New insights in the genetics of TAA and BAV in Turner syndrome (TS)

Aline Verstraeten

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Disclosure of Interest

Speaker name: Aline Verstraeten

- I do not have any potential conflict of interest
Only minority of cases is live-born

SHOX
Short stature
Webbed neck
Congenital heart disease
Pubertal delay
Kidney abnormalities
Aortopathy
Infertility
TS and cardiovascular disease

Cardiovascular features:
• Present in 2/3 of TS girls
• Most commonly: left-sided anomalies
  o Coarctation of aorta
  o Aortic atresia
  o Bicuspid aortic valve (BAV, 15-30%)
  o Aortic aneurysm (TAA, 15-25%)
  o Aortic dissection (TAAD, 1-2%)

X-Haploinsufficiency is not sufficient to cause BAV and/or TAA(D)
TS and cardiovascular disease

<table>
<thead>
<tr>
<th>Karyotype (n)</th>
<th>ASI, cm/m²</th>
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<tbody>
<tr>
<td>46,XX (26)</td>
<td>1.71/0.15</td>
</tr>
<tr>
<td>45X (116)</td>
<td>1.91/0.36</td>
</tr>
<tr>
<td>46,XiXq (15)</td>
<td>1.93/0.30</td>
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<tr>
<td>46,XdelXp (6)</td>
<td>1.90/0.10</td>
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Suggestive for a BAV/TAA locus on short X-arm

Olivieri et al., 2013; Matura et al., 2007
Hypothesis:
X-linked parent-of-origin effects (POE) $\rightarrow$ POE-dependent imprinting

Approach: Examination of aortic valve morphology

Cohorts: $39, X^pO$ mice (N=18)
$39, X^mO$ mice (N=27)
$40, XX$ mice (N=40; controls)
Valve malformations are more frequent in 39,X<sup>m</sup>O (p=0.03)
  - 0% in 40,XX
  - 0% in 39,<sup>p</sup>O
  - 15% in 39,X<sup>m</sup>O

Hinton et al., 2015
Preliminary Evidence for Aortopathy and an X-Linked Parent-of-Origin Effect on Aortic Valve Malformation in a Mouse Model of Turner Syndrome

Robert B. Hinton 1,*, Amy M. Opoka 1, Obah A. Ojarikre 2, Lawrence S. Wilkinson 3,4 and William Davies 3,4

**Approach:** Examination of aortic dimensions

**Cohorts:** 39,X\textsuperscript{p}O mice (N=5)
39,X\textsuperscript{m}O mice (N=5)
40,XX mice (N=9; controls)

**No significant differences** in aortic dimensions between 40,XX – 39,X\textsuperscript{p}O – 39,X\textsuperscript{m}O

- A trend for 39,XO (largest effect for 39,X\textsuperscript{m}O) → lack of power (N=9,5,5)?
- Abnormal smooth muscle cell alignment in 39,X\textsuperscript{m}O and 39,X\textsuperscript{p}O
- Reduced SMA levels in 39,X\textsuperscript{m}O only
Hypothesis: haplo-insufficiency for an X-linked gene + a common variant

Approach: SNP arrays => SNP and CNV data

Autosomal and X Chromosome Structural Variants Are Associated with Congenital Heart Defects in Turner Syndrome: The NHLBI GenTAC Registry

Siddharth K. Prakash,1* Carolyn A. Bondy,2 Cheryl L. Maslen,3 Michael Silberbach,3 Angela E. Lin,4 Laura Perrone,5 Giuseppe Limongelli,5 Hector I. Michelena,6 Eduardo Bossone,7 Rodolfo Citro,7 BAVCon Investigators, GenTAC Registry Investigators, Scott A. Lemaire,8 Simon C. Body,9 and Dianna M. Milewicz1

Prakash et al., 2016
• No genome-wide significant SNPs (max OR 1.5; underpowered)
• No genome-wide significant CNPs
• 1 significant CNP for LSL (p=0.011, OR3.7): 7.4% in BAV TS–2.1% in TAV TS
  o Duplication of *SLC2A14, SLC2A3, NANOGP1*
  o ~CNP also associates with conotruncal heart disease in 22q11.2del carriers
  o Associated with increased risk for TS-related aortic dissection
  o Not associated with TS-related aortic dilatation => trend
  o Not associated with non-syndromic BAV or TAA

• 6 rare CNVs
  o Also observed in non-syndromic BAV or TAA cases
  o Some link with cardiovascular disease (e.g. *HOXA3, CXADR, ZMYM2*)

→ Larger studies needed or is rare genetic variability the answer? 

Prakash et al., 2016
Conclusions

• Very little is known, few studies have been reported

• Large cohorts will be needed → collaborations!
  o Stratification based on karyotype
  o Extreme phenotype stratification (e.g. TAA)
  o BAV/TAA/CoA stratification

• Improved knowledge on X-linked imprinting and escape from X-inactivation would help
Thank you for your attention!