for predicting responses to ovarian stimulation in young and fertile females.

References


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**POLG mutations and age at menopause**

Sir,

We previously reported a dominantly inherited POLG mutation p.Y955C, in the polymerase domain of DNA polymerase gamma, which was associated with premature ovarian insufficiency (POI) and a complex neurological syndrome including ophthalmoplegia and parkinsonism in a three-generation pedigree from New Zealand (Pagnamenta et al., 2006). POLG encodes the catalytic subunit of DNA polymerase gamma (Poly), the only DNA polymerase able to catalyse mitochondrial DNA (mtDNA) replication. Impaired Poly function leads to the accumulation of multiple mtDNA deletions and progressive mtDNA depletion (Longley et al., 2005), resulting in impaired energy production by the oxidative phosphorylation enzymes (13 subunits of which are encoded by mtDNA) and increased reactive oxygen species (ROS)-induced tissue damage. Poly dysfunction has been linked to a range of neurological phenotypes (Copeland, 2012), associated with POI in a small number of cases (Table I), and also to male infertility (Rovio et al., 2001).

The mitochondrial theory of ageing postulates that mitochondrial dysfunction, including the accumulation of multiple mtDNA deletions and abnormal ROS production, is central to normal human ageing (Hekimi et al., 2011). A transgenic mouse model harbouring an error-prone Poly, caused by a mutation in the exonuclease domain of POLG, accumulates multiple mtDNA deletions and appears to mimic an ageing phenotype (Trifunovic et al., 2004). It is not clear whether POLG mutations could lead to premature ageing phenomena such as isolated POI in humans.

To determine whether POLG mutations may be responsible for isolated POI, we have now screened a cohort of British women with POI for p.Y955C and the three most common pathogenic mutations in POLG (p.A467T, p.W748S and p.G848S), using a combination of restriction fragment length polymorphism and Sanger sequence analysis, in order to determine whether these four mutations are major contributors to premature ovarian ageing. We did not identify any of these four POLG mutations in 57 women who presented with POI: 15 with primary amenorrhoea, 42 with secondary amenorrhoea (mean age of onset 23 years, range: 14–32). There was a positive family history in 14 cases. Diagnosis was based on raised FSH >20 IU/l on two occasions, and fragile X premutations had previously been excluded. POLG mutations have now been linked to POI in only 13 published cases, 12 of whom had neurological symptoms typical of mitochondrial disease (Table I). The 13th case was one of a cohort of 201 women with POI screened for the p.R953C mutation in POLG (Tong et al., 2010). The contribution of p.R953C mutation to her POI phenotype is unclear, and may have been a chance finding (Tong et al., 2010). We conclude that the POLG mutations more usually associated with neurological disease are not a common cause of isolated POI, and hypothesize that POLG mutations result in premature ovarian ageing only in the context of complex neurological disease.

Interestingly, a recent meta-analysis of genome-wide association studies searching for loci and potential candidate genes determining age of natural menopause identified POLG amongst the top 11 candidate genes (Stolk et al., 2012). The availability of high throughput next generation DNA sequencing techniques will now allow whole genome analysis in large cohorts of women whose menopausal age is known, in order to establish whether genetic changes in POLG are associated with age at natural menopause. Functional analyses, including assessment of mtDNA integrity and copy number and ROS production in ageing ovarian tissue, will also be important in determining the relative contribution of Poly dysfunction to ovarian ageing. However, the results of the meta-analysis suggest that the individual contribution of Poly dysfunction to the age of natural menopause is likely to be small (Stolk et al., 2012), and that the synergistic effect of many individually small factors probably orchestrates the complex process of natural ovarian ageing.
Table I POLG mutations and POI.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Number of cases</th>
<th>Age of POI (years)</th>
<th>Other clinical features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y955C</td>
<td>4</td>
<td>Primary amenorrhoea-30</td>
<td>PEO, ptosis, muscle weakness, tremor, parkinsonism, neuropathy</td>
<td>Luoma et al. (2004)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>28–35</td>
<td>PEO, ptosis, tremor, sensory ataxia</td>
<td>Pagnamenta et al. (2006)</td>
</tr>
<tr>
<td>0/57*</td>
<td>0/57*</td>
<td>Primary amenorrhoea-32</td>
<td>Isolated POI</td>
<td>Present study</td>
</tr>
<tr>
<td>N468D/A1105T</td>
<td>1</td>
<td>35</td>
<td>PEO, ptosis, muscle weakness, tremor, parkinsonism</td>
<td>Luoma et al. (2004)</td>
</tr>
<tr>
<td>S111N</td>
<td>1</td>
<td>&lt;30</td>
<td>PEO, ptosis</td>
<td>Hudson et al. (2007)</td>
</tr>
<tr>
<td>W748S</td>
<td>1</td>
<td>27</td>
<td>Ataxia, psychiatric symptoms, obesity</td>
<td>Hakonen et al. (2005)</td>
</tr>
<tr>
<td>0/57*</td>
<td>0/57*</td>
<td>Primary amenorrhoea-32</td>
<td>Isolated POI</td>
<td>Present study</td>
</tr>
<tr>
<td>A2492G/Y831C</td>
<td>1</td>
<td>NS</td>
<td>PEO, ptosis, diplopia, parkinsonism, sensory neuropathy, hypertension</td>
<td>Manusco et al. (2004)</td>
</tr>
<tr>
<td>R943H</td>
<td>1</td>
<td>NS</td>
<td>PEO</td>
<td>Blok et al. (2009)</td>
</tr>
<tr>
<td>R953C</td>
<td>1/201*</td>
<td>28</td>
<td>Isolated POI</td>
<td>Tong et al. (2010)</td>
</tr>
<tr>
<td>A467T</td>
<td>0/57*</td>
<td>Primary amenorrhoea-32</td>
<td>Isolated POI</td>
<td>Present study</td>
</tr>
<tr>
<td>G848S</td>
<td>0/57*</td>
<td>Primary amenorrhoea-32</td>
<td>Isolated POI</td>
<td>Present study</td>
</tr>
</tbody>
</table>

NS, not stated; PEO, progressive external ophthalmoplegia; POI, premature ovarian insufficiency.

*Denominator: number of patients with isolated POI screened.

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References


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