The genetics of central hypogonadism and the regulation of puberty and fertility

Angela Delaney, MD
MGL Users Group
October 15, 2014
What are the key initiating factors for the onset of puberty?

• Timing of pubertal onset varies widely
  – Environmental, physiologic, and genetic factors
• GnRH secreted by hypothalamic neurons

Adapted from Balasubramanian et al, Mol Cell Endo 2011
Isolated GnRH Deficiency (IGD)

• Delayed, incomplete, or absent pubertal development

• Rare clinical syndrome, AKA isolated hypogonadotrophic hypogonadism (IHH)

• Difficult to distinguish from constitutional delay of puberty
Clinical heterogeneity of IGD

Balasubramanian et al, Mol Cell Endo 2011
GnRH neuronal migratory patterns

Non-reproductive features

Normal Kallmann syndrome
Non-reproductive features
Non-reproductive features
Non-reproductive features

- Hearing loss/inner ear anomalies
- Dental agenesis
- Ophthalmal logical anomalies
- Bimanual synkinesia
Aims

• To define the spectrum of phenotypic abnormalities
• To utilize contemporary genetic/genomic tools to identify new genes responsible for the physiology of GnRH secretion
• To chart the full genotype/phenotype spectrum of newly identified genes responsible for GnRH physiology
Clinical protocol (12-CH-0050)

• Collaboration: William Crowley, MGH

• Subjects
  – ≥ 14 y/o with delayed, stalled or absent puberty or diagnosis of IGD
  – Discontinue HRT for 6 – 8 weeks

• Comprehensive clinical phenotyping
Genetic causes of IGD

Balasubramanian et al, Mol Cell Endo 2011
“Known genes”

Neurodevelopmental

KAL1
FEZF1

FGFR1
PROKR2
PROK2
CHD7
FGF8
SEMA3A
NSMF
SOX10

Regulation of GnRH secretion/action

KISS1
KISS1R
TAC3
TACR3
GNRHR
GNRH1
WDR11
HS6ST1
Genetics protocol (12-CH-0049)

• All probands
  – Detailed family pedigree and olfactory testing
  – Family member enrollment strongly encouraged
  – Chromosomal microarray/Oligo-SNP Array (Quest)

• Subject selection
  – 22 probands
    • 3 parent-child trios
  – Variety of non-reproductive features
## Subjects

<table>
<thead>
<tr>
<th></th>
<th>Kallmann syndrome</th>
<th>nIHH</th>
<th>CDP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>13</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td><strong>Reversals</strong></td>
<td>1</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Adult onset</strong></td>
<td>1</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Trio submitted</strong></td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Sibling pair submitted</strong></td>
<td>1</td>
<td>0</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Sample preparation

• Samples with insufficient concentration were combined with other samples and concentrated to obtain final 5ug DNA in volume < 117ul

• Microcon YM-30 filter devices:
  – Combined samples for optimal DNA quantity in sample reservoir
  – Centrifuged at 10,000 x g for 5min
  – Placed reservoir upside down in new vial and spun for 3 minutes at 1000 x g
Analysis plan

- Rare, moderate to high-impact variants
  - Known genes
  - Novel candidate genes

- Burden tests using WES data from ~300 subjects (MGH)

- Genotype-phenotype correlations
Conclusions

• Detailed clinical phenotyping and genetic investigation of patients with pubertal disorders will lead to novel insights into the neuroendocrine regulation of human reproductive development
• Implications for diagnostic strategies and therapeutic interventions
• Potential for novel genetic influences on the regulation of puberty