OBJECTIVES

- Embryology and epidemiology of clefting
- Nonsyndromic clefting
- Common genetic syndromes associated with clefting
- Recurrence risk and prevention of clefting
- Surgical repair and management of clefts
- Referrals and references
The Cleft Team

Plastic Surgery
Orthodontics
Speech Pathology
ENT
Genetics
Nutrition
Social Work
Pediatrics
PALATE EMBRYOLOGY

- Palate forms at 7-10 weeks gestation – critical period
- Damage is done by this time – will not close later in pregnancy

HTTPS://WEB.DUKE.EDU/ANATOMY/EMBRYOLOGY/CRANIOFACIAL/CRANIOFACIAL.HTML
EMBRYOLOGY

- Cleft lip with or without cleft palate (CL/P)
  - Failure of the maxillary and medial nasal processes to fuse

- Cleft palate only (CPO)
  - Failure of the palatine shelves to fuse

- [http://www.indiana.edu/~anat550/hnanim/face/JAS_facetween.html](http://www.indiana.edu/~anat550/hnanim/face/JAS_facetween.html)
Epidemiology

Clefting

1/700-1/1,000 live births with CL/P
- 2M : 1F
- 6:3:1 Left:Right:Bilateral

~1/2,500 live births with CPO
- 2F : 1M

Incidence

- Native American: 1/280
- Asian: 1/425
- Caucasian: 1/1,000
- African American: 1/2,000
NON-SYNDROMIC CLEFTING

- Clefting
  - 1/700-1/1,000 live births in US with CL/P
    - 85-90% non-syndromic
  - ~1/2,500 live births with CPO
    - 50-60% non-syndromic
  - TONS of gene associations

Regulatory variant in FZD6 gene contributes to nonsyndromic cleft lip and palate in an African-American family

Nevena Cvjetkovic, Lorena Maili, Katelyn S Weymouth, Shahrukh Hashmi, John B Mulliken, Jacek Topczewski, Ariadne Letra, Qiuping Yuan, Susan H Blanton, Eric C Swindell, and Jacqueline T Hecht
MULTIFACTORIAL INHERITANCE

Consider:

- Number of affected AND unaffected relatives
- Gender
- Age
- Ancestry

Environmental Risks

- Anticonvulsants, Rubella, Thalidomide, Maternal smoking, Alcohol, Folic acid deficiency
EMPIRIC RISKS - CLEFTS

<table>
<thead>
<tr>
<th>Relationship to Proband/Index Case</th>
<th>CLCP (%)</th>
<th>CPO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibs</td>
<td>4.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Sibs (no other affecteds)</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>Sib (2 affected sibs)</td>
<td>10.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Sib and affected parent</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>4.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Affected second-degree relative</td>
<td>&lt;1.0</td>
<td></td>
</tr>
<tr>
<td>Affected third-degree relative</td>
<td>&lt;1.0</td>
<td></td>
</tr>
<tr>
<td>General Population Risk</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phenotype of Proband</th>
<th>CLCP RR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCL</td>
<td>4.0</td>
</tr>
<tr>
<td>UCLP</td>
<td>4.9</td>
</tr>
<tr>
<td>BCL</td>
<td>6.7</td>
</tr>
<tr>
<td>BCLP</td>
<td>8.0</td>
</tr>
</tbody>
</table>
## Recurrence Risks

<table>
<thead>
<tr>
<th>Cleft Type</th>
<th>Recurrence Risk for Future Siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Only proband affected</td>
</tr>
<tr>
<td></td>
<td>Proband + one affected relative</td>
</tr>
<tr>
<td></td>
<td>Proband + two affected relatives</td>
</tr>
<tr>
<td>Unilateral CL/P</td>
<td>2-3%</td>
</tr>
<tr>
<td></td>
<td>3-5%</td>
</tr>
<tr>
<td></td>
<td>5-7%</td>
</tr>
<tr>
<td>Bilateral CL/P</td>
<td>3-5%</td>
</tr>
<tr>
<td></td>
<td>5-7%</td>
</tr>
<tr>
<td></td>
<td>7-10%</td>
</tr>
<tr>
<td>CPO</td>
<td>2-3%</td>
</tr>
<tr>
<td></td>
<td>3-5%</td>
</tr>
<tr>
<td></td>
<td>5-7%</td>
</tr>
</tbody>
</table>
SYNDROMIC CLEFTING

- >500 syndromes involve clefting
  - 10-15% of CLP is syndromic
  - 40-50% of CPO is syndromic
- Inheritance patterns:
  - Dominant
  - Recessive
  - X-linked
PIERRE ROBIN SEQUENCE

- Micrognathia + Glossoptosis + Cleft Palate
- Isolated PRS prevalence 1/8,500 – 1/14,000
- 60-80% of PRS is syndromic
- 35% of syndromic PRS is attributed to Stickler syndrome
DIGEORGE SYNDROME/22Q11 DELETION SYNDROME/ VELOCARDIOFACIAL SYNDROME

- Prevalence 1/4,000-1/5,000
  - Most common genetic cause of CL/P
- 93% de novo
  - Test parents if possible!
- Accounts for ~2% of CL/P
CLINICAL FEATURES

- Congenital heart defects (~74%)
  - ToF most common
- Palatal abnormalities (~69%)
  - Velopharyngeal Insufficiency (VPI)
  - SMCP
- Characteristic facial features
  - Long face, epicanthal folds, square helices, large ears
- Learning difficulties (70-90%)
- Immune deficiency (~77%)
- Hypocalcemia (50%)

- Renal anomalies (31%)
- Hearing loss
- Feeding and swallowing problems
- Laryngotracheoesophageal anomalies
- Growth hormone deficiency
- CNS anomalies/Seizures
- Skeletal anomalies
- Ophthalmologic abnormalities
- Autism (20%)
- Psychiatric illness (schizophrenia) (25%)
STICKLER SYNDROME

- Prevalence: 1/7,500 – 1/9,000
- About 35% of Pierre Robin Sequence have Stickler syndrome
- Variable expressivity, de novo rate unknown

http://www.faces-cranio.org/stories.html
STICKLER SYNDROME

- **Face**: midface hypoplasia, upturned nose, CL/P, PRS
- **Eye**: severe myopia, retinal detachment, glaucoma, cataracts
- **Bones/joints**: scoliosis, kyphosis, early-onset osteoarthritis, joint hypermobility, joint pain
- **Hearing loss**: SNHL
IRF6-RELATED SYNDROMES

- Van Der Woude Syndrome
  - Prevalence 1/35,000 – 1/100,000
  - Accounts for ~2% of all CL/P
  - 2CLP : 1CPO
  - Lip pits (~86%)
  - Variable expressivity
  - Normal intelligence & development
  - Clinical diagnosis
- Popliteal Pterygium syndrome (PPS)
  - Prevalence 1/300,000
  - CL/P (91-97%)

WAARDENBURG SYNDROME

- Prevalence: 1/40,000
- Accounts for ~2-5% of congenital syndromic HL
- 4 types; I and II are most common

**Major criteria**
- Congenital SNHL (45-60%)
- White forelock (~45%), early greying (20-40%)
- Pigmentation abnormality of the iris (15-30%)
- Hypoplastic blue irides (~15%)
- Dystopia canthus, W index >1.95
- Affected first-degree relative

**Minor criteria**
- Skin hypopigmentation (20-35%)
- Medial eyebrow flare (60-75%)
- Broad/high nasal root, prominent columella (50-90%)

Can also have CL/P
TREACHER-COLLINS SYNDROME

- **Features**
  - Mandible and zygomatic bone hypoplasia
  - Ear abnormalities
  - Lower eyelid coloboma, absent eyelashes
  - Hearing loss
  - CL/P, CPO
  - Preauricular hair displacement
  - Airway abnormalities
  - Speech and motor delay
OTHER COMMON SYNDROMES WITH CL/P

- Aarskog
- Aicardi
- Cri-du-chat
- Pallister-Killian
- Wolf-Hirschorn
- Aicardi
- Beckwith-Wiedemann
- Fryns
- Pallister-Hall
- Kabuki
- CHARGE
- Trisomy 13
- Trisomy 18
- Fetal alcohol syndrome
- Ectodermal dysplasia
- Gorlin
- Nager
- Smith-Lemli-Opitz
- MORE!
GENETIC TESTING

- Whole genome sequencing
  - WGS
- Exome sequencing
  - WES
- Chromosomal microarray
  - CMA
- Gene panels
- Single gene
SINGLE GENE TESTING

- Child’s features distinctly resemble a known genetic syndrome
- There is only one gene associated with the syndrome
  - Van der Woude syndrome
- Confirms a clinical suspicion or clinical diagnosis of disease
GENE PANELS

- Testing multiple genes at once (2-100s)
- When a genetic condition can be caused by a change in one of multiple different genes
  - Stickler syndrome
- Reads through multiple different genes at once
CHROMOSOME MICROARRAY (CMA)

- Small deletions or duplications
  - Can include parts of genes or multiple genes
  - DiGeorge syndrome/22q
- First tier testing
  - Common test to obtain after first genetics visit if no specific syndrome in mind
- Developmental delay/Autism
  - Recommended testing by multiple professional organizations
WHOLE EXOME SEQUENCING (WES)

- Most comprehensive clinical testing available
- Reads through ALL genes (>22,000) known to have a function in the human body (exons)
- Requires samples from biological parents when available
- When symptoms are not reminiscent of a particular genetic syndrome and CMA is normal
  - Multiple congenital anomalies
- *Incidental findings*
We found a diagnosis!
- Can explain WHY someone has the symptoms they do
- Able to provide more accurate recurrence risk information
- May be able to offer additional guidance and support

We did not find a diagnosis
- Does NOT mean a child does not have a genetic condition
- Unable to find the genetic CAUSE of the symptoms at this time
- May be other factors influencing the genes
- Genes/pathways we do not understand or have not been discovered
- Ruled out lots of other genetic conditions

DIAGNOSIS! (OR NOT)
GENETIC TESTING LOGISTICS

- ALL genetic testing requires insurance preauthorization when completed as an outpatient
  - Typically takes 4-6 weeks
- INPATIENT does not require preauth
- All genetic tests and testing labs are not created equal
FEEDING

- Often primary concern for providers and parents
- Haberman
- Mead-Johnson
- Pigeon
CLEFT REPAIR

**NAM**
1 week – 3 months (until CL repair)

- Orthodontist brings palate and lip together with appliance to “mold” palate

**Cleft Lip Repair**
3-6 months

- Incisions on each side of cleft, suture lip together
- Reposition muscle to improve sucking/feeding
- BCLP will require 2 surgeries, about one month apart

**Cleft Palate Repair**
9-12 months

- Repair hole and muscles for speech
- Separates oral and nasal cavities
- Complete prior to poor speech developing, but after old enough to handle the surgery
- Secondary speech surgery may be necessary

**Palatal Expansion**
5-7 years as needed

- 25% require expansion to prepare for bone graft
- Creates space for permanent teeth

**Alveolar Bone Graft and Fistula Repair**
6-9 years

- Places bone (from hip) along alveolus and packed into holes in palate
- Close fistulas between gum and nose to prevent nasal regurgitation
- Provide bone for permanent tooth eruption
CLEFT REPAIR

Rhinoplasty
6-9 years as needed
- Tip or intermediate rhinoplasty pending severity as necessary

Orthodontics
6-18 years
- Orthodontics is begun ~6 months following bone graft
- Patients may be missing teeth or have displaced teeth

Orthognathic Surgery
14-18 years
- Common for cleft palate patients
- Correcting maxillary retrusion (upper jaw is behind the lower jaw)
- Surgery at skeletal maturity
- Severe cases which present in childhood may have a distraction osteogenesis at younger age to correct maxillary retrusion

Lip/Nasal Revision
>16 years
- Correction to improve contour of lip and nose
- Often cosmetic

http://www.texaschildrens.org/health/cleft-lip-and-palate
GOALS OF REPAIR (CHEILOPLASTY, PALATOPLASTY)

- Normal anatomy and function
  - Feeding
  - Speech
  - Nasal function
  - Dentition
  - Jaw
- Additional surgeries may be required for speech
  - Pharyngeal flap – decrease hypernasality and nasal emissions
  - Correct acquired VPI
CHALLENGES IN CLEFT CLINIC

- Numerous surgeries throughout childhood and teens
  - Many appointments and many surgeries
  - Costly
  - Missing school
- Function AND appearance must be considered
- Self-esteem
  - Appearance
  - Speech
- Utility of genetic testing
WHEN TO CONSIDER GENETICS

- Is development on track?
- Are there any other congenital anomalies?
  - Heart, kidneys, digits
  - Is eyesight and hearing okay?
- Are other family members affected?
- Were there any prenatal exposures?
  - Did they perform any prenatal testing?
TO REFER

- Genetics Clinic
  - Need clinic notes/testing results of patient
  - MUST have documentation of indication for genetics
  - Phone: 832-822-4280
  - Fax: 832-825-4294

- Plastic Surgery
  - Refer directly to plastic surgery clinic
  - Phone: 832-822-3180, option #2
GENETICS AND CLEFT CLINICS AT TCH

- General Genetics Clinic
  - Clinics on Mondays and Thursdays
  - Approximately 60-70 patients per week
  - 5 month NPV waiting list
- Cleft Lip and Palate Multidisciplinary Clinic
  - Every Monday
  - Anywhere from 30-70 patients per clinic
RESOURCES

- Children's Craniofacial Association

- Cleft Palate Foundation
  - http://www.cleftline.org/

- FACES

- 22q Foundation
  - http://www.22q.org/
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- Marilyn McLaughlin, LCSW
- Julie Edwards, RN
QUESTIONS?

HALEY STREFF, MS, CGC
CERTIFIED GENETIC COUNSELOR
DEPT OF MOLECULAR AND HUMAN GENETICS
BAYLOR COLLEGE OF MEDICINE/TEXAS CHILDREN’S HOSPITAL
6701 FANNIN ST. SUITE 1560
HOUSTON, TX 77030
PHONE: 832.822.4295
STREFF@BCM.EDU

THANK YOU!