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Letter to the Editor

Letter in Response to Tibben et al., Risk Assessment for Huntington's Disease for (Future) Offspring Requires Offering Preconceptional CAG Analysis to Both Partners

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We would like to thank Tibben et al. for reporting their experience of identifying intermediate alleles (IA) reduced penetrance alleles (RPA) or, in one case, a fully penetrant allele (FPA) in the partners of individuals who had undertaken or requested pre-natal diagnosis for Huntington's disease (HD) [1]. They conclude that the guidelines for predictive testing [2] should be altered to include routinely offering to test the unaffected partner for the presence of these alleles and presumably adding a direct assessment of the CAG repeat length when undertaking prenatal diagnosis (PND) or pre-implantation genetic diagnosis (PGD). We think it is correct that such cases are reported and the topic is debated but feel that the case for altering the current guidelines has not yet been made. The principal problem is that we have insufficient information about the behaviour of these alleles in non-HD families.

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There have been a small number of studies on the presence of IAs in the general population but a figure of 6% can be used [3–5] suggesting 1 in 17 of the population can be expected to have an IA. In their study of 3 general population cohorts Kay et al. found 15 people with RPAs and 3 with FPAs; consequently, an estimated 1 in 400 people have an expanded CAG repeat allele [5]. They further estimated that 1,400 individuals from British Columbia ≥65 years should have an RPA. This compares with the 15 individuals they found with their clinical study, 13 of whom were aged ≥65 years. Tibben et al. [1] correctly reported a conclusion of this study, which indicates that the penetrance of these alleles in the general population is much lower that found in clinically symptomatic families. The variation in penetrance in FPAs and RPAs in the general population as compared with those from HD families is incompletely understood. The factors which predispose an IA to expand into the RPA or FPA range and produce a clinical phenotype are also uncertain.

Tibben et al. [1] correctly report the study of Semaka et al. regarding analysis of spermatozoa of men with IAs but these donors were ascertained following predictive testing and thus had a family history of HD [6]. We are not aware of a similar study of men with IAs ascertained from the general population; such a study may prove difficult to conduct since it would involve identifying specific individuals from a general population cohort.

The problem of managing genetic test results whose significance is very uncertain is not unique to HD. In undertaking chromosome microarray analyses in the context of PND some copy number variants may be detected that may predispose to developmental disability or neuropsychiatric illness, but which are highly variable, unpredictable in effect, and seen in unaffected persons. In the UK, there is published guidance on such neurosuceptibility loci, indicating that they should not be reported in the context of a pre-natal micro-array analysis undertaken because of abnormalities detected on a pre-natal ultrasound scan [7].

This suggested recommendation by Tibben et al. [1] of partner testing needs to be seen in the context of risk of preventable problems in offspring of couples planning or in the early stages of a pregnancy. The risk of a severe childhood onset autosomal recessive or X-linked recessive condition that can be identified by testing parents by so-called expanded carrier screening is up to 1 in 255 [8]. This includes conditions such as cystic fibrosis, spinal muscular atrophy and fragile X syndrome, weighted by CCG length. This risk is considerably higher than the chance of a child going on to have HD as a result of the parent without a family history of HD having an IA, RPA. or FPA. Screening for carrier status of autosomal and X-linked recessive conditions should logically be a much higher priority than testing the parent without a family history for an *HTT* CAG repeat length expansion. Interestingly, an accompanying editorial to the article on expanded carrier screening urged a cautious approach and specifically commented that detection of CCG repeat length expansion for Fragile X in the low pre-mutation range is fairly common in the population and the risk of expansion low which could lead to unnecessary pre-natal testing and labelling of children [9].

If 6% of the general population have an IA and 0.2% have an RPA or FPA then estimating the risk of such an IA expanding into the RPA or FPA range and causing HD is particularly difficult. If routine testing of the partner was implemented then in turn that would suggest that cascade screening should be offered to the partner's close relatives if an IA or RPA is detected, thereby extending the uncertainty to more individuals. Given all these uncertainties, we prefer on balance not to recommend routine testing of the partner in the context of PND and PGD when one member of a couple has a family history of HD and a risk of transmitting the condition. Direct testing of the HD allele already occurs in most laboratories in the context of PND (but not exclusion testing) and would negate testing of a partner under these circumstances.

This position may change if more evidence becomes available in the future.

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