PostScript

LETTERS

Correction: no evidence of an association between the T16189C mtDNA variant and late onset dementia (Gibson *et al*)

We believe that the title of Chinnery et al's paper should be corrected because the data the authors present do not include an analysis of the 16189 variant of mtDNA (Table 1).

We defined the 16189 variant as the DNA sequence associated with a polydC tract,[2] resulting from a T16189C transition that may generate heteroplasmic length variation, table 1. Heteroplasmic length variation does not occur when the polymeric tract is interrupted by a c→t transition, which occurs at several different sites but commonly at nucleotice 16186 or 16192. Individuals with these additional polymorphisms are excluded from our definition of the 16189 variant because they no longer have a long homopolymeric c tract. The variant does not alter any coding sequences yet lies near to mtDNA control sequences, which can explain its effects on mitochondrial function. In studies of disease associations with variants in this region we chose to investigate the 16189 variant rather than any other sequence change, because of the likely functional effects of the homopolymeric C tract and heteroplasmic length variation.

Gibson *et al*[1] have shown that the overall prevalence of the T16189C allele in their population is 12.6%, which is substantially higher than the 6.4–8.8 % prevalence of the 16189 variant reported in other studies.[2 3] This is because they have quantfied the prevalence of the T16189C transition per se rather than the variant. Including these additional polymorphisms may dilute out a real association with the 16189 variant. The authors have shown that the T16189C transition per se is not a risk factor for late onset dementia,[1] but to our knowledge this has not, in any case, been implicated with any disease phenotypes. However, they found that the heteroplasmic length variation, which implies the presence of the 16189 variant, was associated with a 2.2 fold increased risk. They did not, however, quantify the relative risk for the 16189 variant per se, which could well be significant, in direct contradiction of their title. From their data, it is possible that the variant might in fact predispose to late onset dementia.

The 16189 variant is a risk factor for type 2 diabetes,[4] thinness at birth,[5] and aged 20 years[6] iron loading in haemochromatosis,[7] dilated cardiomyopathy,[8] endometrial cancer,[9] and other multifactorial disorders.[10] This variant may be mildly detrimental.[11] Unlike many other mtDNA polymorphisms implicated in type 2 diabetes, this variant probably has bona fide functional consequences because it has arisen many times independently in the various populations studied,[2 4 12] excluding a founder effect. Because the authors did not perform mitochondrial haplotyping[1] to exclude a founder effect, their results may reflect the consequences of other co-segregating genes.

Table 1 Sequences of identified variants

Variant	Nucleotides
Wild type sequence	ccccctcccc
Sequences included in Chinnery's analysis	cccccccctcc cctccccccc cccccccccc etc
16189 variant[2]	cccccccccc
Heteroplasmic length variants included within 16189 variant	ccccccccc ccccccccccc etc

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No evidence of an association between the mtDNA 16184-93 polyC tract and late onset dementia

We are grateful to Professor Poulton and Dr Das for clarifying their definition of the 16189 variant. In our study we determined the allele status at position 16189 of mitochondrial DNA (mtDNA), and found no evidence of an association between the 16189C polymorphic sequence variant and late onset dementia.[1] The title of our manuscript therefore reflects our observations and does not need to be corrected. Part of the confusion seems to have arisen because of different definitions of the "16189 variant" in the literature.

The standard "Cambridge" reference mtDNA sequence[2 3] has a run of cytosine residues from nucleotide position (np) 16184 to 16193 interrupted by a thymidine residue at nucleotide position 16189. In approximately 12% of the UK population, there is a T→C substitution at np 16189.[1] In most individuals this results a tract of 10 C residues (polyC tract). This sequence is unstable and is associated with length variation of the polyC tract, probably because of slippage during genome replication,[4] generating larger and smaller polyC tracts within the same individual during life (heteroplasmy).[4] However, occasional individuals have other polymorphisms between np 16184 and 16193, which appear to stabilise the tract and do not lead to the generation of length variants.[4] We suggest a more accurate definition should be used when referring to the homopolymeric C tract that is present in the majority of individuals with the T16189C substitution. The term "mtDNA 16184-93 polyC tract" will hopefully prevent confusion in the future.

Poulton and Das comment on the results of our logistic regression analysis (table 1 in our paper[1]), and suggest that individuals with homopolymeric tract length heteroplasmy have a 2.2 fold increased risk of developing Alzheimer's disease (AD) compared with controls. This would imply an association between their definition of the 16189 variant and late onset dementia. However, the confidence intervals for the relative risk of 2.2 are 0.85 to 5.81, comfortably including 1. The relative risk is therefore not statistically significant and does not support a link between AD and homopolymeric length tract heteroplasmy.

In our original study,[1] we measured homopolymeric tract length heteroplasmy using a trimmed PCR approach with a fluorescent forward primer. However, not all individuals with a 16184-93 polyC tract also have length heteroplasmy. Therefore, to address the concerns of Poulton and Das experimentally, we directly sequenced the relevant region of

Table 1 Frequency of the mtDNA 16184-93 polyC tract in control individuals, patients with dementia with Lewy bodies (DLB) and Alzheimer's disease (AD)

	Frequency of the mtDNA 16184-93 polydC tract		Comparison with controls	
Group	n	% (95% CI*)	Odds ratio (95% CI)	p†
Controls (n = 129)	9	6.98 (3.24 to 12.83)	–	–
DLB (n = 97)	10	10.31 (5.06 to 18.14)	1.53 (0.60 to 3.93)	0.46
AD (n = 182)	11	6.04 (3.06 to 10.56)	0.85 (0.34 to 2.13)	0.81

*Exact 95% confidence intervals for the percentage were calculated using the method of Clopper and Pearson. †Fisher's two tailed exact test. CI, confidence interval. Each group corresponds to the cohort of neuropathologically confirmed cases and controls reported in our paper.[1] Note that table 2 of our original report[1] only includes subjects where the complete *APOE* genotype was also known. This data was not available for two controls, one DLB case, and eight AD cases. The data from these cases are included in this table.

mtDNA in all of the cases and controls that harboured the 16189C variant in our original study,[1] using an established protocol.[5] The frequency of the mtDNA 16184-93 polyC tract in our original control population corresponded to values reported in other studies[6 7] (table 1); 59% of control individuals with the T16189C polymorphic variant had a 16184-93 polyC tract, corresponding to publicly available control sequence data (http://www.genpat.uu.se/mtDB/). We found no evidence of an association between AD or dementia with Lewy bodies and 16184-93 polydC tract in a cohort or neuropathologically defined cases and controls, either by logistic regression analysis, or by directly comparing cases and controls with Fisher's exact test (table 1).

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BOOK REVIEWS

Statistical Methods in Genetic Epidemiology

By D C Thomas. Oxford University Press, 2004, $42.50, pp 435. ISBN 0-19-515939-X

The contemporary research principles of genetic epidemiology are outlined in this book. The author clearly explains the research methodology and statistical analyses required to investigate important genetic epidemiological research questions. These include the following questions: Does a disease cluster in families? (familial aggregation); How does a disease cluster in families? (segregation analysis); Can familial aggregation be explained by genetic or environmental factors? (gene–environment interaction); Can we localise the genetic defect? (linkage and association studies). The theory is mainly illustrated with examples on the genetic epidemiology of cancer. As genetic epidemiology is a hybrid discipline, basic chapters on molecular genetics, epidemiology, statistics, and population genetics are included for those readers who need an introduction to any of these topics.

This book fascinates me because of its high didactic quality. The text is well organised and is easy to read. The content is interesting both to novices and to more advanced readers. The strength of the book is that it gives a complete overview of the different methods used in genetic epidemiology. Owing to its completeness, I would not be surprised if it were used in many semesters or courses on genetic epidemiology around the world. I would expect it also be very useful for the more advanced genetic epidemiologist as an up to date reference text. Readers interested in closely related disciplines such as population genetics, molecular genetics, behaviour genetics, statistical genetics, genomics, and bioinformatics will not find enough detail here and should look elsewhere.

I consider this text to be a standard work in genetic epidemiology and would advise both teachers and researchers in the field to read and use it.

M P Zeegers

Human Evolutionary Genetics: Origins, Peoples & Disease

Edited by M A Jobling, M E Hurles, C Tyler-Smith. Garland Science, 2003, £35.00, pp 458. ISBN 9-780815-341857

With the near completion of the human genome sequence, and the exponential increase in associated information on inter-individual variability, there are enormous opportunities for using these data. Evolutionary geneticists are attempting to understand our origins and revisit the questions of the relative role of selection and drift. For medical geneticists, the search is now on for the genetic causes of complex disease, while forensic science is increasingly exploiting our interindividual differences to solve crimes. All these topics are inextricably linked. This super textbook covers almost everything an undergraduate student in human genetics would need as a basis for any of these areas, but will in fact have a much wider readership. It starts as far back as the structure of DNA, chromosome structure, meiosis, mitosis, and so on, while covering in some depth anthropological and archaeological evidence for the origins of modern humans, the extent and nature of genomic variation, and the principles of human population genetics. It explains clearly how the genome can be considered in blocks, owing to the pattern of historic and prehistoric recombinations and that these pieces of DNA, as well as the Y chromosome and mitochondrial DNA, track back to many ancestors who may have lived in different parts of the world.

This publication is timely, up to date, and has enormous and comprehensive coverage, without being too heavy to carry or costing too much. It is more than just a textbook, because, by using opinion boxes, it discusses contentious and problem issues. Thus as well as providing factual information, the book will stimulate the undergraduate to appraise observations and their interpretation critically. An important example is the discussion of error rates, and the potential impact of errors on interpretation of data. It answers questions that many of us get asked by our non-genetics friends, such as what exactly do we mean when we say that there is 1–2% sequence difference between humans and chimpanzees? How much do the different population groups of the world differ and is the term race meaningful? Clearly, as far as humans are concerned, it is not.

The book will also serve as a very useful introduction to molecular and population genetics for epidemiologists, anthropologists, and others who are new (or indeed not so new) to the field. It contains a wealth of information relevant for medical geneticists who are embarking on association studies. This, for example, includes the effects of selection and the effects of population admixture.

The book is very well laid out, with chapters grouped in six main sections, each of which aims to answer a question (Why study evolutionary genetics? How do we study genome diversity? How do we interpret genetic variation? Where and when did humans originate? How did humans colonise the world? How is an evolutionary perspective helpful?) There is a good index and glossary, so that it is easy to look things up, and there are extensive references at the end of each chapter and recommendations for further reading. Indeed there are but few short-comings. The figures and tables, which are on the one hand very useful and informative, do also have some weaknesses. Whether it is my failing eyesight or heterozygous manifestation of a colour vision anomaly, I often found the blue grey and black shadings and characters extremely difficult to distinguish. The figure legends could also sometimes have been more informative. However Mark Jobling and colleagues are to be congratulated—this book is a good buy, an excellent read, and is to be strongly recommended.

D M Swallow

CORRECTIONS

doi: 10.1136/jmg.2004.020644corr1

In the paper Recent advances in understanding haemochromatosis: a transition state (*JMG* 2004;**41**:721–30) figures 1 and 2 were incorrect. Below are the corrected figures.

A176CV has been changed to A176V and R224G has been changed to R224Q in figure 1.

N114D has been changed to N144D in figure 2. The journal apologises for these errors.

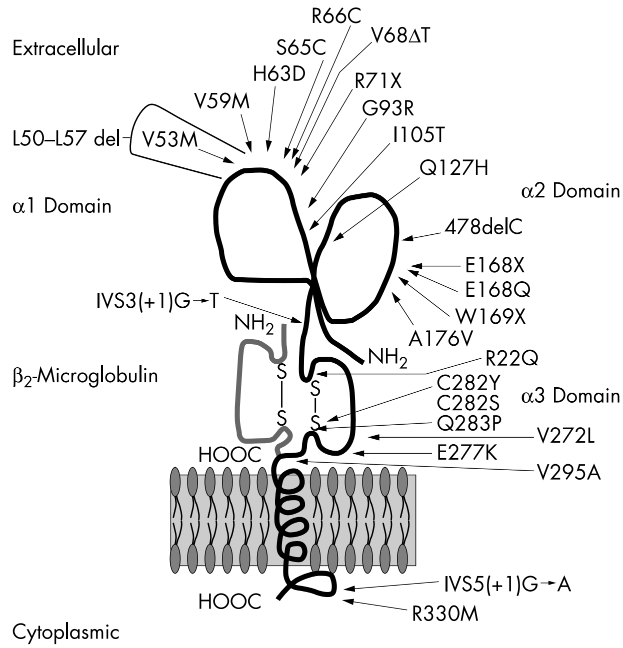

Figure 1

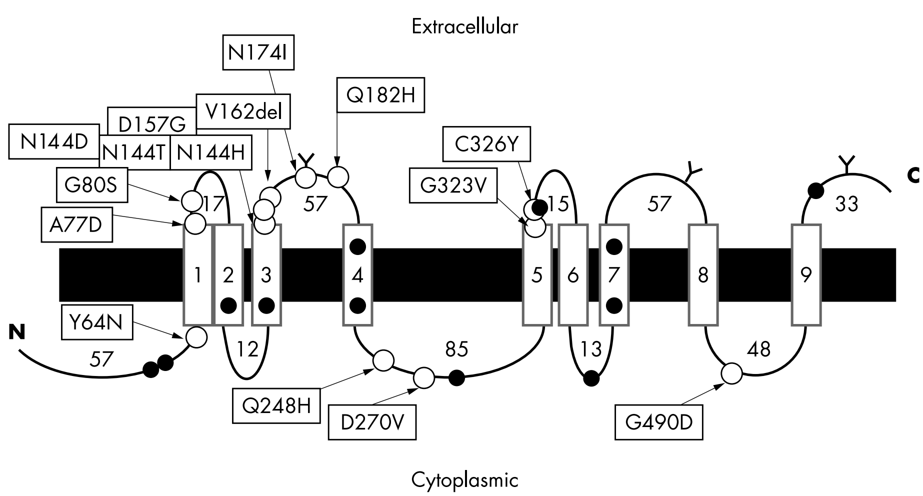

Figure 2

doi: 10.1136/jmg.2004.022111corr1

In the paper Recent advances (*JMG* 2004; **41**:814–25) figure 2 was incorrect. Below is the corrected figures.

A small black bar has been inserted on the line representing the deletion present in the patient number 3273. The author apologies for this error.

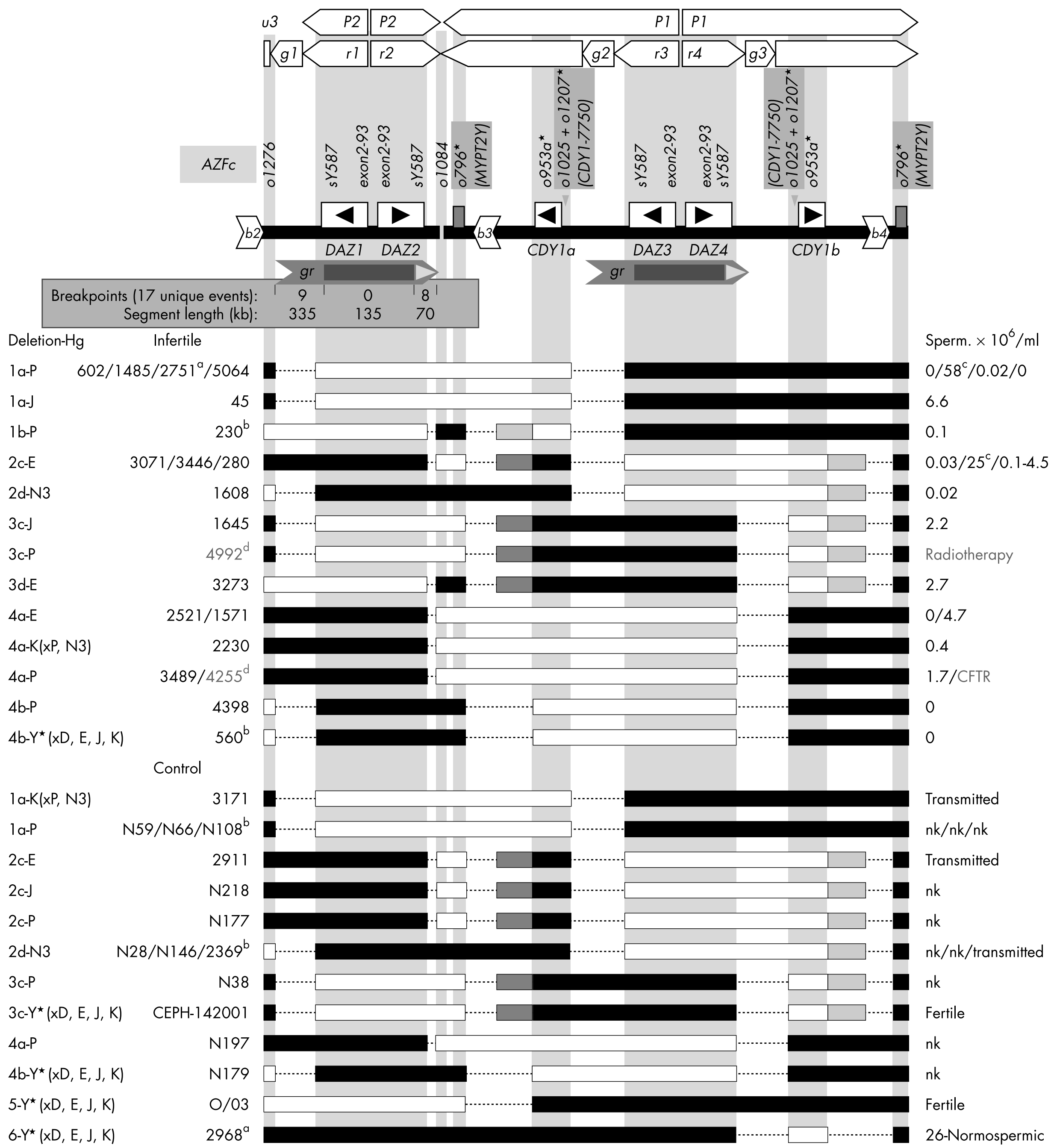

Figure 2