Sharing of PPT mutations between distinct clinical forms of neuronal ceroid lipofuscinoses in patients from Scotland

The neuronal ceroid lipofuscinoses (NCLs, Batten disease) are a group of rare inherited neurodegenerative diseases of childhood classified according to their age of onset and ultrastructural appearance of storage material. A very unusual cluster of NCL cases is found in the west of Scotland. Some patients have early infantile onset, INCL, a disease almost entirely confined to Finland and characterised on ultrastructure by granular osmiophilic deposits (GROD). Other patients have a later, juvenile, onset but are found to have GROD (vINCL/GROD) rather than the fingerprint profiles usually found in juvenile onset cases. INCL in Finland is caused by mutations in the gene encoding palmitoyl-protein thioesterase, PPT.\(^1\) It was recently reported that cases of vINCL/GROD from Scotland (and elsewhere) also result from mutations in this gene.\(^1\) We set out to determine the disease causing mutations in PPT in Scottish INCL patients to establish whether there was any sharing of mutations with vINCL/GROD.

Four patients with a diagnosis of INCL were analysed. Exons of PPT were amplified from genomic DNA by PCR and then sequenced in forward and reverse directions.\(^1\) We found mutations in PPT in all four patients and of the eight chromosomes analysed three different nonsense mutations (Leu1STOP, Lys55STOP, and Arg1STOP) of 122 base pairs, and Arg1STOP, table 1) were present. Therefore, all the INCL patients are homozygous for mutations predicted to result in truncation of PPT. For each patient we amplified parental DNA and were able to show Mendelian inheritance of mutations.

Two of these mutations (Leu1STOP and Arg1STOP) are found in patients with vINCL/GROD.\(^1\) However, in these cases nonsense mutations do not occur in homozygous form and are only found in combination with a missense mutation. Therefore, we show how that two clinically distinct forms of NCL are caused by shared mutations in PPT. The clinical significance of these findings is that the severity of the disease in these patients is dependent on the combination and type of mutations present.

There are several diseases in which different mutations in the same gene cause dissimilar clinical phenotypes, for example, CFT (cystic fibrosis) and congenital bilateral absence of the vas deferens\(^5\)). Types A and B Niemann-Pick disease, like the NCLs, are lysosomal storage disorders which are both caused by mutations in the acid sphingomyelinase gene. As in this study, the same mutation has been found in both forms and the age of onset and severity of the phenotype is dependent on the other allele.\(^6\)

Geographical clustering of a rare autosomal recessive genetic disease suggests a founder effect with patients inheriting the same ancestral disease chromosomes. Detailed genealogical information is not available on these patients. However, all but one of the 18 disease chromosomes in INCL and vINCL/GROD cases are accounted for by two nonsense and one missense mutations (table 1) and it is likely that these are derived from individual ancestral chromosomes.

High resolution haplotype analysis and population studies to determine carrier rates will be required to resolve the issue.

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PTEN and prostate cancer

The PTEN gene (phosphate and tensin homologue), located on 10q23,\(^7\) has been reported to be the Cowden disease susceptibility gene. Germline mutations in PTEN have been found in patients with this syndrome.\(^8\) This disorder is characterised by the development of hamartomas at various sites, as well as an increased predisposition for thyroid cancer and for breast cancer in women.\(^9\) PTEN has also been reported as being altered in other types of cancer including glioblastoma,\(^10\) endometrial carcinoma,\(^11\) and kidney carcinoma.\(^12\) This gene has additionally been suggested to play a role in prostate cancer as PTEN mutations have been found in multiple prostate cancer cell lines.\(^13\)

In order to investigate the role of mutations in the PTEN gene in primary prostate cancer, we analysed microdissected prostate adenocarcinoma tissue from 28 patients with histopathologically confirmed cancer. All nine exons of PTEN were PCR amplified and screened for mutations by single-strand conformational polymorphism analysis (SSCP), Samples displaying mobility shifts were subjected to DNA sequence analysis. This analysis failed to detect homozygous deletions of the PTEN gene in any sample. A heterozygous mutation was identified in only one of the prostate tumour samples and was characterised as a single base deletion in codon 68 (TAG→AC). Additionally, an A→G polymorphism 96 bp upstream of the beginning of exon 2 was found in nine of 28 samples (32.1%). Based on this analysis, we conclude that mutations of the PTEN gene are rare in primary prostate cancers.

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Table 1 PPT mutations in Scottish INCL and vINCL/GROD

<table>
<thead>
<tr>
<th>Case</th>
<th>Disease</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>389</td>
<td>INCL</td>
<td>Arg51STOP/Arg51STOP</td>
</tr>
<tr>
<td>390</td>
<td>INCL</td>
<td>Arg51STOP/Leu55STOP</td>
</tr>
<tr>
<td>392</td>
<td>INCL</td>
<td>Arg51STOP/Leu51STOP</td>
</tr>
<tr>
<td>391</td>
<td>INCL</td>
<td>Arg51STOP/Thr75Pro</td>
</tr>
<tr>
<td>105, 341, 346</td>
<td>vINCL/GROD</td>
<td>Arg51STOP/Leu51STOP</td>
</tr>
<tr>
<td>325, 345</td>
<td>vINCL/GROD</td>
<td>Arg51STOP/Thr75Pro</td>
</tr>
</tbody>
</table>

Bold type indicates mutations present in both INCL and vINCL/GROD.