The influence of genetics on syndromic and non-syndromic cases of cleft lip and cleft palate

By Alice McGarry
Background

- Clefts of the lip and/or palate (CL/P) are congenital deformities of the face which can complicate speech, nutrition, hearing, and psychological development.
- CL/P has a global prevalence of about 1 in 700 live births, though varies greatly by geographical region and socioeconomic status.
  - Mayan populations in Guatemala have higher than average rates of cleft lip
- Prevention efforts focus on environmental factors that may interact with specific genes to cause CL/P
  - CL/P = Cleft of the lip and/or palate
  - CLP = Cleft of the lip with or without palate
  - CP = Cleft palate only
**Background**

** Syndromic **
- Cleft with some other deformity
- 30% of CLP cases, 50% of CP cases
- Caused by any of 300+ syndromes
- Most due to Mendelian genetic mutations, chromosomal abnormalities, teratogens

** Non-Syndromic **
- Cleft of the lip or palate is the only deformity present
- 20% of etiology caused by genetic mutations
- Genes, environmental factors, and their interactions
- Specific genes and interactions have yet to be identified
Hypotheses

• While genetic influences play a role in both syndromic and non-syndromic CL/P, the influence is stronger for syndromic CL/P.

• This will be identified by a greater percentage of syndromic CL/P cases with family history of orofacial clefts compared with non-syndromic CL/P cases.
Methods

• Retrospective cross-sectional study of children in Guatemala with CL/P who received treatment from Smile Train.

• Caretakers of the children were surveyed and provided information on family history of CL/P and presence of other deformities used to determine syndromic status.

• Simple and multivariate logistic regression was used to calculate the odds ratio of family history of CL/P by syndromic status.
  
  • Adjusted for cleft type, age, year of encounter
### Results

<table>
<thead>
<tr>
<th>Total Population</th>
<th>Syndromic</th>
<th>Non-syndromic</th>
<th>Unknown</th>
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</thead>
<tbody>
<tr>
<td><strong>Family History of CL/P</strong></td>
<td></td>
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<tr>
<td>Immediate Family History of CL/P</td>
<td>1817</td>
<td>155 (8.5%)</td>
<td>1436 (79.0%)</td>
</tr>
<tr>
<td>Distant Family History of CL/P</td>
<td>332 (18.3%)</td>
<td>31 (20.0%)</td>
<td>287 (20.0%)</td>
</tr>
<tr>
<td><strong>Cleft Lip with or without Palate (CLP)</strong></td>
<td>1669 (91.9%)</td>
<td>139 (89.7%)</td>
<td>1308 (91.1%)</td>
</tr>
<tr>
<td>Cleft Palate Only (CP)</td>
<td>133 (7.3%)</td>
<td>16 (10.3%)</td>
<td>113 (7.9%)</td>
</tr>
<tr>
<td><strong>Age at first encounter [mean (st dev)]</strong></td>
<td>4.06 (6.88)</td>
<td>4.95 (6.92)</td>
<td>3.93 (6.70)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Common Odds Ratio</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History</td>
<td>1.03 (0.68, 1.56)</td>
<td>1.04 (0.67, 1.61)</td>
</tr>
<tr>
<td>Immediate Family History</td>
<td>0.81 (0.41, 1.56)</td>
<td>0.73 (0.37, 1.44)</td>
</tr>
<tr>
<td>Distant Family History</td>
<td>1.06 (0.66, 1.69)</td>
<td>1.21 (0.74, 1.98)</td>
</tr>
</tbody>
</table>
Conclusions

- Family history of CL/P is not associated with syndromic status
- Possible misclassification of syndromic status
  - Rate of syndromic cases lower than expected
  - 15% of cases of most common syndrome (VWS) don’t have additional deformities, and so appear non-syndromic
  - Cases surveyed at a very young age may not have other deformities present yet
- Limitation in family history information obtained
  - Only two indicator variables were obtained for immediate and distant family history
  - Possible misclassification of family history would be non-differential, and bias results towards the null
  - If more detailed information were collected on the number of family members with CL/P, we might see an association with syndromic status
Recommendations

• A consistent definition of “syndromic” must be developed before research can move forward
  • How should cases that appear non-syndromic, but genetically appear syndromic, be classified?
  • Is there a grey area between syndromic and non-syndromic?

• Family history may still present a way to identify high-risk mothers that would benefit from preventative measures
  • More detailed information about family history might be used to predict syndromic status
Acknowledgements

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https://www.smiletrain.org/