Odds Ratios: Genetic Association
Odds Ratios (ORs) Allele Counting

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td>T</td>
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<td>B</td>
</tr>
<tr>
<td>C</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

\[
OR_T = \frac{\text{odds of disease with } T \text{ allele}}{\text{odds of disease with } C \text{ allele}} = \frac{(A/B)}{(C/D)} = \frac{A \times D}{B \times C}
\]

- Allele counting model essentially assumes an additive model.
- Genotype \( TT \) has twice the risk (or protection) of heterozygous genotype \( CT \).
- Same risk (or protection) for the comparison of heterozygous \( CT \) genotype and homozygous \( CC \) genotype.
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- $OR_T = 1$ implies no association between genotype and disease
- $OR_T > 1$ implies that the $T$ allele is associated with the disease
- $OR_T < 1$ implies that the $T$ allele is protective
Confidence Intervals for Odds Ratios (ORs)

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\[
OR = \frac{A \times D}{B \times C}
\]

\[
s.e.(\log(OR)) = \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}
\]

- Lower limit of 95% CI
  \[
  = \exp(\log(OR) - 1.96 \times s.e.(\log(OR)))
  \]

- Upper limit of 95% CI
  \[
  = \exp(\log(OR) + 1.96 \times s.e.(\log(OR)))
  \]
Confidence Intervals for Odds Ratios (ORs)

<table>
<thead>
<tr>
<th>rs6767450</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>158</td>
<td>392</td>
</tr>
<tr>
<td>C</td>
<td>20</td>
<td>86</td>
</tr>
</tbody>
</table>

\[
OR = \frac{A \times D}{B \times C}
\]

\[
s.e.(\log(OR)) = \sqrt{\frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}}
\]

- Lower limit of 95% CI

\[
= \exp(\log(OR) - 1.96 \times s.e.(\log(OR)))
\]

- Upper limit of 95% CI

\[
= \exp(\log(OR) + 1.96 \times s.e.(\log(OR)))
\]
LHON Example: Confidence Intervals for Odds Ratios (ORs)

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</tr>
<tr>
<td>C</td>
<td>20</td>
<td>86</td>
</tr>
</tbody>
</table>

\[
OR = \frac{158 \times 86}{392 \times 20} = 1.7332
\]

\[
s.e.(\log(OR)) = \sqrt{\frac{1}{158} + \frac{1}{392} + \frac{1}{20} + \frac{1}{86}}
\]

- Lower limit of 95% CI
  \[
  = \exp(\log(OR) - 1.96 \times s.e.(\log(OR)))
  = \exp(\log(1.7332) - 1.96 \times 0.2665) = 1.03
  \]

- Upper limit of 95% CI = 2.92
Odds Ratios (ORs) for Genotypes

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>CT</td>
<td>A′</td>
<td>B′</td>
</tr>
<tr>
<td>CC</td>
<td>C</td>
<td>D</td>
</tr>
</tbody>
</table>

Typically choose a reference genotype. For this example we will let CC be the reference genotype.

\[
OR_{TT} = \frac{\text{odds of disease in an individual with the TT genotype}}{\text{odds of disease in an individual with the CC genotype}}
\]

\[
OR_{CT} = \frac{\text{odds of disease in an individual with the CT genotype}}{\text{odds of disease in an individual with the CC genotype}}
\]
To get odds ratios and confidence intervals for genotypes, logistic regression is used:

\[
\log(\text{odds of disease for individual } i) = \beta_0 + \beta_{CT} I\{G_i = CT\} + \beta_{TT} I\{G_i = TT\} + \epsilon_i
\]

where \( G_i \) is the genotype for individual \( i \), and \( I\{G_i = CT\} \) is 1 if \( G_i = CT \) and 0 otherwise.

The coefficient estimates for \( \hat{\beta}_{CT} \) and \( \hat{\beta}_{TT} \) can be used to calculate odds ratios:

- \( OR_{CT} = \exp(\hat{\beta}_{CT}) \)
- \( OR_{TT} = \exp(\hat{\beta}_{TT}) \)

95% CI for \( OR_{CT} \) is

\[
\exp(\hat{\beta}_{CT} \pm 1.96 \times s.e.(\hat{\beta}_{CT}))
\]
Leber Hereditary Optic Neuropathy (LHON) disease and genotypes for marker rs6767450:

<table>
<thead>
<tr>
<th></th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>6</td>
<td>8</td>
<td>75</td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
<td>66</td>
<td>163</td>
</tr>
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