LETTERS TO THE EDITOR

Meiotic drive at the myotonic dystrophy locus

The mutation underlying myotonic dystrophy (DM, MIM* 160900) is the expansion of a CTG trinucleotide repeat sequence at the 3' untranslated region of a protein kinase gene (MT-PK).¹ The kinetics of this process is influenced by the sex of the transmitting parent and size of the parental allele.²⁻⁴ Congenital DM (CDM) occurs almost always with maternal transmission. Only two patients with CDM have proven paternal inheritance.^{5,6} Maternal transmission is considered to be the result of a large intergenerational increase of the CTG repeat size,⁷ while repeat length contractions are more likely inherited if the mutated allele is of paternal origin.⁸ However, the range of expansions is wider for alleles transmitted by fathers with fewer than 100 repeats (range 41 to 95).⁹ This has suggested a male bias in the generation of new contracted or expanded DM alleles.¹⁰ Carey *et al*¹¹ described an unusual segregation of the MT-PK alleles with a CTG number ≥ 19 in healthy persons heterozygous for repeats in the wild type size range, and suggested the possibility of meiotic drive at the DM locus.

We investigated 251 Italian and Spanish DM pedigrees by clinical and molecular analysis to substantiate differential transmission of the MT-PK alleles. The 210 fathers had CTG repeats in the range of 54 to 1100, while the 178 mothers had expansions in the range of 90 to 2000. Among 897 sibs investigated we found a significant proportion of affected sibs (58.1% *v* 41.9%) ($Z = 4.663$, $p < 0.001$). The 314 DM offspring born from affected fathers had expansions in the range of 100 to 1900, while the 207 DM offspring born to affected mothers had repeats in the range of 70 to 2200. In addition, we observed a striking distortion of segregation with sex. The mutant parental allele was significantly more often transmitted to sons (table). The daughters had received the DM allele in similar proportions from their mother and father (table). Fathers had preferentially transmitted the mutant allele to sibs ($p < 0.001$). The un-

affected sibs had a male to female ratio of 1.020 compared to 1.144 in affected sibs. The average family size was similar in the progeny of affected and unaffected parents (3.5). It is likely that the segregation distortion observed was not the result of a limitation in family size after the birth of an affected child since the average family size of affected fathers was larger than that of affected mothers.

Our results show that DM alleles, unlike the wild type alleles, are transmitted preferentially to sons, and that the sex of the affected parent influences the probability of a child inheriting the disease gene. In fact, more affected sibs are born to affected fathers than to affected mothers. Our data expand the results of Carey *et al*¹¹ and point to distortion in favour of CTG alleles ≥ 19 in male transmission. The present results also support the suggested mechanism of an expansion of the DM gene pool through preferential inheritance of the mutant alleles from male to male.¹⁰ This mechanism could involve cis-acting elements associated with (proto) mutated alleles, affecting gamete viability or fitness, or survival of the zygote. It is noteworthy that inheritance of the cone-rod retinal dystrophy locus, which maps in the DM region (19q13.3-q13.2), is also influenced by meiotic drive.¹²

Although unusual segregation of trinucleotide mutations awaits verification in other diseases, one can speculate that meiotic drive is an evolutionary force which increases the population frequency of dynamic alleles.

We thank the DM families for their cooperation in this study. This work was supported by grants from CNR (PF Ingegneria Genetica), Italian Telethon (Grant no 511), and Ministerio de Sanidad y Consumo (FIS 94/0350).

M GENNARELLI
B DALLAPICCOLA
Department of Public Health and Cell Biology,
'Tor Vergata' University of Rome and,
CSS Hospital, IRCCS,
San Giovanni Rotondo, Italy.

M BAIGET
L MARTORELL
Unidad de Genética Molecular,
Hospital de la Santa Creu i Sant Pau,
Barcelona, Spain.

G NOVELLI
Institute of Medical Genetics,
Catholic University "Sacred Heart",
Largo Francesco Vito 1,
00168 Rome, Italy.

- 1 Brook JD, McCurrach M, Harley HG, *et al*. Molecular basis of myotonic dystrophy: expansion of a trinucleotide (CTG) repeat at the 3' end of a transcript encoding a protein kinase family member. *Cell* 1992;68:799-808.
- 2 Harley HG, Rundle SA, MacMillan JC, *et al*.

- Size of the unstable CTG repeat sequence in relation to phenotype and parental transmission in myotonic dystrophy. *Am J Hum Genet* 1993;52:1164-74.
- 3 Redman JB, Fenwick RG, Fu YH, *et al*. Relationship between parental trinucleotide CTG repeat length and severity of myotonic dystrophy in offspring. *J Am Med Assoc* 1993;269:1960-5.
- 4 Cobo AM, Baiget M, De Munain AL, *et al*. Sex-related difference in intergenerational expansion of myotonic dystrophy gene. *Lancet* 1993;341:1159-60.
- 5 Nakagawa M, Yamada H, Higuchi I, *et al*. A case of paternally inherited congenital myotonic dystrophy. *J Med Genet* 1994;31:397-400.
- 6 Fischbeck KH, Bergoffen J, Kant J, *et al*. Paternal transmission of congenital myotonic dystrophy. *Am J Hum Genet Suppl* 1993;53:A1157.
- 7 Tsilfidis C, MacKenzie AE, Mettler G, *et al*. Correlation between CTG trinucleotide repeat length and frequency of severe congenital myotonic dystrophy. *Nature Genet* 1992;1:192-5.
- 8 Ashizawa T, Anvret M, Baiget M, *et al*. Characteristics of intergenerational contractions of the CTG repeat in myotonic dystrophy. *Am J Hum Genet* 1994;54:414-23.
- 9 Brunner HG, Brüggewirth HT, Nillesen W, *et al*. Influence of sex of the transmitting parent as well as parental allele size on the CTG expansion in myotonic dystrophy (DM). *Am J Hum Genet* 1993;53:1016-23.
- 10 Wieringa B. Myotonic dystrophy reviewed: back to the future? *Hum Molec Genet* 1994;3:1-7.
- 11 Carey N, Johnson K, Nokelainen P, *et al*. Meiotic drive at the myotonic dystrophy locus? *Nature Genet* 1994;6:117-8.
- 12 Evans K, Fryer A, Inglehearn C, *et al*. Genetic linkage of cone-rod retinal dystrophy to chromosome 19q and evidence for segregation distortion. *Nature Genet* 1994;6:210-13.

Natural history and postmortem anatomy of a patient with tetra-amelia, ectodermal dysplasia, peculiar face, and developmental retardation (MIM 273390)

We would like to document the follow up details of an infant originally reported by us in 1987¹ with a probable new malformation syndrome. The clinical features of the male proband, at that time 1 year old, included tetra-amelia, hypotrichosis, upward slanting palpebral fissures, lack of lacrimal openings, hypoplastic lacrimal ducts and sacs with exterior openings, prominent bulbous nose, large downturned mouth, high narrow palate, sacral dimple, absence of the inner half of the right clavicle, bilaterally undescended testes, and developmental retardation. The clinical features of the next sib (a therapeutically aborted fetus) closely resembled those of the proband. As the parents were second cousins, we postulated that this malformation syndrome was the result of the homozygous state of a rare autosomal recessive mutation.

Since the parents refused to care for the proband at home, he was admitted into an institution for severely mentally and physically handicapped children. His temperature increased when the ambient temperature was high, and he suffered from persistent constipation. He never developed eyebrows, eyelashes, or hair on his head. Although the findings of his electroencephalogram were within normal limits, a CT scan of the brain showed ventriculomegaly and increased subarachnoid space. At 8 years 5 months of

Transmission of the DM alleles to the progeny

	Paternal DM origin				Maternal DM origin			
	DM	Normal	Total	p	DM	Normal	Total	p
Sons	166	105	271	<0.001 99% confidence limits (115-156)	112	71	183	0.002 99% confidence limits (75-108)
Daughters	148	106	251	0.004 99% confidence limits (106-145)	95	94	189	0.884 99% confidence limits (77-112)
Total	314	211	525	<0.001 99% confidence limits (234-291)	207	165	372	0.026 99% confidence limits (162-210)

age his mental age was evaluated as being 5 months.

His feeding difficulty continued and he suffered frequently from dehydration. His abdomen, lumbar region, and pelvis remained remarkably underdeveloped. His maximum lifetime weight was 6.9 kg aged 6 years 2 months. Subsequently, he suffered repeatedly from fever, vomiting, and dehydration and died at the age of 8 years 7 months. His height (crown to rump) at death was 49.0 cm, weight 4.96 kg, and head circumference 48.2 cm. At necropsy, regurgitant oesophagitis, a poorly developed small intestine, a small, thick walled (approximately 9 mm) urinary bladder, and small undescended testes were found.

The ethics of keeping such a child alive for eight years may seem to be questionable. However, passive euthanasia of such a case as this patient would not be readily acceptable in Japan.

SHOZO OHDO

Department of Paediatrics,
National Sanatorium Miyazaki Hospital,
Kawaminami 19403-4, Koyu-gun,
Miyazaki 889-13, Japan.

TOHRU SONODA

KEN-ICHI OHBA
Department of Paediatrics,
Miyazaki Medical College,
Kihara 5200, Kiyotake-cho,
Miyazaki 889-16, Japan.

- 1 Ohdo S, Madokoro H, Sonoda T, *et al.* Association of tetra-amelia, ectodermal dysplasia, hypoplastic lacrimal ducts and sacs opening towards the exterior, peculiar face, and developmental retardation. *J Med Genet* 1987;24: 609-12.

BOOK REVIEWS

If you wish to order or require further information regarding the titles reviewed here, please write to or telephone the BMJ Bookshop, PO Box 295, London WC1H 9JR. Tel 071 383 6244. Fax 071 383 6662. Books are supplied post free in the UK and for BFPO addresses. Overseas customers should add 15% for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank or by credit card (Mastercard, Visa, or American Express) stating card number, expiry date, and full name. (The price and availability are occasionally subject to revision by the Publishers.)

Genetics and Alcoholism. Evelyn Dumont-Damien, Michel Duyme. Paris: Editions INSERM. 1993.

In the latter part of last century many held the view that alcoholism was inherited. The pendulum of opinion swung, and by the 1960s there was little doubt in the minds of the great majority of its investigators that the origin of alcoholism was psychosocial. Today, with the developing knowledge in biology and especially in the genetics of behaviour, it is possible to contemplate some genetic contribution to its aetiology. For this several factors are responsible. Numerous diseases are known which result from a combination of

genetic and environmental elements. For example, one parallel to alcoholism is cancer of the lung, where the environmental factor is clear but only a proportion of heavy smokers develop the disease. Genetic studies have become possible, for the alcoholism phenotype has been better defined, and there are many genetic markers which allow a search for the location of genes producing susceptibility to any disease.

The authors of this book have drawn together almost all the accessible publications on genetic studies of alcoholism and have reviewed them critically. Their object is to make a balanced appraisal of present knowledge. They envisage alcoholism as a complex behavioural feature, and apply to it the methods of genetic analysis of behaviour.

Immediately in chapter 1 the principal problems that hinder genetic analysis are squarely faced: problems of definition, measurement of the phenotype, lack of clarity of the underlying biological mechanisms, and therefore of possible functional markers. It concerns types of alcoholics, aetiological models, measures of alcoholism, and the several hypotheses involving neurobiology. The chapters that follow summarise the different types of study.

Chapter 2 is devoted to family studies, of which there are approximately 200, comparing relatives of different degrees sharing similar family environments. They show familial concentration of alcoholism, so that the risk is greater for a person, particularly for a male, who has numerous alcoholic relatives, and they suggest an aetiological heterogeneity manifesting in variations in the precocity and severity of the condition. The authors identify topics on which future research could most profitably concentrate.

Chapter 3 draws together the numerous twin studies, 34 published in the period 1939 to 1991. These do not exclude genetic influence and indeed strongly suggest to the authors a multifactorial aetiology, the genetic contribution to which is most apparent in male twins who are alcohol dependent.

The next chapter is devoted to adoption studies, usually considered essential for distinguishing genetic and environmental effects. There have been about a dozen such studies, though the authors show that most of these are biased and use research designs that are not very informative. One finding emerges clearly from the subgroup of studies which are less open to criticism, namely a link between the biological father and his son brought up by adoptive parents. These sons knew nothing of the behaviour of their biological fathers; their biological mothers as well as their two adoptive parents were effectively non-alcoholic. These findings do not of course provide formal proof, but they favour the hypothesis of a transmission of some genetic factor from the father to the son. The result supports the suggestion from the family and twin studies that there is a dominating male influence.

The studies in chapter 5 complement these classical approaches, for they deal with sibs and half sibs brought up apart and unrelated children brought up together. There are only four studies of this type. Criticisms can be levelled at all, especially in the small number of variables considered or the lack of rigour in their specification, so their findings can only be taken as indications. But despite their drawbacks they support the interpretation from the investigations in the previous chapters that there is some genetic influence on alcoholism.

The crucial proof that there is a genetic contribution to the aetiology of alcoholism will come from the discovery of one or more markers, genes, or DNA segments. The searches for these have been numerous and the authors restrict their survey to those studies of characters whose chromosomal locations are known. There are 140 such studies, covering more than 50 markers, the majority being searches for association (to establish relative risks) and only a few using linkage (to establish location). The studies as a whole, dealt with in chapter 6, show that to date there is no certainty that any of the characters analysed is a marker for alcoholism. But these studies give valuable pointers to the methodological precautions to be taken and the paths to be followed in future investigations. The book closes with a series of 14 appendices, dealing in detail with key topics mentioned in earlier chapters but where fuller consideration would have interrupted the flow of the argument. These topics include for example the principal definitions of alcoholism, its classification and typologies, clinical and biological indicators, and aetiological models of alcoholism proposed in the period 1972 to 1988, ending with those of Donovan and of Radouco-Thomas. The list of some 850 references covers only those published in English or French.

The conclusions of the authors after their critical examination of hundreds of published works is that it is not yet definitely established that genetic differences between persons account for their variation in behaviour regarding the pathological taking of alcohol. Nevertheless there are strong indications that at least in some persons there is a genetic vulnerability to the abuse of, or dependence on, alcohol, especially males whose father and several ascendant relatives were alcoholic. The task now for genetic epidemiologists is to find the genes that predispose to the different types of alcoholism.

This book is positively written. From its critical appraisal of existing works, and their lack of conclusive findings, it draws lessons as to the points that future studies should attack and the methodological weaknesses that should be avoided. It is moreover carefully written, well balanced, well organised, a meticulous appraisal of the numerous works examined by the authors. It is the most comprehensive survey of the subject yet produced, and one which any investigator of the subject cannot afford to ignore.

D F ROBERTS

Diagnostic Criteria for Neuromuscular Disorders. Editor A E H Emery. (Pp 72.) UK: ENMC Publishing. 1994.

As Research Director for the European Neuromuscular Centre (ENMC), Baarn, The Netherlands, A E H Emery has participated in around 30 workshops designed to co-ordinate and encourage European research groups involved in the isolation and characterisation of the genes responsible for diverse neuromuscular disorders. This publication is introduced as a discussion document and presents, with some modifications, a series of articles which have appeared in *Neuromuscular Disorders* (Pergamon Press) setting out the diagnostic criteria proposed at each workshop. At the times of a number of