nonsense mutations do not occur in homozygous form and are only found in combination with a missense mutation. Therefore, we conclude that there are two clinically distinct forms of NCL 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, CFFR (cystic fibrosis and congenital bilateral absence of the vas deferens). Types A and B Niemann-Pick disease, like the NCLs, are lysosomal storage disorders which are both caused by mutations in the acidic C2-domain of the lipidosesine 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. 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 vJNCIJ/vGROD 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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Table 1 PPT mutations in Scottish INCL and vJNCIJ/vGROD

<table>
<thead>
<tr>
<th>Case</th>
<th>Disease</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>389</td>
<td>INCL</td>
<td>Arg151STOP/Arg151STOP</td>
</tr>
<tr>
<td>390</td>
<td>INCL</td>
<td>Arg151STOP/Arg151STOP</td>
</tr>
<tr>
<td>392</td>
<td>INCL</td>
<td>Arg151STOP/Arg151STOP</td>
</tr>
<tr>
<td>391</td>
<td>INCL</td>
<td>Arg151STOP/Arg151STOP</td>
</tr>
<tr>
<td>105, 341, 346</td>
<td>vJNCIJ/vGROD</td>
<td>Arg151STOP/Arg151STOP</td>
</tr>
<tr>
<td>325, 345</td>
<td>vJNCIJ/vGROD</td>
<td>Arg151STOP/Arg151STOP</td>
</tr>
</tbody>
</table>

Bold type indicates mutations present in both INCL and vJNCIJ/vGROD.

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PTEN and prostate cancer

The PTEN gene (phosphate and tensin homologue), located on 10q23, has been reported to be the Cowden disease susceptibility gene. Germline mutations in PTEN have been found in patients with this syndrome. 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. PTEN has also been reported as being altered in other types of cancer including glioblastoma, endometrial carcinoma, and kidney carcinoma. This gene has additionally been suggested to play a role in prostate cancer as prostate mutations have been found in multiple prostate cancer cell lines.

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 homozgyous 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 → ACG). 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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Sharing of PPT mutations between distinct clinical forms of neuronal ceroid lipofuscinoses in patients from Scotland.

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