E Genetic aspects/testing

E.1 INTERMEDIATE ALLELES FOR HUNTINGTON'S DISEASE: PATIENT UNDERSTANDING AND CURRENT GENETIC COUNSELLING PRACTICES

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Background: Predictive testing (PT) for Huntington's disease (HD) has the ability to "predict" whether an individual will ever develop HD and thus have the ability to pass the disease onto their children. Some individuals who undergo PT receive an unusual test result called an "intermediate allele" (IA). Individual with an IA will never develop HD yet there remains a risk for their children to develop HD.
Aims: Numerous studies have examined the PT experience and psychosocial consequences of receiving a positive or negative test result. Despite the characterisation of IA over 15 years ago, no studies have provided insight into the clinical, psychological and social experience of individuals who receive an IA result. The purpose of this study is to explore IA carriers' understanding of the result implications and the current genetic counselling practices regarding IA.
Methods: Using grounded theory qualitative methodology, 18 IA carriers and five medical genetics professionals from three Canadian sites participated in open-ended interviews. Interviews were transcribed and analysed using the constant comparative method and the coding procedures of grounded theory.
Results: 55% of participants were unaware that their children remained at risk of developing HD, despite being counselled about this clinical consequence. Those IA carriers who were aware of the risk to their children experienced psychological distress, uncertainty and guilt. Medical genetics professionals described inconsistent counselling practices regarding the type of information on IA exchanged during PT. Family history appears to influence both patient understanding and professional counselling practices.
Conclusions: This study represents the first empirical study on the PT experience of IA carriers. The results of this study will contribute to the development of PT guidelines specific to IA that will provide guidance to clinicians on how to provide appropriate education, counselling and support to this unique subset of patients.

E.2 PREDICT–HD: A COMPANION STUDY EXPLORING ATTITUDES OF PARTNERS TO PREDICTIVE TESTING AND PARTICIPATION IN RESEARCH

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Background: Huntington's disease (HD) has a major impact on the family system. A limited amount of qualitative research has explored the effects from the perspectives of partners. PREDICT–HD is an international collaborative study investigating symptom onset markers in presymptomatic individuals. Partners of gene carrier individuals are also invited to attend.
Aims: The aim of this qualitative study was to investigate the effects of predictive testing and participation in PREDICT–HD from the partners' perspectives.
Method: 12 partners of carrier individuals attending PREDICT follow-up appointments in Manchester were interviewed about their experiences of HD and predictive testing, coping with the knowledge that their spouse would one day develop HD and attitudes to involvement in research. Interviews were transcribed in full and analysed using the constant comparison method.
Results/Outcome: Participants all reported feeling pleased that their spouse had had the predictive test; even those partners who initially reported misgivings or who had subsequently experienced difficulties in their relationship. The main benefit of testing was seen as preparation for the future and rehearsal for their role as carer. Participants used their experience with their spouses' families or previous experience as carer to act as a template for how they viewed their role as support person. This focused on two key areas—communication within the family and anticipated extent of involvement in physical care. The option to participate in research was welcomed by all partners; primarily as a means of providing hope, if not for their own family for future generations. The PREDICT appointment did, however, have the potential to raise difficult issues for couples and heightened awareness to the possibility of early symptoms.
Conclusions: Participants recommended that partners continue to be involved in research and that psychological support should be included as an integral part of research studies.

E.3 ATTACHMENT AND EMOTION REGULATION IN PREDICTIVE TESTING FOR HUNTINGTON'S DISEASE

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Background: Based on early experiences with caregivers, individuals develop mental working models of self and others in close relationships. These working models of attachment may be secure or insecure, depending on the degree to which they are characterised by anxiety or the avoidance of others. In a previous study, we found more insecure attachment in individuals with a Huntington's disease (HD) family background. Working models of attachment are activated in threatening situations, in which they influence the use of emotion regulation strategies. Insecure attachment (high anxiety and/or high avoidance) is associated with emotional instability. As predictive DNA testing for HD can be perceived as a threatening situation, attachment style may predict emotion regulation and psychological outcomes of testing, in both testees and partners.
Aims: To investigate relationships between attachment style, emotion regulation and psychological reactions to testing for HD.
Methods: Before testing, attachment style, cognitive emotion regulation, social interactions and psychological wellbeing are assessed in testees and partners. One week and 6 months after receiving test results, the psychological wellbeing of participants is assessed. Comparisons are made with testees for other neurodegenerative disorders and for hereditary breast and ovarian cancer.
Results: Inclusion of participants is ongoing. An outline of the study will be presented. We hypothesise that individuals with secure working models of attachment have more adaptive emotion regulation strategies and higher levels of psychological wellbeing. Because of different family dynamics, attachment is expected to be more insecure in individuals with an HD family background.
Conclusions: Knowledge about attachment working models and emotion regulation may enhance understanding of individual reactions to testing for HD. It can be useful for adequate psychosocial counselling.

E.4 NEGOTIATING A SPACE BETWEEN HEALTH AND ILLNESS: EXPERIENCES OF THOSE TESTING POSITIVE FOR HUNTINGTON'S DISEASE AND THOSE WHO PARENT WITH THEM

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Background: Technological advances in molecular genetics mean that those who know from their family history that they are at risk

for late-onset genetic disorders (such as Huntington's disease; HD) can choose to undergo predictive testing in order to resolve the uncertainty of their status.

Aim: The aim of this presentation is to present perceptions of health and illness of mothers and fathers living with the certain knowledge of their gene-positive status. Although not yet symptomatic, it is almost inevitable that they will develop HD in later life. It touches on how perceptions change for those who suspect they are beginning to become symptomatic and their partners.

Methods: Qualitative in-depth interviews were conducted with men and women testing positive and those who parent with them. Theoretical sampling involved recruiting men and women who had tested positive, parenting under a range of circumstances and with dependent children of different ages. Analysis was aided by a grounded theory model of responsibility generated from earlier research. This model encapsulated what families found important when making decisions about becoming parents.

Results: It will be argued that developments are generating new landscapes of health and illness. Examples will be given of how parents construct, negotiate and maintain this previously unknown space—described as ''living in no man's land''. They will show how spatial and temporal dimensions are used to create boundaries between the healthy, affected, at-risk, tested and future sufferers. Boundaries are tentative as uncertainty remains about when those tested positive will become symptomatic.

Conclusions: Entering this space fulfils an important moral purpose, ie, enabling parents to negotiate different positions of agency and responsibility before becoming symptomatic.

E.5 DIAGNOSIS AND RESEARCH OF HUNTINGTON'S DISEASE: SPANISH EXPERIENCE IN A GENETIC SERVICE

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Introduction: The genetic service of the FJD hospital has been working on diagnosis of Huntington's disease (HD) since 1994, following the quality standards established by the European Molecular Genetics Quality Network since 2000. We work in a multidisciplinary team together with the representative of the Spanish Huntington's Disease Association. Our experience in 1500 families includes predictive and diagnostic tests, prenatal and preimplantation genetic diagnosis (PGD) and research studies. The last innovations incorporated are the analysis of fetal DNA circulating in maternal plasma and PGD studies.

Materials and Methods: Six pregnancies among 30 prenatal diagnoses were selected for fetal DNA circulating studies in maternal plasma. In all of them the father was the gene carrier. 10 informative couples were requested for PGD; it had already been done in two of them. DNA was extracted from peripheral blood, maternal plasma, chorion villi and abortion remains. Direct and indirect studies with fluorescent primers were performed and analysed by capillary electrophoresis.

Results: In four out of six cases, by analysis from maternal plasma, the fetus could be correctly diagnosed. In two cases this diagnosis was not possible due to the length of the expansion. Both were from the same family and the fetuses showed a considerable number of CAG repeats, 78 and 114, respectively. Differences in the number of repeats were not observed in different tissues from abortion remains of the fetus with 114 repeats. In PGD results, no clinical pregnancy was obtained from the first family. Results for the second family are not yet available.

Conclusions: A combination of research and diagnostic studies could provide additional information to be considered for appropriate genetic counselling.

E.6 HUNTINGTON'S DISEASE: THE SAGA TO GET THE CORRECT DIAGNOSIS OF A NEURODEGENERATIVE DISEASE IN A POPULATION WITH SCARCE RESOURCES AND TECHNOLOGY IN NORTHEASTERN BRAZIL

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Feira Grande (FG) is a small city (with approximately 23 000 inhabitants, predominantly young) of Alagoas, northeastern Brazil. In the 1980s, while still a child, I did not understand why an elderly couple of married cousins from the neighbourhood displayed a progressive imbalance of movements. I saw others in the municipality with worse symptoms, and adult people used to describe this to me as a hereditary terminal disease called ''nervous''. Over time, I consulted local physicians, who referred to it as Parkinson's disease, prescribing dopamine-type drugs to patients. When I attended the disciplines of genetics and biochemistry (Federal University of Alagoas, UFAL), during my graduation in dentistry in the capital, I constructed a simple pedigree with data collected from the relatives of live or dead patients in FG. But the local physicians had no interest in it and after concluding my first degree and returning to FG, I joined the Program for Family Health. So I found other family groups with neurodegenerative symptoms. From 2001 to 2003, I built a more complex pedigree and found a genetic correlation of symptoms in six generations; this did not corroborate the diagnosis of Parkinson's disease. With the support of my former Professor of Biochemistry, who also managed to add to this cause the backing of three clinical geneticists of UFAL, I founded a group to define the markers that would be screened to identify the neurodegenerative disease in FG. After referring patients to clinical, neurological, biochemical and genetic evaluation (2005), the true diagnosis was finally obtained—Huntington's disease (HD). This was announced to the Brazilian Society of Huntington (2006), which, perplexed with the record on coverage of HD cases, sent its representatives to FG (2007) to advise family and HD patients (treatment, genetic counselling and rights). There is now a commitment from the government for the installation of a multidisciplinary centre to support relatives and carriers of HD.

E.7 HUNTINGTON'S DISEASE AND HUNTINGTON-LIKE PHENOTYPE: 10 YEARS OF LOCAL MOLECULAR DIAGNOSTIC EXPERIENCE

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CGPP/IBMC is the reference laboratory for Huntington's disease (HD) in Portugal. we performed more than 1000 HD tests over the past 10 years, including diagnosis, predictive and prenatal tests.

Only 58% of all diagnostic requests were confirmed; from those excluded, we selected 200 patients and studied them for HD-like genes: an extra eight octapeptide repeats in the PRNP gene (HDL1); a CTG/CAG repeat in the junctophilin (JPH3) gene (HDL2); a CAG expansion in two SCA genes—ATN1 (DRPLA) and TBP (HDL4/SCA17); as well as others included in the differential diagnosis of HD: neuroferritinopathy (FTL gene) and benign hereditary chorea (TITF-1 mutations).

Expansion of CAG repeats in ATN1 and the insertion on PRNP were excluded in all cases. One family (mother and son with chorea since childhood, myoclonus, falls and dysarthria) carried a nonsense mutation in TITF-1. An FTL mutation was detected in one gypsy family (mother asymptomatic and son with mild non-progressive mental retardation and gait disturbances by the age of 13 years; both had pallidal involvement on magnetic resonance imaging). We also found a CAG expansion in TBP (a patient with behavioural disturbances, epilepsy, aphasia, imbalance and gait ataxia). Finally, we found a 47 CTG/CAG expansion in the JPH3 gene in a Brazilian white patient with a familiar history of disease (onset at age 44 years of bradipsychism, mutism, dysarthria, cognitive deterioration and chorea, as well as ataxic gait; he had cortical atrophy).

This work stresses the importance of also performing the exclusion of HD-like disorders whenever the HD mutation has been excluded and it is clinically indicated.