Genetics link congenital heart disease and neurodevelopmental abnormalities

Martina Brueckner
Congenital heart disease:

- Affects 1% of liveborn infants, most common cause of mortality from congenital defects
- 90% of patients survive to adulthood, but many suffer co-morbidities including neurodevelopmental abnormality and respiratory disease
- Genetic contribution likely in 90%
- Chromosomal aneuploidy and copy-number variation contributes to at least 23%
- High genetic heterogeneity makes identification of specific genes underlying CHD difficult
10-20% of all CHD patients have some neurodevelopmental impairment

Marino et al., *Circulation*, 2012
Broad range of neurodevelopmental abnormalities in CHD:

- Cognitive impairment
- Learning disability
- Executive functioning
- School functioning
- Deficits in fine and gross motor skills
- Behavioral difficulty
- Autism-Spectrum disorder

Nattel et al, Canadian Journal of Cardiology, 2017
Neurodevelopment in Congenital Heart Disease: possible mechanisms

- Circulatory abnormalities impacting brain development pre- and postnatally
- Complications of surgical and medical management
- Psychosocial stresses associated with disease and management
- Developmental pathways shared between brain and heart development
Complications of surgery:

- Cyanosis
- Impaired cerebral perfusion during cardio-pulmonary bypass
- Perioperative acidosis
- Microemboli
- ICU interventions
But: Cardiac surgery had no significant impact on ND outcome in school-age children with Down Syndrome

<table>
<thead>
<tr>
<th></th>
<th>DS+CHD (n = 7)</th>
<th>DS−CHD (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preschoolers age (year)</td>
<td>5.7 ± 1.3</td>
<td>5.2 ± 1.5</td>
<td>.403</td>
</tr>
<tr>
<td>PLS-5 expressive</td>
<td>46.25 ± 14.8 (n = 7)</td>
<td>52.71 ± 15.8 (n = 31)</td>
<td>.428</td>
</tr>
<tr>
<td>PLS-5 auditory</td>
<td>40.67 ± 18.21 (n = 7)</td>
<td>51.9 ± 13.39 (n = 31)</td>
<td>.2</td>
</tr>
<tr>
<td>PB VISUAL MOTOR</td>
<td>90.75 ± 9.91 (n = 4)</td>
<td>100 ± 19.9 (n = 15)</td>
<td>.55</td>
</tr>
<tr>
<td>PB GRASPING</td>
<td>41.5 (40.25–44.25) (n = 4)</td>
<td>42 (42–44) (n = 15)</td>
<td>.35</td>
</tr>
<tr>
<td>PB fine motor</td>
<td>7.5 (5.25–11.25) (n = 4)</td>
<td>7 (5.5–10.5) (n = 13)</td>
<td>.549</td>
</tr>
</tbody>
</table>

Alsaid et al, *Congenital Heart Disease*, 2016
Early brain and heart development temporally overlap
Many molecular and cellular building blocks are shared between heart and brain development.

Regulation of transcription/
Chromatin remodeling

Cilia

Neural crest cells
Causes of CHD:

- aneuploidy
- CNV
- known gene recessive
- de-novo chromatin SNV
- other de-novo SNV
- known gene dominant
- environmental
- unknown

Inheritance patterns of CHD:
There are many ways to get a broken heart:
Human genetics predicts 300-500 genes associated with CHD

- Effort by NHLBI B2B (Bench-to-Bassinet) program
- Multi-center collaboration >12,000 patients
- Whole-exome sequencing ~3,500 patient-parent trios
- Highly heterogeneous: 300-500 genes
- Genetic cause may be predictive of outcome, and may influence management of CHD
- Identified novel developmental mechanisms for heart development

Samir Zaidi, Peter (Shen Chih) Jin
The low-hanging fruit: *de-novo* mutations in CHD

- *De-novo* mutations account for 8% of CHD
- 3% of isolated CHD
- 28% of CHD + extracardiac abnormalities and NDD
- Approximately 440 genes contribute to CHD by a *de-novo* dominant mechanism

De-novo mutations are enriched in patients with CHD and neurodevelopmental abnormality

Mutations in genes that are co-expressed in the developing heart and brain are associated with neurodevelopmental abnormalities and CHD.
De-novo mutations affecting chromatin remodeling genes contribute to 2.3% of CHD
Chromatin remodeling globally regulates transcription
Mutations affecting chromatin remodeling predict a high risk of neurodevelopmental abnormalities

ND pos: answered “yes” to ? Developmental delay, MR, learning disability, autism
Genetic overlap between autism susceptibility and congenital heart disease genes

The contribution of de novo coding mutations to autism spectrum disorder

Synaptic, transcriptional and chromatin genes disrupted in autism
Enrichment of overlapping genes with LoF or damaging *de novo* mutations between CHD and autism cohorts

<table>
<thead>
<tr>
<th>Genes with LoF <em>de novo</em> mutations overlapping between CHD and autism cohorts</th>
<th>35</th>
<th>16.83</th>
<th>2.08</th>
<th>2.9×10⁻⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes with damaging <em>de novo</em> mutations overlapping between CHD and autism cohorts</td>
<td>112</td>
<td>81.23</td>
<td>1.38</td>
<td>2.0×10⁻⁴</td>
</tr>
</tbody>
</table>

10⁶ permutations were performed to estimate the empirical distribution of the number of overlapping genes between CHD and 2 autism cohorts. The empirical p-value is calculated as the proportion of the expected number of overlapping genes that exceeds the observed number of overlapping genes. For the detailed approach, please see Methods. *These two autism cohorts refer to: (1) Iossifov et al. *Nature* 2014 515, 216-221, and (2) De Rubeis et al. *Nature* 2014 515, 209-215.
Enrichment of overlapping high heart expressed and high brain expressed genes with damaging *de novo* mutations between CHD and autism cohorts

<table>
<thead>
<tr>
<th>HHE + HBE Genes with LoF <em>de novo</em> mutations overlapping between CHD and autism cohorts</th>
<th>Observed # genes</th>
<th>Expected # genes</th>
<th>Enrichment</th>
<th>Empirical P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>3.68</td>
<td>5.16</td>
<td>&lt;10(^{-6})</td>
<td></td>
</tr>
<tr>
<td>HHE + HBE Genes with damaging <em>de novo</em> mutations overlapping between CHD and autism cohorts</td>
<td>48</td>
<td>17.35</td>
<td>2.77</td>
<td>&lt;10(^{-6})</td>
</tr>
</tbody>
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10\(^6\) permutations were performed to estimate the empirical distribution of the number of overlapping high heart expressed (HHE) + high brain expressed (HBE) genes between CHD and 2 autism cohorts. The empirical p-value is calculated as the proportion of the expected number of overlapping genes that exceeds the observed number of overlapping genes. For the detailed approach, please see Methods. *These two autism cohorts refer to: (1) Iossifov et al. *Nature* 2014 515, 216-221, and (2) De Rubeis et al. *Nature* 2014 515, 209-215.
Gene ontologies may predict clinical risks better than specific gene defects.

CHD, LVOT abnormalities
Neurodevelopmental abnormalities

Chromatin remodeling genes:

CHD, laterality defects, respiratory complications

Cilia genes
Genetic defects affecting heart and brain development are likely to underlie some neurodevelopmental abnormalities in CHD patients.
### Clinical approach: clinical risk stratification

**Categories of Pediatric CHD Patients at High Risk for Developmental Disorders or Disabilities**

<table>
<thead>
<tr>
<th>1. Neonates or infants requiring open heart surgery (cyanotic and acyanotic types), for example, HLHS, IAA, PA/IVS, TA, TAPVC, TGA, TOF, tricuspid atresia.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Children with other cyanotic heart lesions not requiring open heart surgery during the neonatal or infant period, for example, TOF with PA and MAPCA(s), TOF with shunt without use of CPB, Ebstein anomaly.</td>
</tr>
<tr>
<td>3. Any combination of CHD and the following comorbidities:</td>
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<tr>
<td>3.1. Prematurity (&lt;37 wk)</td>
</tr>
<tr>
<td>3.2. Developmental delay recognized in infancy</td>
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<tr>
<td>3.3. Suspected genetic abnormality or syndrome associated with DD</td>
</tr>
<tr>
<td>3.4. History of mechanical support (ECMO or VAD use)</td>
</tr>
<tr>
<td>3.5. Heart transplantation</td>
</tr>
<tr>
<td>3.6. Cardiopulmonary resuscitation at any point</td>
</tr>
<tr>
<td>3.7. Prolonged hospitalization (postoperative LOS &gt;2-wk in the hospital)</td>
</tr>
<tr>
<td>3.8. Perioperative seizures related to CHD surgery</td>
</tr>
<tr>
<td>3.9. Significant abnormalities on neuroimaging or microcephaly</td>
</tr>
<tr>
<td>4. Other conditions determined at the discretion of the medical home providers</td>
</tr>
</tbody>
</table>

Marino et al, *Circulation*, 2012
Clinical approach: genetic risk stratification

Cardiac and extracardiac phenotype, family history, Previous genetic testing (including prenatal)

- Suspect aneuploidy (trisomy 13, 18, 21, Turner)
  - Karyotype (or FISH if emergent)
  - Test and counsel other family members

- High suspicion for DiGeorge, William
  - FISH

- Severe CHD, or CHD + extracardiac abnormality
  - Chromosomal microarray

- High clinical suspicion of CHD as part of a defined syndrome
  - (Targeted sequencing)

If negative:

- Known pathogenic variant

If negative:

- WES
  - Variant of unknown significance

Possible pathogenic variant
  - Test parents
# Neurodevelopmental evaluation in CHD patients, AHA recommendations

## Domains and Suggested Instruments for Developmental Evaluation of Children and Adolescents With CHD

<table>
<thead>
<tr>
<th>Age</th>
<th>Evaluation component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (0-1 year)</td>
<td>Developmental History, Growth, Feeding history, Neuromotor evaluation, Audiologic evaluation</td>
</tr>
<tr>
<td>Toddler (1-3.5 yr)</td>
<td>Standardized developmental measure, Behavior parent report</td>
</tr>
<tr>
<td>Preschooler (3.5-5yr)</td>
<td>Standardized developmental measure, Speech-language evaluation, Behavior parent report</td>
</tr>
<tr>
<td>Child and adolescent (6-18 yr)</td>
<td>Intelligence, Academic achievement, Language, Visual construction and perception, Attention, Processing speed, Memory, Executive function, Fine motor skills, Gross motor skills, ADHD, Behavioral functioning, Adaptive functioning</td>
</tr>
</tbody>
</table>
Current lab members:
- Svetlana Makova
- Jeff Drozd
- Syndi Barish
- Shiaulou Yuan
- Isabella Berglund-Brown
- Nancy Cross

WES project:
- Richard Lifton
- Peter (ShengChih) Jin
- Michael Sierant
- Weilai Dong
- Xue Zeng

ICOs project:
- Zhaoxia Sun
- Lu Zhao

YCGA:
- Kaya Bilguvar
- Shrikant Mane

Patients and families

Funding: NHLBI, Hartwell foundation