Broader geographical spectrum of Cohen syndrome due to COH1 mutations


Cohen syndrome (COH1: MIM 216550) is an autosomal recessive disorder, first described in 1973.1 Cardinal clinical features of Cohen syndrome include microcephaly, non-progressive mental retardation, characteristic facial features, neutropenia, and ophthalmologic findings.2 It is overrepresented in Finland, though cases have been reported worldwide.

The genetic locus for Cohen syndrome was mapped to chromosome 8q in several Finnish pedigrees.3,4 Recently, a novel gene, COH1, in this locus was shown to carry mutations in many patients with Cohen syndrome.5 COH1 is a large gene, consisting of 62 exons and encoding a protein of 4022 amino acids, whose biological function is not known. So far all the patients with reported mutation in the COH1 gene are of Finnish or other northern European origin. Therefore it has not been known if the COH1 gene is responsible for those cases of Cohen syndrome outside northern Europe.

Here we report novel mutations in the COH1 gene in four non-Finnish (Omani, Saudi Arabian, Japanese, and French) pedigrees, demonstrating that COH1 mutations are responsible for Cohen syndrome in non-Finnish populations. Variable phenotypes among these patients supports the idea that the typical Finnish Cohen syndrome phenotype, for instance in lacking microcephaly, showing that the clinical spectrum of COH1 mutations is wider in non-Finnish populations. This may be consistent with the absence of the Finnish founder mutation in our study population.

We performed the first expression analysis of the COH1 homologue (Coh1) in the mouse brain. Coh1 is expressed widely in neurons of the postnatal brain, but has a low level of expression embryonically, suggesting that the cardinal role of the COH1 gene may be in neuronal differentiation, but not in proliferation.
(DIG)-labelled cRNA probe generated from the PCR product and frozen mouse brain sections.

RESULTS AND DISCUSSION

Mutation detection

We have identified four novel COH1 mutations and one previously reported mutation in the four pedigrees studied (fig 1). The identified mutations are summarised in table 2. Patients in the Omani pedigree were homozygous for a novel mutation, 7934 G>A in exon 43. This mutation is predicted to substitute aspartic acid for glycine at residue 2645 (G2645D), which changes charge and so is very likely harmful. Both parents were confirmed to be heterozygous for this mutation. The clinical features of the patients in the Omani family are not milder than others with nonsense or frameshift mutations, suggesting that this missense mutation is also probably a null mutation.

Affected individuals in the Saudi Arabian pedigree were homozygous for a second novel mutation, 1219 C>T transition in exon 9. This mutation changes a glutamine residue at position 407 of 4022 to a termination codon (Q407X), creating a severely truncated predicted protein. Parents were heterozygous for the mutation, and the unaffected sibling tested was homozygous for the wild-type allele.

Table 1

<table>
<thead>
<tr>
<th>Pedigree</th>
<th>Patient number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Head circumference</th>
<th>Typical facial features</th>
<th>Ophthalmologic findings*</th>
<th>Neutropenia†</th>
<th>Brain MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omani</td>
<td>1</td>
<td>10</td>
<td>Female</td>
<td>-5.6 SD</td>
<td>Yes</td>
<td>Myopia, retinal dystrophy</td>
<td>No</td>
<td>Relatively large corpus callosum</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>8</td>
<td>Male</td>
<td>-5.8 SD</td>
<td>Yes</td>
<td>Myopia</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
<td>Male</td>
<td>-5.3 SD</td>
<td>Yes</td>
<td>Myopia</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Saudi Arabian</td>
<td>4</td>
<td>9</td>
<td>Female</td>
<td>-5.0 SD</td>
<td>Yes</td>
<td>Retinal dystrophy</td>
<td>N/A</td>
<td>Relatively large corpus callosum, mild inferior vermian hypoplasia</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>7</td>
<td>Male</td>
<td>-4.6 SD</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2</td>
<td>Female</td>
<td>-3.8 SD</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>Normal</td>
</tr>
<tr>
<td>Japanese</td>
<td>7</td>
<td>13</td>
<td>Female</td>
<td>-0.6 SD</td>
<td>Yes</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>11</td>
<td>Male</td>
<td>-2.7 SD</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>French</td>
<td>9</td>
<td>27</td>
<td>Male</td>
<td>-2.1 SD</td>
<td>Yes</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>24</td>
<td>Female</td>
<td>-1.2 SD</td>
<td>Yes</td>
<td>Maculopathy with amblyopia (left), peripheral pigmentation abnormalities (right), bilateral polar cataracts</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>24</td>
<td>Female</td>
<td>-2.7 SD</td>
<td>Yes</td>
<td>Myopia, astigmatism, bilateral polar cataracts</td>
<td>Yes</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Ophthalmologic findings are according to formal examination by ophthalmologists. Electroretinography was not performed; †presence or absence of neutropenia was determined according to reference range set by each laboratory where the blood count measurement was performed. Patients with no neutropenia did not undergo repeated measurements. N/A, not available.

Figure 1 Pedigree structure and novel mutations in the four families with Cohen syndrome. (A) The Omani family carried a homozygous 7934 G>A transition in exon 43, which results in a G2645D missense mutation. (B) The Saudi Arabian family carried a homozygous 1219 C>T transition in exon 9, resulting in Q407X nonsense mutation. (C) The Japanese family was a compound heterozygote with a heterozygous one base pair deletion (7221delG) in exon 40, which results in frameshift. No other mutant allele was found in this family in the coding region of the COH1 gene. (D) The French family was a compound heterozygote with a one base pair deletion (11598delA) in exon 61, which results in frameshift, and a previously reported 7051 C>T transition in exon 39, resulting in R2351X nonsense mutation (not shown). Nucleotides mutated in the patients are indicated by arrowheads. Deletion followed by frameshift is indicated by “ΔFS……...”. In the heterozygous patients (proband of C and D), protein translation of the mutant allele is shown.
Patients in the Japanese pedigree were heterozygous for a novel COH1 mutation, 7221delG in exon 40. This mutation creates a translational frameshift after residue 2407, with predicted premature termination at residue 2413 (Q2407H...V2414X). Their mother also carried this base pair change in the heterozygous state, while their father was not available for testing. These siblings are presumably compound heterozygotes for two different COH1 gene mutations, but a second mutation was not found despite complete sequencing of all known coding exons of the full-length COH1 transcript.

The patients in the French pedigree were all compound heterozygotes for COH1 mutations. One mutation, 7051 C>T in exon 39, has already been reported in a Belgian patient, and is predicted to change an arginine residue at position 2351 to a termination codon (R2351X). The other mutation, 11598delA in exon 61, has not been reported before, and causes a translational frameshift, leading to premature termination after the addition of 10 abnormal amino acids (E3867K...V3877X; fig 1). None of the four novel mutations we found were observed in at least 56 Caucasian (112 chromosomes) and 26 Middle Eastern (Omani) unrelated normal control individuals (52 chromosomes).

It is interesting to note that we did not find in any of the pedigrees we studied the mutation that seems to be most prevalent in Finland, 3348_3349delCT. Out of 27 Finnish patients who were studied previously, 26 had at least one allele of this mutation. Furthermore, it appears likely that different mutations prevail among different ethnic groups, although further mutation screening is necessary to confirm this.

### Genotype-phenotype correlation

No clear genotype-phenotypic correlation was apparent in the patients we studied. However, the patients reported here seem to show more phenotypic variability compared to the Finnish Cohen syndrome patients, who have a highly homogeneous clinical phenotype. For example, patients 7 and 10 in our study lack microcephaly. In addition, patients 1, 2, 3, and 7 were not found to have neutropenia, though neutropenia may be intermittent, and this cannot be ruled out as these patients had blood counts tested on one occasion. Both microcephaly and neutropenia appear to be invariant features in reported Finnish patients, and reported patients from other populations may lack these features. The variability in clinical features that we found may be consistent with the absence of a Finnish founder mutation in our study population and, possibly, in other reported non-Finnish Cohen syndrome patients.

One of the mutations found in the French family was a novel frameshift mutation that truncates only the C-terminal region of the predicted protein. Perhaps this mutation results in partial loss of function of the COH1 protein, which may account for the relatively preserved head circumference in this pedigree, though otherwise it shows a classic phenotype similar to the Finnish Cohen syndrome. Though the biological function of the COH1 protein is not known, there is a potential endoplasmic reticulum retention signal detected by the PSORT II program at the C-terminal region; therefore, the French mutation may partially disrupt the function of the protein by interfering with subcellular localisation.

###Identification of the mouse homologue of the COH1 gene and in situ hybridisation

A partial sequence for the mouse homologue of the COH1 gene was identified through BLAST searches. Predicted mouse transcripts for the RIKEN cDNA c330002D13 gene (GenBank accession no. XM_283276 and Celera ID no. mCT5410), which appear to represent a partial sequence of the mouse COH1 homologue (Coh1), were identified. The predicted amino acids translated from XM_283276, for example, are 90% identical to the first 415 amino acids of the human COH1 protein. In situ hybridisation was performed using a probe designed from this sequence. In the mouse brain at postnatal day 21, roughly equivalent to early childhood in juvenile age in humans, the Coh1 gene was expressed widely in the central nervous system. In the cerebellum, a high level of expression was seen in the internal granule layer and Purkinje cells, but not in the white matter (fig 2A). In the cerebral cortex, a high level of expression was seen in all cortical layers except for layer I, but expression was absent in the subcortical white matter (fig 2B). A high level of expression was also seen in the dentate gyrus of hippocampus and throughout Ammon’s horn. The adult mouse brain showed a similar pattern of expression (data not shown). These data suggested that all or most neurons in the adult brain express Coh1, with no obvious regional differences.

In contrast to the adult brain, the embryonic mouse brain showed low or undetectable levels of Coh1 expression using

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Table 2

<table>
<thead>
<tr>
<th>Pedigree</th>
<th>Mutation</th>
<th>Protein change</th>
<th>Exon</th>
<th>Homozygous/heterozygous</th>
<th>Novel/reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omani</td>
<td>7934 G&gt;A</td>
<td>G2465D</td>
<td>43</td>
<td>Homozygous</td>
<td>Novel</td>
</tr>
<tr>
<td>Saudi</td>
<td>1219 C&gt;T</td>
<td>Q407X</td>
<td>9</td>
<td>Homozygous</td>
<td>Novel</td>
</tr>
<tr>
<td>Arabian</td>
<td>7221delG</td>
<td>Q2407H...V2414X</td>
<td>40</td>
<td>Heterozygous</td>
<td>Novel</td>
</tr>
<tr>
<td>Japanese</td>
<td>7051 C&gt;T</td>
<td>R2351X</td>
<td>39</td>
<td>Homozygous</td>
<td>Reported</td>
</tr>
<tr>
<td>French</td>
<td>11598delA</td>
<td>E3867K...V3877X</td>
<td>61</td>
<td>Heterozygous</td>
<td>Novel</td>
</tr>
</tbody>
</table>

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Figure 2  In situ hybridisation of the mouse homologue of the COH1 gene. (A) Cerebellum of the mouse at postnatal day 21. A high level of expression is seen in the internal granule layer (g), and little expression is seen in the molecular layer (m) and white matter (wm). Purkinje cells ( inset) also show expression. (B) Cerebral cortex of the mouse at postnatal day 21. Many cells in layers II through VI of the cerebral cortex (II–VI) show expression, but only a few cells are positive in layer I of the cortex (I) and white matter (wm). (C) Cerebral wall of the mouse at embryonic day 1.4. A low level of expression is seen in both the cortical plate (cp) and ventricular zone (vz). Scale bars represent 100 μm in A and C, 250 μm in B.
the same labelled probe (fig 2C). Repeated attempts gave a low signal not greatly different from background and less intense than hybridisation seen with a sense control probe. Thus, COH1 appears to be widely expressed in neurons of the postnatal and adult brain, but is not highly expressed in the embryonic brain.

Our results indicate that the gene is expressed widely in the neurons of the central nervous system. However, there was little expression in the white matter tracts of cerebrum and cerebellum, suggesting that the gene is not expressed in glial cells at a high level. In addition, the level of expression appeared to be higher in the postnatal brain than in the embryonic brain. This may suggest that the COH1 gene primarily functions in postmitotic neurons, and not in neuronal progenitor cells. These findings are consistent with the fact that patients with Cohen syndrome are generally born with normal head circumference and develop microcephaly postnatally. COH1 mutations may cause microcephaly by disrupting, for example, dendritic or axonal outgrowth, which continues postnatally and is important for normal postnatal brain growth.

Further molecular genetic studies, in combination with biochemical studies of the COH1 protein, will likely help us understand the pathogenetic mechanism of Cohen syndrome. In addition, studying additional patients with atypical phenotypes (for example, less severe mental retardation or without neutropenia) may provide additional insights into the function of the COH1 gene. Furthermore, defining the clinical-genetic spectrum of Cohen syndrome will potentially benefit patients and their families by allowing accurate diagnosis of the syndrome.

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