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 polyC tract, 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 nucleotide 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 choose 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 4 have shown that the overall prevalence of the T16189 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. 5,6 This is because they have quantified the prevalence of the T16189 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 T16189 transition per se is not a risk factor for late onset dementia, 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 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, 7 thinness at birth, 8 and aged 20 years iron loading in haemochromatosis, 9 dilated cardiomyopathy, 9 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 has been shown to have a c→t transition, which occurs at several different sites but commonly at nucleotide 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 choose 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.

J Poultun, S Das 1
Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Women’s Centre, John Radcliffe Hospital, Oxford, UK

Correspondence to: Professor J Poultun, Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Women’s Centre, John Radcliffe Hospital, Oxford, OX3 9DU, UK; joanna.poulton@oas.ox.ac.uk

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References


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)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>% (95% CI)</th>
<th>Odds ratio (95% CI)</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n = 129)</td>
<td>9</td>
<td>6.98 (3.24 to 12.83)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>DLB (n = 97)</td>
<td>10</td>
<td>10.31 (5.06 to 18.14)</td>
<td>1.53 (0.60 to 3.93)</td>
<td>0.46</td>
</tr>
<tr>
<td>AD (n = 82)</td>
<td>11</td>
<td>6.04 (3.06 to 10.56)</td>
<td>0.83 (0.34 to 2.13)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*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 neurologically 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.

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S M Keers, A M Gibson, D M Turnbull, and P Chinnery

Correspondence to: D P F Chinnery, Department of Neurology, The Medical School, Framlington Place, Newcastle Upon Tyne, NE2 4HH, UK; p.chinnery@ncl.ac.uk
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References

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


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 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 superb textbook covers almost everything an undergraduate student in evolutionarily related fields would need as a basis for any of these areas, but will in fact have a much wider readership. It starts far back as the structure of DNA, chromosome structure, meiosis, mitosis, and so on, while covering in some depth anthropological, palaeoanthropological, 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 patterns 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 comprehensive coverage, without being too heavy to carry or costing too much. It is more than just a textbook, it is a research resource, by using opinion both from the top of genetic epidemiology around the world. 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

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

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