September 12-14
2018
Les Comtes de Méan
Liège, Belgium

6th International Meeting on Aortic Diseases

New insights into an old problem CHU Liège, APF

www.chuliege-imaa.be

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

Aline Verstraeten

September 13, 2018

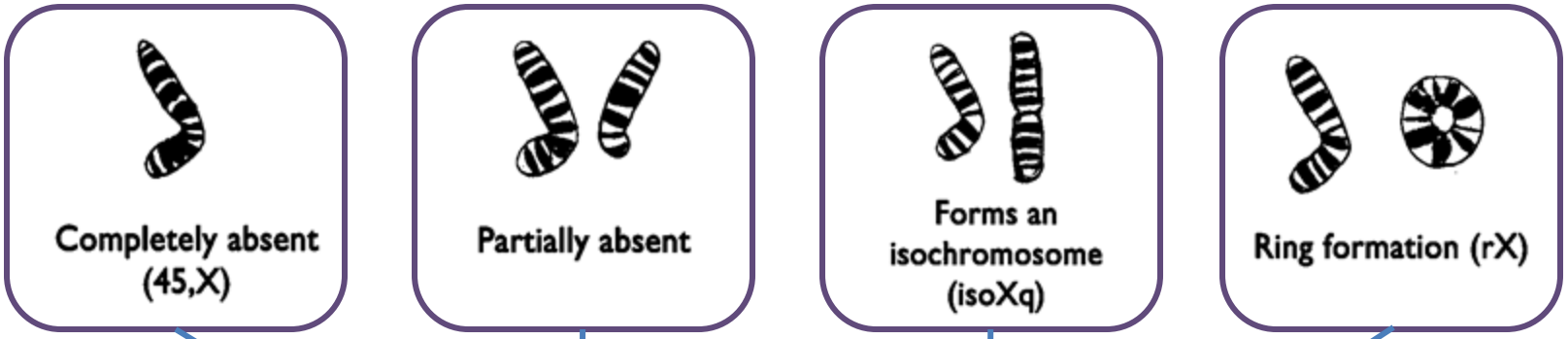
CHU de Liège

Disclosure of Interest

Speaker name: **Aline Verstraeten**

- I do not have any potential conflict of interest

TS genetics



Only minority of cases is live-born

SHOX

Short stature

Webbed neck

Kidney abnormalities

Congenital heart disease

Aortopathy

Pubertal delay

Infertility

TS and cardiovascular disease

Cardiovascular features:

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

Incomplete penetrance

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

TS and cardiovascular disease

BAV

	BAV	TAV	Totals
45,X	57 (36%)	101	158
IsoQ	5 (22%)	18	23
Pdel	1 (9%)	10	11
Qdel	0	4	4

TAA

Karyotype (n)	ASI, cm/m^2
46,XX (26)	1.71/0.15
45X (116)	1.91/0.36
46,XiXq (15)	1.93/0.30
46,XdelXp (6)	1.90/0.10
	1.49/0.30

Genetic diversity

→ **Suggestive for a BAV/TAA locus on short X-arm**

Olivieri et al., 2013; Matura et al., 2007

TS and BAV

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]

Hypothesis:

X-linked parent-of-origin effects (POE) → POE-dependent imprinting

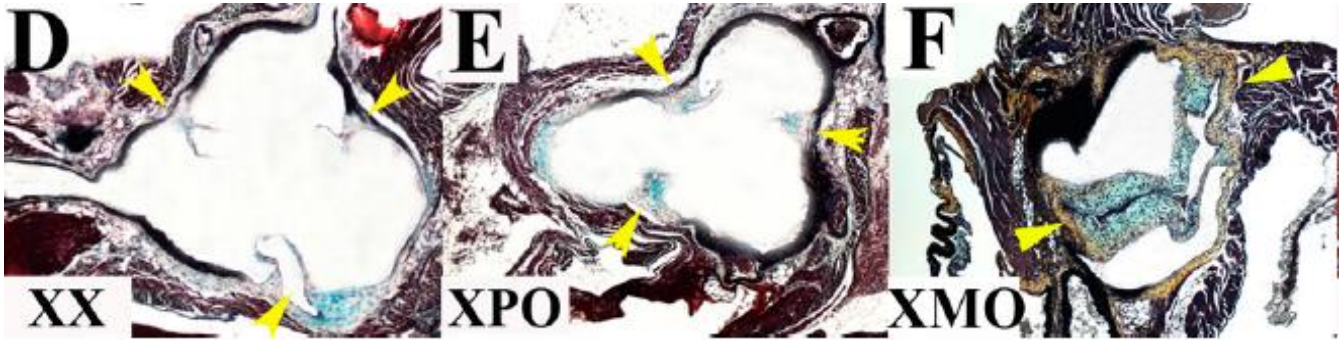
Approach: Examination of aortic valve morphology

Cohorts: 39,X^pO mice (N=18)
39,X^mO mice (N=27)
40,XX mice (N=40; controls)

Hinton et al., 2015

TS and BAV

- Valve malformations are more frequent in 39,$X^{m}O$ (p=0.03)
  - **0%** in 40,XX
  - **0%** in 39,$X^{p}O$
  - **15%** in 39,$X^{m}O$



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Approach: Examination of aortic dimensions

Cohorts: 39,X^pO mice (N=5)
39,X^mO mice (N=5)
40,XX mice (N=9; controls)

No significant differences in aortic dimensions between 40,XX – 39,X^pO – 39,X^mO

- A trend for 39,XO (largest effect for 39,X^mO) → lack of power (N=9,5,5)?
- Abnormal smooth muscle cell alignment in 39,X^mO and 39,X^pO
- Reduced SMA levels in 39,X^mO only

Hinton et al., 2015

TS and BAV/TAA

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. Milewicz[1]

Hypothesis: haplo-insufficiency for an X-linked gene + a common variant

Approach: SNP arrays => SNP and CNV data

Prakash et al., 2016

TS and BAV/TAA

- 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
  - Duplication of *SLC2A14*, ***SLC2A3***, *NANOGP1*
  - ~CNP also associates with conotruncal heart disease in 22q11.2del carriers
  - Associated with increased risk for TS-related aortic dissection
  - Not associated with TS-related aortic dilatation => trend
  - Not associated with non-syndromic BAV or TAA
- 6 rare CNVs
  - Also observed in non-syndromic BAV or TAA cases
  - 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!
  - Stratification based on karyotype
  - Extreme phenotype stratification (e.g. TAA)
  - BAV/TAA/CoA stratification

- Improved knowledge on X-linked imprinting and escape from X-inactivation would help

Fondation Leducq

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Thank you for your attention!

Hartstichting

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