depression scores (p = 0.004 and p= 0.02 respectively) at follow up. With all 20 subjects included, the decrease in the Anxiety score was marginally significant (p = 0.07) however, differences were not found to be significant for depression (p = 0.17). There were no individuals in the diagnostic range for either anxiety or depression.

Interestingly, a follow up questionnaire was completed by eight individuals who had shown significant levels of anxiety (cut off >8) at baseline, andexcept for one individual who tested negative for the gene mutation, none were identified with abnormal levels of anxiety at follow up (Table 3).

Summary of Results

Approximately one third of the at-risk population (33/102) chose to be counseled and tested. Baseline risk perception was 50%. Planning for the future medically and generally were the strongest motivators cited for the decision to test. The pre-test HADS testing showed nine of the 29 had elevated anxiety, seven had clinically significant levels of anxiety and two had borderline anxiety. One year after genetic testing, all nine individuals had improvements in the anxiety levels. Five of these nine individuals with baseline anxiety, tested positive for the gene mutation. At follow up, there was a significant absence of depression and the incidence of elevated anxiety was similar to that reported in the healthy population.

DISCUSSION

The uptake for genetic testing in this population was 32% which is significantly higher than the range of 4–24% as reported worldwide in a review of the HD literature by Tibben et al. (Tibben, 2007). The higher uptake in VCP disease may be attributable to any number of factors. The most likely factor could be related to the personality and cognitive changes associated with HD. HD is an incurable disease with symptoms' onset at approximately 40 years of age; subsequently leading to death in ~15–20 years due to neuropsychiatric decline. PDB is treatable with bisphosphonates but the other two major symptoms of the disease spectrum including muscle weakness and dementia are progressive and individuals typically die of respiratory failure in their 40's – 60's. The age of death is similar in both groups; however, VCP disease is not typically associated with the almost universal psychiatric component that is considered to be the most destructive aspect of HD. Therefore, the psychological impact of the disease on the individual and the extended family is very different. Furthermore, it is likely that the reduced penetrance of dementia amongst affected individuals with VCP disease encourages individuals to pursue testing with the knowledge that there is still hope that, though they carry the gene mutation they might be lucky enough to not develop symptoms. Therefore, it would be interesting to explore hope and optimism in this population in the future.

The higher uptake of genetic testing may also be explained by the fact that the genetic testing was indeed done in a special context where the relatives had already been subjects involved in the causative gene identification study which might have made the individuals more aware of the disease; though it may also indicate that the individuals were more participative and more curious in nature which seems unlikely given that the literature shows that, for HD at least, the decision to test is an individual rather than familial decision (Evers-Kiebooms & Decruyenaere, 1998). It is also possible that the lack of cost to participants for the genetic testing and counseling may also have increased the uptake rate; however, many of the previous HD studies reported uptake rates at university and public hospitals in Europe,

where out of pocket expenses were low or non-existent (Codori et al., 1994; Kessler, 1994; Tyler et al., 1992).

It was interesting to observe that at-risk family members were equally concerned about myopathy as they were about dementia regardless of whether they were thinking of themselves or other family members. When one thinks about the Health Belief Model, it suggests that an individual's decision to attend a clinic is affected by their perceived susceptibility, perceived severity and the perceived benefits and barriers (Janz & Becker, 1984); (Rosenstock, 1988). Perceived susceptibility and severity combined is known as the "health threat." The way the question was worded in our study means we have a measure of the health threat, however we cannot tease apart perceived susceptibility versus perceived severity (How concerned are you about the following for yourself? Myopathy… Paget's disease of bone… frontotemporal dementia). This is important for VCP disease as myopathy occurs in 90% of mutation positive individuals whereas FTD occurs in 30%. Given that the "health threat" score is similar for both could suggest that the perceived severity of FTD would be higher than myopathy but further studies would be needed to more accurately measure both components.

A number of studies have reviewed psychological impact of predictive genetic testing in the last 15 years (Broadstock, Michie, & Marteau, 2000; Duisterhof, Trijsburg, Niermeijer, Roos, & Tibben, 2001; Meiser & Dunn, 2000; Tibben, 2007). In our study, the baseline mean scores of anxiety and depression were within the normal range. If one uses 8 as a cut-off on the HADS scale for high anxiety and depression, in our study 31% (9/29) of the participants had significant levels of anxiety whereas only 21% in German control population were found to havehigh anxiety sample (Crawford et al., 2001; Del Rosso et al., 2013; Hinz & Brahler, 2011; Watkins et al., 2013) and the difference was not statistically significant. Our study sample is small and there for has limited power to detect a difference. Only one individual was borderline for symptoms of depression at baseline which is significantly lower than the 23% with high depression reported in the German control sample (Crawford et al., 2001; Del Rosso et al., 2013; Hinz & Brahler, 2011; Watkins et al., 2013). These data suggest that the subgroup electing to proceed with the testing may be self-selecting as has been observed previously in the HD population (Codori et al., 1994; Kessler, 1994; Tyler et al., 1992). The incidence of increased anxiety at baseline is similar to those observed in control sample (Hinz & Brahler, 2011). By one year, post receipt of the results, there were no individuals scoring above cut-off for anxiety. There was a statistically significant decrease in anxiety scores in the subgroup (8 of the 20) with above cutoff anxiety at either one or both visits. Although selection bias is present, the analysis captures the difference seen in the anxiety scores in the subgroup at follow up. There was a statistically significant absence of depression both at baseline and at follow up when compared with the control sample. This lack of depression mirrors what was seen by Steinbart and Bird (Steinbart, Smith, Poorkaj, & Bird, 2001) when they used the HADS scale to assess the impact of presymptomatic testing for FTD and Alzheimer disease. A lack of depression, as assessed by the Beck Depression Inventory, was also noted in populations who were offered presymptomatic genetic testing for Machado-Joseph disease and familial amyloid polyneuropathy type I (Rolim et al., 2006). In terms of time-points, when looking at the HD literature one observes that depression is highest up to 2–3 months post receipt of results but

this reverts to baseline levels by 1 year (Huggins et al., 1992) (Wiggins et al., 1992) and the same is true for anxiety (Bloch et al., 1992) (Huggins et al., 1992). Other studies which have only looked at depression one year post testing found levels similar to those levels observed at baseline (Codori, Slavney, Young, Miglioretti, & Brandt, 1997) (Decruyenaere et al., 1996) and it is this baseline score, not test results which best predicts the follow up psychosocial scores (Codori et al., 1997; Decruyenaere et al., 1996; Tibben et al., 1993). We did not observe such a correlation in our study though. Given the small study sample which limits statistical power, one cannot draw any conclusion either way. However, we did observe that all those individuals who were significantly anxious at baseline had a reduction in their scores by the follow up.

In our study we found that planning medically and generally for the future were the strongest predictors of the decision to test, and these were followed by the desire to end uncertainty and inform their children of their risk. These findings were similar to those seen in families with Alzheimer's or Pick's disease (Tibben et al., 1997), FTD (McRae, Diem, Yamazaki, Mitek, & Wszolek, 2001) and HD (Evers-Kiebooms & Decruyenaere, 1998) (Hagberg et al., 2011). It appears that the top two most important reasons in this study were more pragmatic (planning) than the desire to end uncertainty which was more prevalently mentioned in the HD literature (Baum, Friedman, & Zakowski, 1997). Three individuals mentioned that "planning for suicide" was a significant factor in their decision to choose testing. Two out of three tested negative. The remaining individual was clinically anxious at baseline and was therefore referred for appropriate psychological treatment and follow up counseling. At the follow up, HADS scores had decreased to the normal range. The improvement in psychological well-being in that person may have resulted from the counseling intervention or the end of the uncertainty. Suicidal behavior is well recognized in the HD population (Robins Wahlin et al., 2000) (Kessler, Field, Worth, & Mosbarger, 1987, pp. 259–270. The study by Wahlin et al. (2000) reported no significant differences between 13 gene mutation positive and 21 mutation negative participants in pretest attitudes, but both groups showed high suicidal ideation and self-injurious behavior and contrary to expectations, mutation negative participants had a very high frequency of attempted suicide (Robins Wahlin et al., 2000). Long term follow up studies testing for health related outcomes post predictive genetic testing in HD population reported no catastrophic events including major depressive disorder or psychiatric hospitalization, declared suicide attempt or suicide (Dufrasne et al., 2011) (Paulsen et al., 2013).

Study Limitations

The small study sample means that these results likely are not generalizable to the entire IBMPFD population. The questionnaires were administered at baseline and 1 year follow up so it is possible that there was an increase in depression and anxiety in the short-term which this study failed to capture. As mentioned previously, statistical power is also limited and since only 8/29 baseline HADS questionnaire scores for anxiety demonstrated abnormal elevations, effects shown in comparisons by averaging will be "diluted" by the more numerous normal scores. Another issue is whether a parametric statistical model actually represents this population well, a difficult question when small numbers are involved and selection bias is acknowledged and expected. Furthermore, no adjustment to significance

values was made for multiple comparisons in this small study. Thus, significant p-values should be interpreted cautiously until results are confirmed in a larger study. Caution must be taken to avoid over-interpretation of the results. As there were no questionnaires returned for those declining testing, no comparison could be made between those choosing and declining testing.

Conclusions

In conclusion, this study had some interesting findings. Baseline risk perception was 50% in this study sample which matched their *a priori* risk. A third of those who received an invitation elected to proceed with predisposition testing. At baseline, in this population, there was a significant lack of depression and expected levels of anxiety suggesting that those choosing testing were possibly self-selecting. Although selection bias is present, there was a significant decrease seen in the anxiety scores in the subgroup with above cutoff anxiety on HADS. Participants were equally concerned about myopathy as they were about frontotemporal dementia but further research is needed to explore the extent to which this concern is governed by perceived susceptibility and perceived severity. If larger studies demonstrate a statistical lack of anxiety and depression in this population as a result of genetic testing then this will be reassuring as it becomes more wide-spread in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding of this study is from the NIAMS, National Institutes of Health (RO1 AR050236), Muscular Dystrophy Association, Paget Foundation and the ICTS, University of California, Irvine. This work was also supported by the Muscular Dystrophy Association [Development grant to GW, JV] and NIH 1K01AR056002-01A2 trainee award [GW]. Aideen McInerney-Leo is supported by a University of Queensland graduate scholarship. We thank the individuals for their participation in this study and their health care providers for referring the patients to our study. We thank Mehrdad Zolekhian for technical assistance.

References

167320 , O.: Retrieved from http://www.omim.org/entry/167320.

Babul R, Adam S, Kremer B, Dufrasne S, Wiggins S, Huggins M, … Hayden MR. Attitudes toward direct predictive testing for the Huntington disease gene. Relevance for other adult-onset disorders. The Canadian Collaborative Group on Predictive Testing for Huntington Disease. JAMA. 1993; 270(19):2321–2325. [PubMed: 8230594]

Baum A, Friedman AL, Zakowski SG. Stress and genetic testing for disease risk. Health Psychol. 1997; 16(1):8–19. [PubMed: 9028812]

Beighton P, Hayden MR. Huntington's chorea. S Afr Med J. 1981; 59(8):250.

Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002; 52(2):69–77. S0022399901002963 [pii]. [PubMed: 11832252]

Bloch M, Adam S, Wiggins S, Huggins M, Hayden MR. Predictive testing for Huntington disease in Canada: the experience of those receiving an increased risk. Am J Med Genet. 1992; 42(4):499–507. DOI: 10.1002/ajmg.1320420416 [PubMed: 1535177]

Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. Eur J Hum Genet. 2000; 8(10):731–738. DOI: 10.1038/sj.ejhg.5200532 [PubMed: 11039571]

Codori AM, Hanson R, Brandt J. Self-selection in predictive testing for Huntington's disease. Am J Med Genet. 1994; 54(3):167–173. DOI: 10.1002/ajmg.1320540303 [PubMed: 7810574]

Codori AM, Slavney PR, Rosenblatt A, Brandt J. Prevalence of major depression one year after predictive testing for Huntington's disease. Genet Test. 2004; 8(2):114–119. DOI: 10.1089/1090657041797275 [PubMed: 15345107]

Codori AM, Slavney PR, Young C, Miglioretti DL, Brandt J. Predictors of psychological adjustment to genetic testing for Huntington's disease. Health Psychol. 1997; 16(1):36–50. [PubMed: 9028814]

Cosco TD, Doyle F, Ward M, McGee H. Latent structure of the Hospital Anxiety And Depression Scale: a 10-year systematic review. J Psychosom Res. 2012; 72(3):180–184. S0022-3999(11)00194-2 [pii]. DOI: 10.1016/j.jpsychores.2011.06.008 [PubMed: 22325696]

Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol. 2001; 40(Pt 4):429–434. [PubMed: 11760618]

De Souza J, Jones LA, Rickards H. Validation of self-report depression rating scales in Huntington's disease. Mov Disord. 2010

Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, Demyttenaere K, … Van den Berghe H. Predictive testing for Huntington's disease: risk perception, reasons for testing and psychological profile of test applicants. Genet Couns. 1995; 6(1):1–13. [PubMed: 7794556]

Decruyenaere M, Evers-Kiebooms G, Boogaerts A, Cassiman JJ, Cloostermans T, Demyttenaere K, … Van den Berghe H. Prediction of psychological functioning one year after the predictive test for Huntington's disease and impact of the test result on reproductive decision making. J Med Genet. 1996; 33(9):737–743. [PubMed: 8880572]

Decruyenaere M, Evers-Kiebooms G, Cloostermans T, Boogaerts A, Demyttenaere K, Dom R, Fryns JP. Psychological distress in the 5-year period after predictive testing for Huntington's disease. Eur J Hum Genet. 2003; 11(1):30–38. [pii]. DOI: 10.1038/sj.ejhg.52009135200913 [PubMed: 12529703]

Del Rosso A, Mikhaylova S, Baccini M, Lupi I, Matucci Cerinic M, Maddali Bongi S. In systemic sclerosis, anxiety and depression assessed by hospital anxiety depression scale are independently associated with disability and psychological factors. Biomed Res Int. 2013; 2013:507493.doi: 10.1155/2013/507493 [PubMed: 23984376]

Demyttenaere K, Evers-Kiebooms G, Decruyenaere M. Pitfalls in counseling for predictive testing in Huntington disease. Birth Defects Orig Artic Ser. 1992; 28(1):105–111. [PubMed: 1340218]

Djamshidian A, Schaefer J, Haubenberger D, Stogmann E, Zimprich F, Auff E, Zimprich A. A novel mutation in the VCP gene (G157R) in a German family with inclusion-body myopathy with Paget disease of bone and frontotemporal dementia. Muscle Nerve. 2009; 39(3):389–391. DOI: 10.1002/mus.21225 [PubMed: 19208399]

Dufrasne S, Roy M, Galvez M, Rosenblatt DS. Experience over fifteen years with a protocol for predictive testing for Huntington disease. Mol Genet Metab. 2011; 102(4):494–504. S1096-7192(10)00561-5 [pii]. DOI: 10.1016/j.ymgme.2010.12.001 [PubMed: 21220204]

Duisterhof M, Trijsburg RW, Niermeijer MF, Roos RA, Tibben A. Psychological studies in Huntington's disease: making up the balance. J Med Genet. 2001; 38(12):852–861. [PubMed: 11768388]

Durr A, Gargiulo M, Feingold J. Predictive testing: presymptomatic diagnosis in neurogenetic disorders. Med Sci (Paris). 2005; 21(11):934–939. DOI: 10.1051/medsci/20052111934 [PubMed: 16274644]

Evers-Kiebooms G, Decruyenaere M. Predictive testing for Huntington's disease: a challenge for persons at risk and for professionals. Patient Educ Couns. 1998; 35(1):15–26. S073839919800086X [pii]. [PubMed: 9832893]

Evers-Kiebooms G, Swerts A, Cassiman JJ, Van den Berghe H. The motivation of at-risk individuals and their partners in deciding for or against predictive testing for Huntington's disease. Clin Genet. 1989; 35(1):29–40. [PubMed: 2522360]

Forman MS, Mackenzie IR, Cairns NJ, Swanson E, Boyer PJ, Drachman DA, … Kimonis VE. Novel ubiquitin neuropathology in frontotemporal dementia with valosin-containing protein gene mutations. J Neuropathol Exp Neurol. 2006; 65(6):571–581. [PubMed: 16783167]

Guyant-Marechal L, Laquerriere A, Duyckaerts C, Dumanchin C, Bou J, Dugny F, … Campion D. Valosin-containing protein gene mutations: clinical and neuropathologic features. Neurology. 2006; 67(4):644–651. DOI: 10.1212/01.wnl.0000225184.14578.d3 [PubMed: 16790606]

Hagberg A, Bui TH, Winnberg E. More appreciation of life or regretting the test? Experiences of living as a mutation carrier of Huntington's disease. J Genet Couns. 2011; 20(1):70–79. DOI: 10.1007/s10897-010-9329-6 [PubMed: 20878217]

Haubenberger D, Bittner RE, Rauch-Shorny S, Zimprich F, Mannhalter C, Wagner L, … Zimprich A. Inclusion body myopathy and Paget disease is linked to a novel mutation in the VCP gene. Neurology. 2005; 65(8):1304–1305. [PubMed: 16247064]

Hayden MR, Bloch M, Wiggins S. Psychological effects of predictive testing for Huntington's disease. Adv Neurol. 1995; 65:201–210. [PubMed: 7872141]

Hinz A, Brahler E. Normative values for the hospital anxiety and depression scale (HADS) in the general German population. J Psychosom Res. 2011; 71(2):74–78. S0022-3999(11)00007-9 [pii]. DOI: 10.1016/j.jpsychores.2011.01.005 [PubMed: 21767686]

Huggins M, Bloch M, Wiggins S, Adam S, Suchowersky O, Trew M, … Hayden MR. Predictive Testing for Huntington Disease in Canada - Adverse-Effects and Unexpected Results in Those Receiving a Decreased Risk. American Journal of Medical Genetics. 1992; 42(4):508–515. DOI: 10.1002/ajmg.1320420417 [PubMed: 1535178]

Janz NK, Becker MH. The Health Belief Model: a decade later. Health Educ Q. 1984; 11(1):1–47. [PubMed: 6392204]

Johnson JO, Mandrioli J, Benatar M, Abramzon Y, Van Deerlin VM, Trojanowski JQ, … Traynor BJ. Exome sequencing reveals VCP mutations as a cause of familial ALS. Neuron. 2010; 68(5):857–864. S0896-6273(10)00978-5 [pii]. DOI: 10.1016/j.neuron.2010.11.036 [PubMed: 21145000]

Kessler S. Predictive testing for Huntington disease: a psychologist's view. Am J Med Genet. 1994; 54(3):161–166. DOI: 10.1002/ajmg.1320540302 [PubMed: 7810573]

Kimonis VE, Kovach MJ, Waggoner B, Leal S, Salam A, Rimer L, … Gelber D. Clinical and molecular studies in a unique family with autosomal dominant limb-girdle muscular dystrophy and Paget disease of bone. Genet Med. 2000; 2(4):232–241. doi:10.109700125817-200007000-00006. [PubMed: 11252708]

Kumar KR, Needham M, Mina K, Davis M, Brewer J, Staples C, … Mastaglia FL. Two Australian families with inclusion-body myopathy, Paget's disease of bone and frontotemporal dementia: novel clinical and genetic findings. Neuromuscul Disord. 2010; 20(5):330–334. DOI: 10.1016/j.nmd.2010.03.002 [PubMed: 20335036]

Langston AL, Ralston SH. Management of Paget's disease of bone. Rheumatology (Oxford). 2004; 43(8):955–959. [PubMed: 15187244]

Lawson K, Wiggins S, Green T, Adam S, Bloch M, Hayden MR. Adverse psychological events occurring in the first year after predictive testing for Huntington's disease. The Canadian Collaborative Study Predictive Testing. J Med Genet. 1996; 33(10):856–862. [PubMed: 8933341]

Leentjens AF, Dujardin K, Marsh L, Richard IH, Starkstein SE, Martinez-Martin P. Anxiety rating scales in Parkinson's disease: a validation study of the Hamilton anxiety rating scale, the Beck anxiety inventory, and the hospital anxiety and depression scale. Mov Disord. 2011; 26(3):407–415. DOI: 10.1002/mds.23184 [PubMed: 21384425]

McRae CA, Diem G, Yamazaki TG, Mitek A, Wszolek ZK. Interest in genetic testing in pallido-ponto-nigral degeneration (PPND): a family with frontotemporal dementia with Parkinsonism linked to chromosome 17. Eur J Neurol. 2001; 8(2):179–183. 198. [pii]. [PubMed: 11284997]

Mehta SG, Watts GD, Adamson JL, Hutton M, Umberger G, Xiong S, … Smith CD. APOE is a potential modifier gene in an autosomal dominant form of frontotemporal dementia (IBMPFD). Genet Med. 2007; 9(1):9–13. doi:10.1097GIM.0b013e31802d830d. [PubMed: 17224685]

Meiser B, Dunn S. Psychological impact of genetic testing for Huntington's disease: an update of the literature. J Neurol Neurosurg Psychiatry. 2000; 69(5):574–578. [PubMed: 11032605]

Miller TD, Jackson AP, Barresi R, Smart CM, Eugenicos M, Summers D, … Stone J. Inclusion body myopathy with Paget disease and frontotemporal dementia (IBMPFD): clinical features including sphincter disturbance in a large pedigree. J Neurol Neurosurg Psychiatry. 2009; 80(5):583–584. DOI: 10.1136/jnnp.2008.148676 [PubMed: 19372299]

Neumann M, Mackenzie IR, Cairns NJ, Boyer PJ, Markesbery WR, Smith CD, … Forman MS. TDP-43 in the ubiquitin pathology of frontotemporal dementia with VCP gene mutations. J Neuropathol Exp Neurol. 2007; 66(2):152–157. 00005072-200702000-00007 [pii]. DOI: 10.1097/nen.0b013e31803020b9 [PubMed: 17279000]

Norton S, Cosco T, Doyle F, Done J, Sacker A. The Hospital Anxiety and Depression Scale: a meta confirmatory factor analysis. J Psychosom Res. 2013; 74(1):74–81. S0022-3999(12)00305-4 [pii]. DOI: 10.1016/j.jpsychores.2012.10.010 [PubMed: 23272992]

Paulsen JS, Nance M, Kim JI, Carlozzi NE, Panegyres PK, Erwin C, … Williams JK. A review of quality of life after predictive testing for and earlier identification of neurodegenerative diseases. Prog Neurobiol. 2013; 110:2–28. S0301-0082(13)00081-6 [pii]. DOI: 10.1016/j.pneurobio.2013.08.003 [PubMed: 24036231]

Quaid KA, Morris M. Reluctance to undergo predictive testing: the case of Huntington disease. Am J Med Genet. 1993; 45:41–45.

Quaid KA, Sims SL, Swenson MM, Harrison JM, Moskowitz C, Stepanov N, … Westphal BJ. Living at risk: concealing risk and preserving hope in Huntington disease. J Genet Couns. 2008; 17(1):117–128. DOI: 10.1007/s10897-007-9133-0 [PubMed: 17943424]

Robins Wahlin TB, Backman L, Lundin A, Haegermark A, Winblad B, Anvret M. High suicidal ideation in persons testing for Huntington's disease. Acta Neurol Scand. 2000; 102(3):150–161. [PubMed: 10987374]

Rohrer JD, Lashley T, Schott JM, Warren JE, Mead S, Isaacs AM, … Warren JD. Clinical and neuroanatomical signatures of tissue pathology in frontotemporal lobar degeneration. Brain. 2011; 134(Pt 9):2565–2581. awr198 [pii]. DOI: 10.1093/brain/awr198 [PubMed: 21908872]

Rolim L, Leite A, Ledo S, Paneque M, Sequeiros J, Fleming M. Psychological aspects of pre-symptomatic testing for Machado-Joseph disease and familial amyloid polyneuropathy type I. Clin Genet. 2006; 69(4):297–305. CGE606 [pii]. DOI: 10.1111/j.1399-0004.2006.00606.x [PubMed: 16630162]

Rosenstock IM. Enhancing patient compliance with health recommendations. J Pediatr Health Care. 1988; 2(2):67–72. [PubMed: 3351739]

Schneider SA, Klein C. What is the role of genetic testing in movement disorders practice? Curr Neurol Neurosci Rep. 2011; 11(4):351–361. DOI: 10.1007/s11910-011-0200-4 [PubMed: 21465148]

Siris E. Zoledronate in the treatment of Paget's disease. Br J Clin Pract Suppl. 1996; 87:19–20. discussion 22. [PubMed: 8995014]

Steinbart EJ, Smith CO, Poorkaj P, Bird TD. Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. Arch Neurol. 2001; 58(11):1828–1831. noc10087 [pii]. [PubMed: 11708991]

Tibben A. Predictive testing for Huntington's disease. Brain Res Bull. 2007; 72(2–3):165–171. S0361-9230(06)00329-7 [pii]. DOI: 10.1016/j.brainresbull.2006.10.023 [PubMed: 17352941]

Tibben A, Duivenvoorden HJ, Vegter-van der Vlis M, Niermeijer MF, Frets PG, van de Kamp JJ, … Verhage F. Presymptomatic DNA testing for Huntington disease: identifying the need for psychological intervention. Am J Med Genet. 1993; 48(3):137–144. DOI: 10.1002/ajmg.1320480305 [PubMed: 8291567]

Tibben A, Stevens M, de Wert GM, Niermeijer MF, van Duijn CM, van Swieten JC. Preparing for presymptomatic DNA testing for early onset Alzheimer's disease/cerebral haemorrhage and hereditary Pick disease. J Med Genet. 1997; 34(1):63–72. [PubMed: 9032652]

Timman R, Roos R, Maat-Kievit A, Tibben A. Adverse effects of predictive testing for Huntington disease underestimated: long-term effects 7-10 years after the test. Health Psychol. 2004; 23(2):189–197. 2004-11615-012 [pii]. DOI: 10.1037/0278-6133.23.2.189 [PubMed: 15008664]

Tyler A, Ball D, Craufurd D. Presymptomatic testing for Huntington's disease in the United Kingdom. The United Kingdom Huntington's Disease Prediction Consortium. BMJ. 1992; 304(6842):1593–1596. [PubMed: 1385747]

Wahlin TB, Lundin A, Backman L, Almqvist E, Haegermark A, Winblad B, Anvret M. Reactions to predictive testing in Huntington disease: case reports of coping with a new genetic status. Am J Med Genet. 1997; 73(3):356–365. [pii]. DOI: 10.1002/(SICI)1096-8628(19971219)73:3<356::AID-AJMG24>3.0.CO;2-H [PubMed: 9415699]

Watkins LL, Koch GG, Sherwood A, Blumenthal JA, Davidson JR, O'Connor C, Sketch MH. Association of anxiety and depression with all-cause mortality in individuals with coronary heart disease. J Am Heart Assoc. 2013; 2(2):e000068. 2/2/e000068 [pii]. doi: 10.1161/JAHA.112.000068 [PubMed: 23537805]

Watts GD, Thorne M, Kovach MJ, Pestronk A, Kimonis VE. Clinical and genetic heterogeneity in chromosome 9p associated hereditary inclusion body myopathy: exclusion of GNE and three other candidate genes. Neuromuscul Disord. 2003; 13(7–8):559–567. S0960896603000701 [pii]. [PubMed: 12921793]

Weihl CC, Temiz P, Miller SE, Watts G, Smith C, Forman M, … Pestronk A. TDP-43 accumulation in inclusion body myopathy muscle suggests a common pathogenic mechanism with frontotemporal dementia. J Neurol Neurosurg Psychiatry. 2008; 79(10):1186–1189. 79/10/1186 [pii]. DOI: 10.1136/jnnp.2007.131334 [PubMed: 18796596]

Wiggins S, Whyte P, Huggins M, Adam S, Theilmann J, Bloch M, … Hayden MR. The psychological consequences of predictive testing for Huntington's disease. Canadian Collaborative Study of Predictive Testing. N Engl J Med. 1992; 327(20):1401–1405. DOI: 10.1056/NEJM199211123272001 [PubMed: 1406858]

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983; 67(6):361–370. [PubMed: 6880820]

Table 1

Population characteristics

Number accepted testing	33/102 (32.3%)
Number to complete baseline questionnaire	29
Average age	42 years (range 26–66 years)
Gender	19 Females 10 Males
Marital Status	19 married; 10 Single
Children	17 had children
Ethnicity	All Caucasian
Mutation Status	18 mutation positive 11 mutation negative
Number to complete follow up questionnaire	20
Average age	42 years (range 26–61 years)
Gender	14 Females 6 Males
Marital status	12 married
Children	13 had children
Mutation Status	13 mutation positive 7 mutation negative

Table 2

Baseline risk perception and concern regarding specific disease characteristics (n=29)

Baseline risk perception	50.09% (0–100%)
How concerned are you about developing the following yourself?*	
Myopathy	2.48
Paget disease bone	2.07
Frontotemporal dementia	2.52
How concerned are you about the following in your family?*	
Myopathy	2.93
Paget disease bone	2.56
Frontotemporal dementia	2.86

*(scored 0–4 with mean score for 29 individuals)

Table 3

Hospital Anxiety and Depression Scale (HADS) Scores

	Anxiety			**Depression**		
Baseline (n=29)						
Mean	6.17 (SD 4.1)			2.59 (SD 2.6)		
Number with scores ≥8	9 (7 scored 11 or above)			1*		
Follow up (n=19)	Total	Mutation positive	Mutation Negative	Total	Mutation Positive	Mutation Negative
Mean	5.65 (SD 1.6)	5.38	6.14	2.40 (SD 1.6)	2.46	2.28
Number with scores ≥8	4 (0 scored 11 or above)	2	2	0*	0	0

*Using Chi-square analysis these figures are significantly lower than would be expected in the general population