PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Juvenile Huntington's disease: a population-based study using the General Practice Research Database
AUTHORS	Rawlins, Michael; Douglas, Ian; Evans, Stephen; Smeeth, Liam; Tabrizi, Sarah; Wexler, Nancy

VERSION 1 - REVIEW

REVIEWER	Patrick J Morrison, MD DSc, Honorary Professor of Human Genetics, belfast City Hospital. UK. I have no competing interests.
REVIEW RETURNED	02-Oct-2012

RESULTS & CONCLUSIONS	this is an interesting study and provides important and very helpful data on the epidemiology of juvenile huntington disease (JHD) - a greatly under-researched condition. Whilst line 2 of the abstract is technically correct, one previous study did publish actual numbers of JHD cases in a complete population confirmed on genetic testing and estimated that JHD accounted for 7% of cases in a prevalence of total HD of 6.4 per 100,000. the number of cases of a subset of childhood onset HD (defined as onset <10 years) was estimated at 3%. the authors should consider referencing this paper: Morrison PJ et al, The epidemiology of Huntington's disease in Northern Ireland. J Med Genet 1995;32:524-30. given that the authors of that paper identified 6 cases alive in 1991, the authors numbers in table 2 of prevalent cases are serious underestimates of actual numbers within the UK. the authors may want to comment on this by expanding paragraph 3 of their discussion. it is likely that stigma of HD and lack of rigorous documentation of cases will give a number greater than 100 cases that they estimate in para 1 of their discussion.
GENERAL COMMENTS	In paragraph 1 of the introduction, although cases of HD with repeat sizes generally have JHD, the converse is not absolute, as I have personally seen cases of JHD with repeat sizes <45 as around 70% of the age of onset is related to triplet repeat size but 30% to other genetic or environmental factors. the authors may want to put in a phrase such as ' although JHD cases have been recognised with much smaller repeats'

REVIEWER	Dr Oliver Quarrell Consultant in Clinical Genetics Sheffield Children's Hospital Sheffield S10 2TH UK I have no competing intrerests
REVIEW RETURNED	07-Oct-2012

GENERAL COMMENTS	Major issues The origin of the definition of JHD being onset under 20 years is obscure. In the past, there has been confusion as to whether onset at 20 years is included but the authors are clear that they are using a definition of onset ≤ 20 years, which is used most frequently these days. There are a number of problems with this definition but one of most concern here is that a person who has an onset at age 18 years but is now aged say 28 years is still usually considered to have had juvenile onset. The most frequently quoted historical reference for JHD is Hoffmann 1888 in which he described an extended family with 2 individuals who had onset in childhood. The person he described in most detail was aged 36 years at the time of his report but had onset of abnormal movements before her school years ended and lost the ability to do handicrafts at the age of 21 or 22 years. The authors seem to have changed the definition to those who are symptomatic and are ≤ 20 years because their headline minimum prevalence figure is 6.8/million of the population under 21 years. This may well be a valuable figure but it is not the usual definition of JHD. At the very least, I think the issues in this paragraph need to be discussed. I wonder if the title could reflect this "Juvenile Huntington's Disease under 21 years: an epidemiological study based on the Clinical Practice Research Datalink" Leading on from the above, I would like to ask for clarification of Table 2. For example, in 2008 there were 8 cases alive under 21 years but the following year there were only 3 cases. Is it that 5 patients died or did some or all of these become over 20 years and were then excluded? I assume, but do not know, that prevalent case in 1990, 1991 and 1992 was the same person. There will be national census data for the number of people aged ≤ 20 years for the years 1991 and 2001 and there may be estimates for other years. This could be used to estimate the percentage of this population covered by the database. I assume it increased over the 20 year period. Could this information be included in the paper? I think the statement that there are no published estimates of the prevalence of JHD is not wholly correct. Before the gene was cloned, many prevalence studies were undertaken and the number of JHD cases reported as a percentage of the HD patients in that study. My colleagues and I have recently published a meta-analysis of this data (Quarrell et al 2012 PLOS Currents HD). We looked at studies published since 1980 which used multiple methods of ascertainment and came from high income countries as defined by the World Bank. We reported that the percentage of JHD cases was 4.81% with a 95% confidence interval of 3.31% - 6.58%. Based on this we estimated that there would be approximately 300 cases of JHD in the UK (of course some of these would be over 20 years, see above). I think this paper should be included in the discussion.

	The definition of JHD is based on age of onset of the condition which is not the same as the age of diagnosis but as I understand the method, if a person was aged 21 or 22 years etc when they were entered onto the register then they would not have been included in this study. Such a person may well have had symptoms related to HD as a teenager but just not diagnosed as such. I think this point needs to be included in the limitations of this study. Like the definition of JHD itself, the origin of the idea that JHD is associated with more than 60 CAG repeats is obscure. It is true that an individual with more than 60 CAG repeats is very likely to have juvenile onset but is not true the other way around: a person with JHD may have less than 60 repeats (see page 142 of the book *Juvenile Huntington's Disease (and other trinucleotide repeat disorders).* I can appreciate that a detailed discussion of this point is not relevant to the paper but I would suggest that a phrase such as: whilst alleles with 60 or more CAG repeats result in the juvenile form of the disease this is not exclusive as some JHD cases may have a CAG repeat length which overlaps with those with adult onset. This is congruent with the idea that JHD is a convenient and arbitrary classification rather than a distinct biological entity. I agree fully with the comment that there is no evidence base for the medications which are prescribed for JHD. It may be relevant that we have also published information on the prescriptions used for JHD see Robertson et al 2012 (PLoS Currents HD). I think there should be a reference to this in the discussion. Minor point There is a typo in the first line of the discussion I assume it should be 21 not 211 and it is followed by 2 commas.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Patrick Morrison.
Both Patrick Morrison and Oliver Quarrell (below) describe studies of the prevalence of HD that have provided either the number of juvenile HD patients, or the percentage of juvenile HD patients, in a total HD population. It is not possible, however, to infer from these reports the prevalence of juvenile HD because none provide any estimate of the "at risk" popuation (ie the size of the population under 21 years). For this reason, such numbers or percentages are not estimates of prevalence. This issue is now considered in the first paragraph of the Discussion of the revised paper and refernces to the paper by Patrick Morrison and Oliver Quarrel is included.
The word "usually" has been included in the last paragraph of the Introduction to cover the point about those with juvenile HD with less than 60 CAG repeats.
Reviewer 2: Oliver Quarrell
We are aware that some authorities have suggested that juvenile onset should be characterised as onset below 20 years rather than below 21 years as is the case in the present study. We take comfort from the fact the Oliver Quarrell appears to accept that our approach is reasonable and in line with the

general consensus.
As this reviewer correctly summises, our study is confined to patients under 21 years with a recorded diagnosis of HD and we have attempted to make this clear in the text of our paper. The reasons for patients leaving the GPRD are described in the "Participants" paragraph of the Methods section. We accept, however, that our explanation lacked clarity; and have included an additional item to indicate that patients were no longer included once they reached the age of 21 years.
Table 2 shows the numbers of people under 21 years of age included in the database
I have discussed in response to Patrick Morrison (above) the issue of prevalence estimates based on the percentage of total HD populations with the juvenile HD and included a reference to Oliver Quarrell's meta-analysis.
We accept that some patients with early symptoms of juvenile HD may only present some years later but it impossible from the GPRD records to evaluate this. The insomnia, noted for a few premanifest (or at least pre-diagnosed) juvenile HD patients may be one reflection of this.
We are grateful to this referee for pointing out the paper by Robertson et al which I am ashamed to say we missed. We now make reference to it!

VERSION 2 – REVIEW

REVIEWER	Quarrell, Oliver Sheffield Children's Hospital, Clinical Genetics No competing interests
REVIEW RETURNED	28-Nov-2012

GENERAL COMMENTS	I think the data should be published. I agree with almost everything in the paper; however, I would suggest that the authors consider making a couple of issues more explicit. The first concerns the sentence that "alleles with 60 or more CAG repeats usually result in JHD". This is true. The issue is that a signifigant proprtion of patients with JHD have less than 60 repeats. I think this caveat should be added to the sentence. JHD is not defined explicitly in the introduction so not adding a caveat to that sentence might imply that JHD is defined by CAG repeat length wich is not correct. The second point also relates to the definition of JHD. The usual definition of JHD is onset before 20 years or 21 years. (Onset before 21 years allows the inclusion of patients with onset at 20 years.) A consequence of that definition is that a patient with onset at say age 18 years and now aged 28 years would still count as JHD. The authors estimate that there are 100 children and adolescents living with JHD in the UK. This is a valuable figure. The previous work on the proportion of JHD cases based on prevalence studies would have included an adult patient with onset under 21 years. I think it is important to be explicit about the definition of JHD so that this paper is placed in the context of previously published work.

VERSION 2 – AUTHOR RESPONSE

1) We now stated in the Introduction that juvenile HD my occur with less than 60 CAG repeats.
2) We empphasise in the Methods that we used <21 years as our definition of juvenile HD onset.
3) We now state in the Discussion that our estimate of the total prevalent juvenile HD population does not include individuals who are aged >20 years but whose diagnosis was fisrt made when they were <21 years of age. This issue does not, of course, influence our estimate of incidence.