LETTERS TO THE EDITOR

Psychological aspects of von Recklinghausen neurofibromatosis (NF1)

In the December 1995 issue of your journal, McRae et al. reviewed the psychological aspects of NF1. They provided an excellent insight into many issues, such as the frequency of poor self-image and psychiatric disturbance. However, there have been a number of recent publications, which were not included in the review, and which provide a number of areas of consensus concerning the cognitive phenotype of patients with NF1.

(1) Mutations in the NF1 gene are associated with a lowering of IQ in at least, a subset of patients. The mean full scale IQ score (for a clinic derived population) is in the range of 90-94. Hoffman et al. also reported a significant pairwise difference between each child with NF1 and an unaffected sib on full scale IQ, verbal IQ, and Judgement of Line Orientation (a test of visuospatial function).

(2) There does not appear to be an association between the left shift in IQ and any clinical variable (such as clinical severity of disease, macrocephaly, or family history of NF1).

(3) There is a slight increase in the incidence of mental retardation in NF1 (4-8%) compared to the general population.

(4) At least 40% (and probably more) patients with NF1 have learning disabilities. In our study of 40 children (aged 8 to 16 years), 65% had impaired performance (that is, more than 2 SD below the mean) on at least one test of academic achievement.

(5) There does not appear to be a specific profile of learning disabilities in patients with NF1. There is no consistent discrepancy between verbal and performance IQ. The Judgement of Line Orientation (a test of visuospatial function) is consistently abnormal in all studies to date and thus, at some level, is a robust indicator of NF1 related neuropsychological deficits. However, language based learning problems (for example, reading and spelling) are more common than non-verbal learning deficits. Poor attentional and organizational skills affect performance in many areas, although increased distractibility is not usually associated with hyperactivity.

(6) There have been a number of recent studies concerning the significance of areas of hypointense T2 signal on MRI (UBO or unidentified bright objects) in relation to cognitive deficits in patients with NF1. In our study, children with areas of increased signal intensity on MRI (UBO+) had significantly lower IQ scores than children without these lesions. However, the association between “UBOs” and learning disabilities remains controversial. Moore found no statistical difference in overall IQ scores between the UBO+ and UBO- groups. However, when the results were analysed according to the site of increased T2 lesions, there was a significant association between deficits in IQ, memory, motor function, and attention span and T2 signal lesions in the thalamus and hypothalamus. Hoffman et al. and Denckla et al. found that the number and volume of T2 signal lesions were highly correlated with specific cognitive deficits in UBO+ scores (compared to unaflected sibs). In addition they found an association between impaired visuospatial function (as shown in the Judgment of Line Orientation) and the volume of T2 signal lesions in the basal ganglia.

Although there appears to be some association between T2 signal lesions on MRI and cognitive deficits in children with NF1, the exact nature of this association and its relationship to the number, volume, and location of lesions remains to be elucidated. The available evidence suggests that these T2 signal lesions represent areas of dysplastic gliosis and aberrant myelination in the developing brain. If the relationship between MRI lesions and cognitive deficits in NF1 is validated then this association may provide important insight into the pathogenesis of cognitive deficits in patients with NF1.

KATHRYN N NORTH
Royal Alexandra Hospital for Children, PO Box 3515, Parramatta, Sydney, NSW 2124, Australia

6 Moore BD, NF1, cognition and MRI. Neurology 1995;45:1029.

The male excess in Down’s syndrome

Mutton et al. confirmed earlier reports of a male excess in cases of Down’s syndrome (DS). The cause of this excess is not yet established, but it appears to be not sex selective spontaneous abortion: in their data, these cases numbered 63 males and 51 females. I should like to suggest a cause of this excess. It is that in cases of DS, the timing of insemination in relation to ovulation is not optimal. It is widely believed (at least amongst non-geneticists) that timing of fruiting body coitus within the human menstrual cycle is associated with offspring sex ratio, male zygotes being preferentially formed when the fruitful insemination is either early or late. In a meta-analysis of studies, Gray estimated that fruitful inseminations around ovulation
resent a parent testing him or her "when you were too young to remember". Controlled surveys are unrealistic but we could discover the views of up to 20 year olds. Has anyone asked them?

A CAROLINE BERRY
Division of Medical & Molecular Genetics, Guy's Hospital, 7th or 8th Floors Guy's Tower, St Thomas Street, London SE1 W7 UK

This letter was shown to Drs Michele and Marteau, who reply as follows.

Dr Berry raises several important questions concerning predictive genetic testing in children: the age at which a child's opinion about his/her own testing should be sought, whether a proxy should give an opinion in the case of a young child, and the extent to which a child should have a say in the decision about whether and when to be tested.

In the absence of data to inform these questions directly, research concerning children's informed consent in other areas can shed some light.1 The general trend over the last decade has been one of discovering genetic co-morbidity in young children more often than previously attributed and of giving them a greater responsibility for decisions about, for example, their medical treatment and participation in research.2

Views about whether parents should be allowed to make such decisions for their children vary and, again, we lack the evidence of the impact on children and family life of parents either being allowed to make this decision or of not being allowed to make this decision. Our recently reported single case study suggested that the latter can lead to anger both within the family and with health professionals.3 Dr Berry argues that teenagers may resent having been tested as a child. In the case study found resentment of not having been tested as a child. As Dr Berry states, we need more information about what children and teenagers think about these issues.

We are currently conducting a multicentre trial to investigate the psychological impact of predictive test results on children and their parents. Much more research is needed if we are to have an informed debate on these important issues.

SUSAN MICHEL, THOMAS MARTEAU
Psychology & Genetics Research Group, UMDNJ, Ground Floor, Old Medical School Building, Guy's Campus, London SE1 9RT, UK


BOOK REVIEWS

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As possession of the Y chromosome provides the clearest evidence for a genotype with a predisposition to antisocial behaviour, a possible subtitle for this could be "Adam and evil". The problem is to see how far one can concentrate on an evaluation of non-Y linked genetic factors. As several contributors point out, an inclination to aggression is integral to our survival mechanism and thereby provides a survival mechanism for us. Criminality is not a biological characteristic, it is a social construct; labelling particular constellations of behaviours as "disorders" can therefore be unhelpful. Several other important reservations are addressed in this volume. For example, many would agree with Cairns (p55) that "there is a special folly in recent attempts to identify the 'gene' for aggressive behaviours, whether by the methods of molecular genetics or by pedigree analysis". I think we all recognise that behaviours are plastic and genetically rather intricable by virtue of their distance from the primary levels of gene function. In spite of these and other considerations, there are compelling reasons for investigating the role of genetic factors in antisocial behaviour. Many current experimental approaches are covered including animal studies, the evaluation of specific candidate loci, linkage mapping, and familial correlations. The proceedings conclude with highly readable chapters providing both evolutionary and sociological insights and a consideration of behavioural genetics in context of individual responsibility.

For my money, there is too much emphasis on previously reported attempts to assign the relative contribution of genes and environment through the interpretation of adoption and twin studies. Much of the text is also devoted to the discussions, which follow each chapter and each section; these could be extensively edited without significant loss. So, for those with a pressing schedule, it would be worth concentrating on the clear introduction and concise conclusions by Rutter. The contributions by Goldman and Brunner with a major emphasis on the contributions of molecular approaches are also highly recommended.

The chapter by Maxson provides a balanced account of the practical advantages and theoretical problems to be encountered in mouse models for human aggression. A very positive aspect of a book role is also taken by Cairns, who discusses aggression from a developmental perspective. One of the mainstays of animal studies has been linkage mapping, either of discrete traits or via surrogates for quantitative trait loci (QTL). This approach has been notable recently through the identification of loci implicated in the aetiology of stress (Flint et al. Science 1995;269:1432-5). Another major contribution from animal studies is through "gene knock-out". The example discussed in this context is that of the 5-HT1Db serotonin receptor. Perhaps surprisingly, mice lacking this genotype show normal aggression, although males show a twofold increase in frequency of attacks on intruders. While judgement should be suspended as to the consequences of equivalent aberrations in human behaviour, two more dramatic examples of neurotransmission defects resulting in aggression in "knock-out" mice have been reported recently for the monoamine oxides, MAO A, and neuronal nitric oxide synthase, NOS1, genes.

It is instructive to note that the most direct and controversial implication of a gene defect in human aggressive behaviour also involves the MAO locus (see McGuffin & Farmer). In contrast, attempts to confirm the role of many candidate genes identified through allelic association have, in general, been unsuccessful. As noted by several contributors, marker associations have often proved to be fragile and unreliable.

In conclusion, the symposium underscores how difficult it is to separate cultural, sociological, and emotional influences from hard science in behavioural studies. We can now hope that the rapid advances in molecular biology will increasingly enable the roles of specific candidate genes (such as MAO A) with small total impact, but with well-established psychopharmacological function, to be teased out. Evidence for the roles of both genes and environment and even for their interaction has been generally accepted for a decade. What emerges from the symposium is a fairly resounding confirmation of these general conclusions. The next 10 years should see some of the contributing factors hung on more specific pegs. So, although already dated, these remain a very worth studying by those involved in the field and particularly by the advanced guard of molecular biologists moving into this challenging area.

IAN CRAIG


This excellent pocket sized text book encompasses, very successfully, the fundamentals of genetics, functional aspects of genetics, and information about genomic organisation. It is aimed towards students of medical sciences and biology but would also be a very useful reference book for physicians who are beginning genetic research and who wish to read a basic but comprehensive text book.

The book has been written so that each page of text has opposite a full page of explanatory diagrams. These are all in colour and have been well thought out so that they complement the text. This makes it easy to read and the information is very accessible. Instead of being put off by pages of turgid text full of jargon the reader feels encouraged to read on or at least to look at all the pictures.
Predictive genetic testing in children.

A C Berry

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