CLINICAL RESEARCH

Genetic prediction and family structure in Huntington's chorea

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Abstract

A deoxyribonucleic acid marker linked to the locus for Huntington's chorea exists, but its possible use in the prediction of this disorder depends on the pedigree structure of individual families. Analysis of data from a population register for Huntington's chorea in south Wales showed that only a minority of subjects at risk had the appropriate members of their family living to allow the presence or absence of the gene to be definitively predicted. However, the structure of the family allowed a degree of prediction (in particular, exclusion of the disorder) to be made for the fetus during pregnancies of these subjects in almost 90% of cases. Such a prediction need not alter the risk state for the parent at risk. The structure of the family will remain crucial for prediction even when current limitations of the linked marker have been overcome.

Introduction

The identification of a deoxyribonucleic acid (DNA) sequence (G8) showing close genetic linkage to Huntington's chorea on chromosome 4 has raised the possibility of its clinical application in genetic prediction for families with this disorder.[1] There will probably be practical limitations to such a prediction,[2] depending on factors such as whether there is more than one genetic locus for Huntington's chorea, the precise distance between the disease and marker loci, and the proportion of subjects in whom the marker genotype is informative (about 75%). Work is in progress to identify and reduce these limitations. Other limitations arise from the structure of individual families with Huntington's chorea, notably whether an affected parent or grandparents are living and available for study. We examined these limitations, which could be less easy to overcome than those concerning the marker itself and have so far received less attention.

The families chosen for genetic linkage study of Huntington's chorea have, understandably, been extensive and have contained numerous subjects available for study. Generally, however, they are not typical of families with Huntington's chorea, which are often small and fragmented, with key members dead or unavailable. As part of a study of the applicability of the G8 marker in prediction[3] we analysed the structure of families with Huntington's chorea in south Wales to determine in what proportion a genetic prediction could be achieved for either the subject at risk or a pregnancy of that subject.

In this study we ignored the limitations of the G8 marker and assumed that the marker genotype received from each parent or grandparent could be unequivocally distinguished in all cases. The recent identification of additional polymorphisms at the G8 locus means that about 90% of subjects are heterozygous for at least one polymorphism.[4]

Subjects and methods

Records of all families with Huntington's chorea on a register for south Wales were studied. This register, containing 160 affected patients and roughly 1000 subjects at high risk (greater than one in 10) of developing the disorder, is based on a total ascertainment study within the counties of Glamorgan and Gwent[5] and is maintained prospectively to record all births to subjects at risk.[6]

Data on two separate groups were analysed: those subjects aged 16-45 whose risk of developing Huntington's chorea was greater than one in 10, representing those in the reproductive age group most likely to wish to undergo genetic prediction of the presence or absence of the Huntington's chorea gene; and 100 consecutive pregnancies (occurring during 1979-83) in parents whose risk of developing Huntington's chorea was greater than one in 10.

The data studied that were relevant to prediction included whether parents and relevant grandparents were living, whether a parent was affected or at risk, and whether there were affected siblings. A relative was recorded as living or dead according to the most recent updating of information (annually), except in the series of pregnancies, in which the situation at the child's year of birth was recorded.

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Figure 1 shows the relevant pedigree structures required to make a genetic prediction. In the simplest and most informative case (fig 1(*a*) and (*b*)) information must be available on three generations—namely, the person at risk, parent, and grandparent—if a prediction is to be made for the person at risk. Prediction is less easy when information on only two generations is available (fig 1 (*c*)) as there is no indication as to whether the type of marker that has been transmitted is that on the same chromosome as the Huntington's chorea gene or that on the other "normal" chromosome. Availability of data on the previous generation provides this information with the proviso that there will be a possibility of error that equals the rate of recombination (θ) between the marker and locus of Huntington's chorea. If one parent or grandparent (most commonly the affected one) has died or is unavailable for study (fig 1 (*d*)) it may be possible to deduce that subject's genotype from those of the spouse and children.

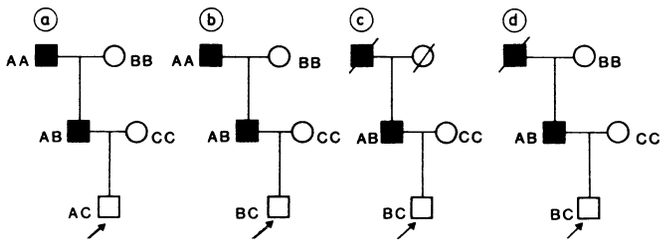

FIG 1—Pedigree structures required for prediction of subjects at risk of developing Huntington's chorea (subject requesting prediction arrowed). (*a*) Both grandparents living. Affected parent has received Huntington's chorea and A marker type from grandparent. As child has also inherited A marker he would be predicted as being affected in absence of recombination. (*b*) Offspring has inherited B marker type from affected parent, which has come from unaffected grandparent, so normality would be predicted. (*c*) Neither grandparent living. Prediction is impossible because although subject at risk has received B marker type from affected parent, it is not known whether this came with the Huntington's chorea gene or from unaffected grandparent. (*d*) Affected grandparent is dead but must have carried A marker and transmitted it with Huntington's chorea to affected son. Thus normality can be predicted for subject at risk.

Information from two generations may enable prediction if affected siblings are available for study. The expected error in prediction, however, would be greater than θ as affected siblings could themselves have resulted from recombination. Unaffected siblings are more often available for study, but then there is the additional problem of uncertainty in all but the oldest of whether they might still develop the disorder. Information from more distant relatives is likely to be contributory only in those few large families in which a particular type of marker is clearly transmitted with the Huntington's chorea gene in multiple members.

By contrast, prediction for a fetus with a parent at 50% risk of developing the disease (or for children born to such a parent) may be possible even when prediction is not possible for that parent (fig 2). A result as in fig 2 (*b*) or (*d*) would suggest that the fetus has inherited the marker allele C from the healthy grandparent, and thus Huntington's chorea can be excluded (in the absence of recombination). In fig 2(*a*) the fetus has inherited the marker allele A, which was received by the parent from the grandparent with Huntington's chorea. Thus Huntington's chorea cannot be excluded, and the fetus has the same 50% risk of developing the disease as the parent.

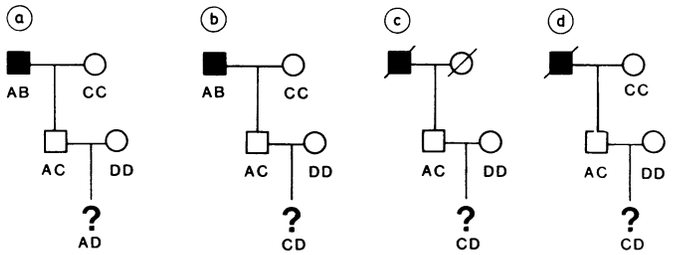

FIG 2—Pedigree structures for prediction for fetus at risk of developing Huntington's chorea. (*a*) Although no prediction can be made for parent at risk, fetus has inherited A marker type from affected grandparent and is thus at same 50% risk as parent. (*b*) Fetus has inherited C marker type from healthy grandparent; Huntington's chorea can thus be excluded in absence of recombination. (*c*) No prediction can be made for fetus as both grandparents are dead. (*d*) Huntington's chorea can be excluded in fetus as it has inherited C marker from healthy grandparent.

This result does not in any way alter the parent's risk of developing the disease as we do not know whether the grandparent had the Huntington's chorea gene on the same chromosome as the A allele.

Results

The table shows the data relevant to prediction for subjects on our register who were in the reproductive age group (16-45 years) and whose age adjusted risk for Huntington's chorea exceeded one in 10. It also gives comparable data for the 100 consecutive pregnancies.

Our results showed that few subjects, whether a parent in the pregnancy series or not, had a pedigree structure allowing prediction for an adult at risk. In both series under 20% of subjects had at least one grandparent living to allow such prediction, and the number with affected siblings was also small (3% in the pregnancy series and 10·5% for the adults at risk). By contrast, in most cases the pedigree structure allowed some prediction as to the outcome of pregnancy or for offspring already born, at least one parent (grandparent to the fetus) being alive in nearly 90% of both series (87·8% for adults at risk, 89% for actual pregnancies).

Discussion

Genetic prediction of Huntington's chorea has been a much debated issue, generally in terms of the problems of telling subjects at risk whether they have inherited the gene. The ethical issues are difficult and have been intensified by the discovery of the closely linked DNA polymorphism G8.

Although prediction for those at risk would probably be feasible in selected large families, our results showed that the overall pedigree structure of families with Huntington's chorea in south Wales imposed limitations on prediction using any linked DNA marker, quite apart from the limitations of the marker itself. In particular, prediction for an adult at risk would not be possible in most cases (around 85%) as grandparents have died and siblings are rarely affected. By contrast, in most cases (around 90%) prediction would be possible for the fetus (or offspring) of such subjects, with exclusion of the disorder

Number (%) of subjects in south Wales at risk of developing Huntington's chorea

	Affected or at risk parent living	One or both parents living	Affected grandparents living	At least one grandparent living	Affected siblings living
		Adults aged 16-45 at greater than 10% genetic risk			
Affected parent (n = 344)	152 (44·2)	265 (77·0)	7 (2·0)	40 (11·6)	66 (19·2)
Affected grandparent (n = 293)	263 (81·8)	282 (96·3)	25 (8·5)	57 (19·5)	1 (0·3)
Total (n = 637)	423 (66·4)	559 (87·8)	32 (5·0)	99 (15·5)	67 (10·5)
		*Pregnancies at risk**			
Affected parent† (n = 67)	38 (56·7)	61 (91·0)	2 (3·0)	12 (17·9)	3 (4·5)
Affected grandparent† (n = 33)	28 (84·8)	28 (84·8)		7 (21·2)	
Total (n = 100)	66 (66·0)	89 (89·0)	2 (2·0)	19 (19·0)	3 (3·0)

*Consecutive series of pregnancies in mothers (or their husbands) at greater than 10% risk.
†Relationship to pregnant woman (or husband), not to fetus.

being expected in half and a high risk of developing it in the other half (the same risk as for the parent). A definitive prediction of inheriting Huntington's chorea would be feasible only for the fetuses of those subjects at risk in whom prediction was already possible (a small proportion as mentioned above).

Making a prediction during pregnancy, as described above, does not alter the risk for the parent in any way, which is important practically as fear of such an implication might influence attitudes towards prediction during pregnancy. This lack of an effect on the existing risk is the rule rather than the exception, which is not widely understood by the families concerned.

In view of our findings we suggest that in the initial clinical applications of the genetic prediction of Huntington's chorea it may be more feasible and possibly more acceptable to monitor fetuses at risk than to attempt prediction for subjects already born. This would mean that those at risk could bear children in whom the disorder had been excluded during pregnancy with the option of termination if the pregnancy were predicted to be at high risk (50%). Although ethical reservations may understandably be raised at our considering termination of pregnancy for a disorder of relatively late onset when the fetus is only at 50% risk, termination in such circumstances is not uncommon at present for fetuses at risk of developing Huntington's chorea. The feasibility of detecting DNA polymorphisms by chorion biopsy may make prediction more acceptable to couples than if an approach at mid-trimester such as amniocentesis was required.

Before this clinical use of the G8 marker can be advocated further information is required on the closeness of the linkage and the absence of genetic heterogeneity in Huntington's chorea, as well as further development of the polymorphisms so that the origin and transmission of the Huntington's chorea gene can be recognised in most subjects. These aspects are currently being studied at several centres, but their resolution will not remove the limitations imposed by pedigree structure that have been discussed in this paper. Only when a specific test for the Huntington's chorea gene itself is discovered may it be feasible to make a prediction for an isolated subject without studying the family unit; such a development seems to be some way away. Meanwhile, families are likely to request, and benefit from, prediction along the lines indicated; it is important that they and those considering using the test are aware of both the limitations and the possibilities and of the need for the structure of the family to be considered.

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Reciprocal change in ST segment in acute myocardial infarction: correlation with findings on exercise electrocardiography and coronary angiography

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Abstract

The clinical relevance of reciprocal changes in the ST segment occurring at the time of acute myocardial infarction was studied prospectively in 85 consecutive uncomplicated cases. Reciprocal depression of the ST segment was defined as depression of 1 mm or more in electrocardiogram leads other than those reflecting the infarct. All patients underwent maximal, symptom limited treadmill stress testing two weeks after the infarct and coronary angiography six weeks after infarction. Forty six patients had inferior, 34 anterior, and five true posterior infarction.

Of the 51 patients with reciprocal changes, 45 (88%) developed exercise induced ST segment depression in areas remote from the infarction zone. At angiography all 45 patients were shown to have stenoses greater than 70% in at least two major vessels. Four patients had negative exercise electrocardiograms and were subsequently shown to have single vessel disease subtending their infarct, and the remaining two patients had a false negative treadmill test result. Of the 27 patients without reciprocal changes, 21 (78%) had negative treadmill stress test results associated with single vessel coronary disease. Five had positive stress test results and multivessel coronary disease, and one had a false negative stress test result. The remaining seven patients had ST segment elevation without Q wave formation in the reciprocal areas and were assessed separately. Of these, six had positive stress test results and multivessel coronary disease and one had a negative stress test result and single vessel coronary disease to the infarct area. Twenty one patients with anterior infarcts (62%) and 27 with inferior infarcts (59%) had reciprocal changes. No differences emerged in the

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