A Patient With Arthrogryposis And Hypotonia

- **History**
  - Normal pregnancy – nuchal lucency
  - Chromosomes by CVS 46XX
  - Normal fetal echocardiogram at 19 weeks

- **Physical at birth**
  - camptodactyly
  - arachnodactyly and long feet
  - a midline facial nevus flammeus
  - hypotonia
• Clinical Course
  – failure to thrive – weight below 1st percentile, height at 5th %
  – delayed walking until 24 months
  – normal cognitive development

• Physical at 18 months
  – decreased bulk in the appendicular and axial muscles, inverted nipples with diminished subcutaneous fat, low tone and diminished reflexes throughout
Bifid Uvula
Metopic ridge
Retrognathia
Hypertelorism
Tubular nose
Malar Hypoplasia

Axial > Appendicular weakness
Minimal subcutaneous fat
Weight below 1\textsuperscript{st} Percentile

Normal aortic root dimensions
Normal skin
Normal wound healing
Normal palatal arch
Normal cognitive function
<table>
<thead>
<tr>
<th>Candidate Genes:</th>
<th>Related Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidate Genes:</td>
<td>Implicated Pathways</td>
</tr>
<tr>
<td>Transcriptome:</td>
<td>Expression + Sequence</td>
</tr>
<tr>
<td>Exome:</td>
<td>Sequence</td>
</tr>
</tbody>
</table>
camptodactyly  camptodactyly  camptodactyly  camptodactyly
arachnodactyly  arachnodactyly  arachnodactyly  arachnodactyly
joint laxity  joint laxity  joint laxity  joint laxity
scoliosis  scoliosis  scoliosis  scoliosis
MVP  MVP  MVP  MVP
hypomyoplasia  hypomyoplasia  hypomyoplasia  hypomyoplasia
dolichostenomelia  dolichostenomelia  dolichostenomelia  dolichostenomelia
aortic dilatation  aortic dilatation  aortic dilatation  aortic dilatation
pectus deformity  pectus deformity  pectus deformity  pectus deformity
pes planus  pes planus  pes planus  pes planus
lens dislocation  lens dislocation  lens dislocation  lens dislocation
MFS
A New Aortic Aneurysm Syndrome

Like Marfan syndrome:
- Curvature of spine
- Chest wall deformity
- Long fingers
- Aortic root aneurysm

Unique:
- widely-spaced eyes
- cleft palate/bifid uvula
- premature skull fusion
- club foot deformity
- congenital heart disease
  (PDA, BAV, ASD)
- arterial tortuosity
- diffuse aneurysms
- rupture w/ small dimensions
- death @ 26 y.o.

(> 200 families)

Loeys-Dietz syndrome (LDS)
BEALS
- large joint contractures
- ear deformity

MVP
- hypomyoplasia
- dolichostenomelia

MFS
- pes planus
- lens dislocation

LDS
- blue sclerae
- vascular tortuosity
- hypertelorism
- bifid uvula

PDA, VSD, ASD
- camptodactyly
- arachnodactyly
- joint laxity
- scoliosis

aortic dilatation
- pectus deformity

hypomyoplasia
- scoliosis

LDS
- vascular tortuosity
- hypertelorism
- bifid uvula
BEALS
- large joint contractures
- ear deformity

LDS
- blue sclerae
- vascular tortuosity
- hypertelorism
- bifid uvula

MFS
- pes planus
- lens dislocation

MVP
- hypomyoplasia
- dolichostenomelia

PDA, VSD, ASD
- camptodactyly
- arachnodactyly
- joint laxity
- scoliosis

aortic dilatation
pectus deformity

hypertelorism
bifid uvula
Key Observations in Bea’s Syndrome

- Hypomyoplasia with Weakness
- Bifid Uvula and Craniofacial Changes
- Overlap with Autosomal Dominant Syndromes
- Wild-type: \(FBN1\ & \ FBN2\) and \(TGFBRI \ & \ II\)
- Normal Connective Tissue: skin, great vessels

...at risk for vascular disease?
A Working Hypothesis

- Autosomal Dominant
  - New mutation
- Affects regulatory or signaling pathways involving TGFβ or family member
- Genetic Model?
  - Haplo-insufficiency Loss of Function
  - Dominant Negative
  - Gain of New Function
Parents: The Filter for New Variants in the Child

~3M Variants/g

91-238 New Variations/g/gen or 0-3/ exome

Working up a Sporadic

Candidate Genes: Related Syndromes

Candidate Genes: Implicated Pathways
- Interactome
- Site of Pathology

Transcriptome: Expression + Sequence

Exome: Sequence
Homozygous Recessives in Child (Parents are heterozygous)

- 932 dHom-pHet
  - 56 novel nucleotide variants
  - 876 known variants including rare alleles

- Location
  - 5’ UTR 101
  - Coding
    - 184 synonymous
    - 81 non-synonymous
  - Intronic 66
  - 3’ UTR 398
<table>
<thead>
<tr>
<th>Protein</th>
<th>Source</th>
<th>1</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β1</td>
<td>human</td>
<td>ALDTNYCFSST--EKNCCVRLQYIDFRKDLGWKWIHEPKGYHANFCLGCPY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2</td>
<td>human</td>
<td>ALDAAYCFRNV--QDNCCLRPLYIDFKRDLGWKWIHEPKGYNANFCAGACPY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β3</td>
<td>human</td>
<td>ALDTNYCFRNL--EENCCVRLPLYIDFRQDLGWKVHEPKGYYANFCGSCYP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β4</td>
<td>chicken</td>
<td>DLLTDYCFLPNGETKNCVEPLYIDFRKDLQWIIHEPKGYMANFCMGP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β5</td>
<td>X. laevis</td>
<td>GVQGEYCFGN--GPNCCKPQLNYFRKDLGWKWIHEPKGYEANYCLGNCPY</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HHHHHHH aaaa aaaHHHHHH bbb bbb bbb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Protein</th>
<th>51</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
<th>110</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-β1</td>
<td>IWSLDTQYSKVLALYNQHNGAVSAAPCCVPALEPLIVYYVGRKPKVQEQLSNMIVRSCKCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β2</td>
<td>LWSSDTQHRSVLSLYNTINPEASAPCCVSQDLEPLITLYYYGTKPKEQLSNMIVKSCKCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β3</td>
<td>LRSADTTHSTVLGLYNTLNPEASAPCCVQDPLEPLITLYYYGVRTPKVQEQLSNMIVSKCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β4</td>
<td>IWSADTQYTKVLALYNQHNGAVSAAPCCVPQTLDLPILYYVGRNVREQLSNMIVRACKCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGF-β5</td>
<td>IWSMDTQYSKVLALYNQHNGAVSAPCCVPDLEPLIPYYVGRRAKVEQLSNMIVRSNCNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary structure</td>
<td>HHHHHHHHHHHHH</td>
<td>ccccc ccccccccc cddddddddd dddd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BEALS
- large joint contractures
- ear deformity

MVP
- hypomyoplasia
- dolichostenomelia

MFS
- pectus deformity
- lens dislocation

LDS
- blue sclerae
- vascular tortuosity
- hypertelorism
- bifid uvula

CES
- muscle weakness
- reduced fat
- hearing loss
- hyperostosis

PDA, VSD, ASD
- camptodactyly
- arachnodactyly
- joint laxity
- scoliosis

Aortic dilatation
- pectus deformity

Scoliosis
BEA’S SYNDROME

- camptodactyly
- joint laxity
- hypomyoplasia
- blue sclerae
- hypertelorism
- bifid uvula
- pectus deformity
- pes planus
- muscle weakness
- reduced fat
- muscle weakness
The Distribution of Nearly Normal
Translational Research: Potential Flaws in the Strategy?

- Favor Specialist over Generalists?
- Neglect Basic Science? We need details.
- Corporatize labs even more?
- Drugs as probes not products?
- Hand off to who?
Managing Beatrice

Monitor her vasculature
Continue ARAs (ibersartan)?
Further the investigation
Find other Beatrices
The Ultimate Charmer