Pedigree 4. Incest (H1) vs. No incest (H2)
When plotted against each other, these values would fall Log10(LR) – exact linked

Estimation of Linkage between D12S391 and vWA

Methods

Logarithm of odds (LOD score) analysis [7] is used to estimate the most probable value for the recombination rate between two loci using family genotype data. The LOD score (often called z) is given by log10(LR(r)) – exact linked. In other analyses, the LOD score determines how much more likely it is that two markers are linked with a certain recombination frequency of “exact” compared to being unlinked (where recomb = 0.5). In linkage analysis, the value of “exact” can be altered from 0 to 0.5. The value that maximizes the LOD score is the most probable recombination frequency.

Linkage analysis was performed using the program LINKAGE [4]. Six multi-generation Caucasian families (109 meioses total) were genotyped at D12S391 and vWA. For some meioses, the phase was unknown (leading to non-informative values for r and θ). Caucasian allele frequencies [11] were used to estimate the recombination rate for non-informative meioses (e.g., homozygous parent or both parents had same genotype). The support interval was computed based on the 1-t method (θ) and a 95% confidence interval was calculated with the BINOM program [7].

For each case scenario, genotypes of the involved individuals were simulated 10,000 times under each hypothesis.

DNA profiles were simulated with haplotype frequencies taken from O'Connor et al. [1] and θ = 0.089 was used as the recombination frequency (θ) between D12S391 and vWA.

Results

Table 1. Difference (computed as a ratio) between LR values calculated assuming unlinked markers (r = 0.5) or assuming linkage (θ = 0.089) between D12S391 and vWA. (Difference ratio = LR(linkage)/LR(unlinked)).

<table>
<thead>
<tr>
<th>Case scenario</th>
<th>Simulated under H1</th>
<th>Simulated under H2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median minimum</td>
<td>maximum</td>
</tr>
<tr>
<td></td>
<td>minimum maximum</td>
<td></td>
</tr>
<tr>
<td>Pedigree 1</td>
<td>0.72 0.23</td>
<td>3.14 0.60</td>
</tr>
<tr>
<td>Pedigree 2</td>
<td>0.95 0.60 2.82</td>
<td>0.86 0.60 3.03</td>
</tr>
<tr>
<td>Pedigree 4</td>
<td>0.82 0.71</td>
<td>3.05 0.63</td>
</tr>
</tbody>
</table>

From Table 1, the difference ratios vary between 0.72 and 0.95, which indicates that linkage has a significant impact on LR values in all cases. The maximum difference ratios are observed in Pedigree 2, where the difference ratio is 3.05.

Conclusions

If linkage is ignored in a true incest case when:
• No confidence interval was reported
• Using 109 meioses, we refined the estimated recombination frequency between D12S391 and vWA to 0.89

Thus, allele or haplotype frequencies can be used for LR calculations involving D12S391 and vWA. If one assumes LE between D12S391 and vWA, it is easier to infer haplotype frequencies from allele frequencies (particularly for unobserved haplotypes in population samples).

Results for LE vs. LD comparisons were similar for all case scenarios and hypotheses. All r-values were greater than 0.96. Thus, one representative figure is provided below.

Pedigree 4 simulated under H1

Pedigree 4 simulated under H2

Overall, ignoring linkage between D12S391 and vWA has a greater impact on LR values for incest cases than for other more common kinship scenarios, particularly when recombination has occurred between the markers.

References

[1] K.L. O'Connor, et al., Corrigendum to Linkage disequilibrium analysis of D12S391 and vWA in U.S. population scenarios was tested with Pearson's correlation coefficient (r).