Genetic Architecture of Familial Vitiligo

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The Power of Informatics to Advance Health Symposium
Heritability = The proportion of phenotypic variance attributable to genetic factors

→ Broad Sense $H^2$ = any form of genetic variation
→ Narrow Sense $h^2$ = additive genetic variation

**Missing Heritability** = $\hat{h}^2_{\text{PED}} - \hat{h}^2_{\text{SNP}}$

Variants associated with complex traits generally explain only a small proportion of total $h^2_{\text{PED}}$
Proposed Sources of “Missing Heritability”

• Unobserved variants
  § Structural variants
• Insufficient power to identify associated variants
  § Rare variants
  § Many variants with very small effect sizes
• Non-additive effects
  § Gene-gene interaction (epistasis)
  § Gene-environment interaction
  § Dominance effects
• Overestimation of $h^2$ in family-based studies
  § Shared environment of close relatives

- The genetic architecture of familial and sporadic complex disease are different??
Vitiligo

- Autoimmune destruction of skin melanocytes
- Prevalence ~0.2-2.0% (~0.4% in Europeans)
- Genetically complex
  - $\hat{h}^2_{\text{PED}} \sim 75\%$
    - Estimates range from 46% to 84%
  - $\hat{h}^2_{\text{SNP}} \sim 50\%$
    - ~22.5% of $h^2_{\text{SNP}}$ is explained by 50 genome-wide significant loci
Do we really expect the genetic architecture of vitiligo in the **Multiplex Family Case** to be similar to the **Sporadic Case**?

- **Sporadic Vitiligo**
  - 0% of cases for vitiligo $h^2_{PED}$ estimation
  - ~88% of cases for vitiligo $h^2_{SNP}$ estimation

- **Multiplex Vitiligo**
  - 100% of cases for $h^2_{PED}$ estimation
  - ~12% of cases for $h^2_{SNP}$ estimation
Polygenic Inheritance

Genetic Risk Score

Disease Threshold

GWAS Loci

Disease Susceptibility

Polygenic

Oligogenic

Near-Mendelian

Mendelian
Genetic Risk Score

\[
\sum_{i} \beta_i G_i
\]

# of autosomal variants identified by vitiligo GWAS

\[\ln(OR)\]

# of Risk Alleles

Low Risk Score

High Risk Score

Low Vitiligo Risk

High Vitiligo Risk

\[\Delta = 1.05 \text{ s.d.}\]

\[P < 10^{-100}\]
Polygenic Inheritance

Genetic Risk Score

Disease Threshold

GWAS Loci

Disease Susceptibility

Polygenic

Oligogenic

Near-Mendelian

Mendelian

Monogenic Inheritance

Linkage Analysis
## Table 1

<table>
<thead>
<tr>
<th>Chromosome and Distance</th>
<th>Marker(s)</th>
<th>LOD (P) in 71 Families</th>
<th>LOD (P) in 102 Families</th>
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<tbody>
<tr>
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<td>71 Families*</td>
<td>102 Families</td>
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<td>2.17 (.000335)</td>
<td>NS</td>
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<td>88.1 cM</td>
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<tr>
<td>7.7 cM</td>
<td>D22S420-D22S539</td>
<td>2.30 (.000561)</td>
<td>2.98 (.000106)</td>
</tr>
</tbody>
</table>
• 13 vitiligo cases
• Identified promoter variant in *FOXD3* (regulator of melanocyte differentiation)
• LOD score maximizes at a penetrance of ~52%
Polygenic Inheritance

Monogenic Inheritance

Disease Threshold

My Prediction:

Sporadic Cases

Familial Cases

Polygenic
Oligogenic
Near-Mendelian
Mendelian

High Genetic Risk Score

Low Genetic Risk Score
Risk Score in Multiplex Probands

\[ \Delta = 0.17 \text{ s.d.} \]

\[ P = 0.003 \]

Normalized Risk Score

Sporadic Cases

Multiplex Probands
Risk Score in Multiplex Probands

Multiplex Probands by Family Type

- Large Mpx (3-4 Affected): 38%
- Sib Pair: 26%
- Trios: 22%
- Small Mpx: 14%

Normalized Risk Score

- Affected Sib Pairs
- Parent-offspring Trios
- Small Mpx (3-4 Affected Members)
- Large Mpx (5+ Affected Members)
Risk Score in Multiplex Probands

Normalized Risk Score

Highest quintile for vitiligo cases!!
In Summary...

- Family studies estimate $h^2$
- Similar genetic architecture sporadic vs. familial vitiligo?
- Compared risk score
- Risk score is HIGHER in multiplex cases
- Implications:
  - Polygenic inheritance in multiplex families
  - Familial genetic architecture & heritability similar in sporadic and familial cases
  - Family $h^2$ good estimate for sporadic $h^2$
There was a typo in my previous email. It should, of course, read: “please focus completely on GENOME research”