the children's hospital at Westmead

The Sydney children's Hospitals Network

GONADAL PATHOLOGY AND RESPONSE TO GROWTH HORMONE THERAPY IN 45,X/46,XY FEMALES

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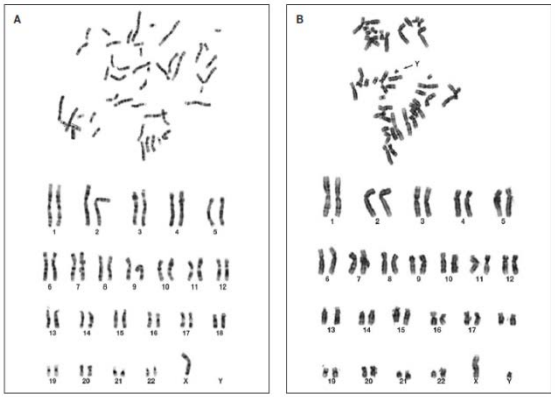
Turner syndrome

- 1/2500 births
- **Variety of karyotypes and phenotypes**
  - **50% 45,X monosomy**
  - **50% mosaic**



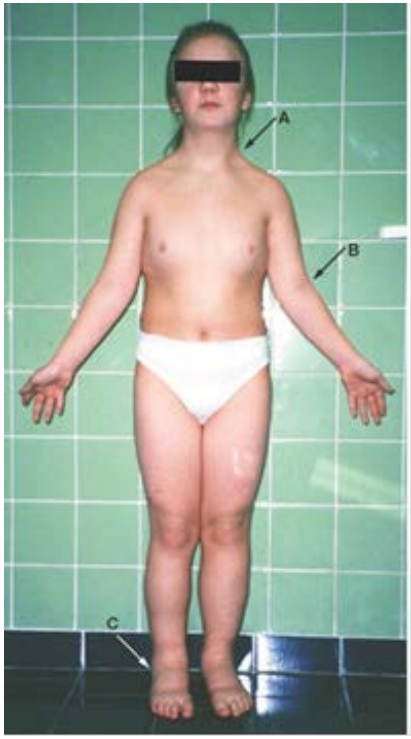
Broad shield like chest with wide spaced nipples, pectus excavatum

Lymphoedema

Elbow- valgus deformity

Webbed neck, low hairline

Cardiac disease



Short stature

Hearing loss

Scoliosis/ kyphosis

Primary or early gonadal failure

Renal anomalies

Coeliac, thyroid disease

Turner syndrome mosaicism with Y material

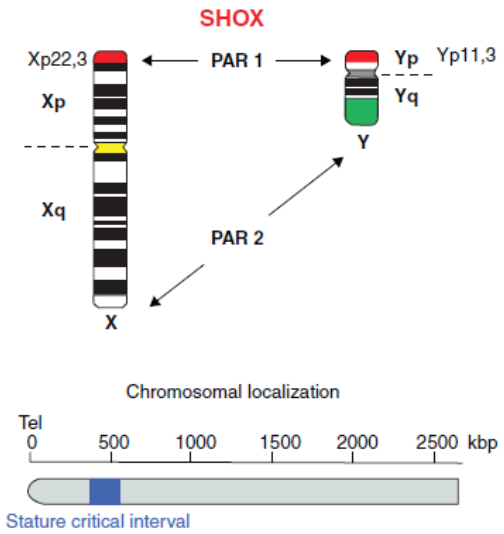
- 45,X/ 46,XY karyotype with female phenotype is rare
  - <1/15 000 births
  - 6-10% of Turner syndrome
  - Female phenotype if low proportion Y material (SRY)

Two unanswered questions

- Does karyotype influence growth potential?
  - In Australia, 45,X/46,XY girls cannot receive growth hormone tx unless have had gonadectomy
- What is the cancer risk in these girls?

Short stature homeobox (SHOX)

- **SHOX gene located on both X and Y chromosomes**
  - More prone to deletions on Xp
  - Usually inherit 2 functional copies
  - Important for growth and bone development

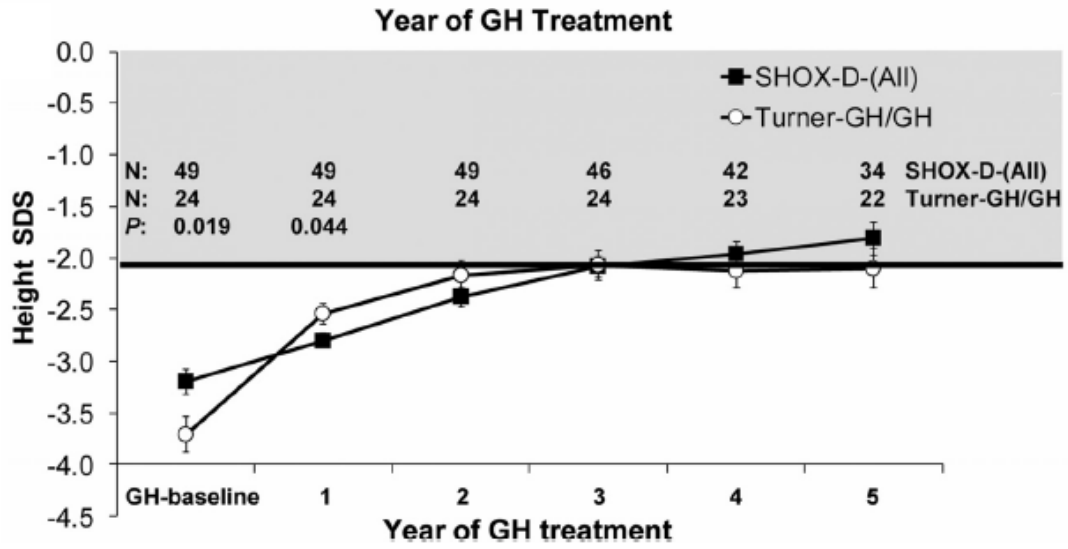


- **SHOX deletion:**
  - 1/2000-5000 worldwide
  - 1/40-150 short stature individuals
  - Haploinsufficiency in Turner syndrome

SHOX deficiency vs Turner: - height and GH response

- 2013 study (Blum et al, 75 pts)
  - Mean ht TS lower than SHOX pre GH tx
  - Ht SD score gain from start of tx to final ht similar (1.32-1.34) with same dose of GH

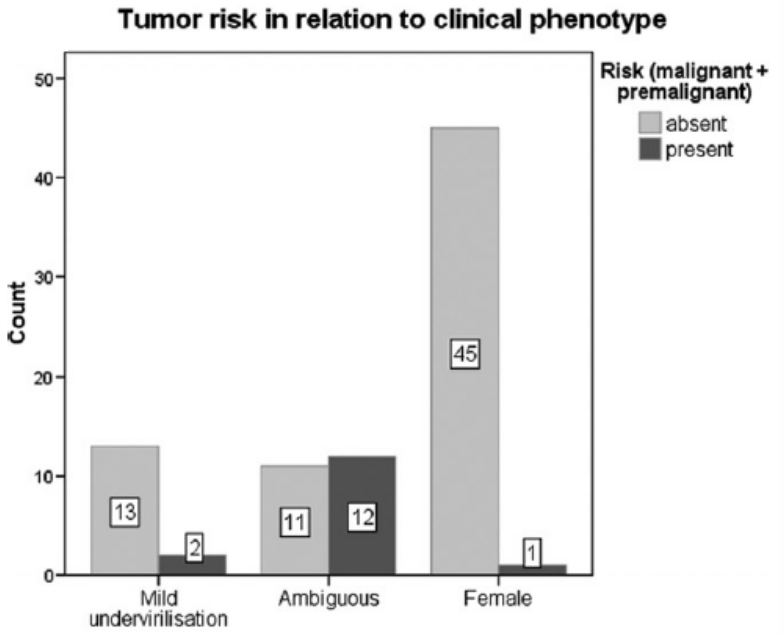
    → **Children with SHOX deficiency responded similarly to TS girls when treated with same GH dose**



Blum WF et al. JCEM 2013; 98(8): E1383-1392.

Gonadoblastoma risk in 45,X/46,XY girls

- Varying risks reported but usually accepted as 10-15%
- Related to testis-specific protein on Y (TSPY) gene?
- **Risk relates to phenotype?**
  - Cools et al (2011) suggest:
    - > 50% risk if ambiguous genitalia at birth
    - 2-3% risk if female phenotype
      - Low incidence testicular tissue
    - 18% unable to identify gonads (? apoptosis)



Cools M et al. JCEM 2011; 96(7): E1171-1180.

What does the literature say re gonadoblastoma risk and female phenotype?

Table 2
Series of Patients with Peripheral Blood Karyotype 45,X/46,XY and Turner Syndrome Phenotype Who Underwent Gonadectomy and Tumor Risk

Study	Number of Patients	Patients with Gonadal Tumors, n (%)
Gravholt et al (2000)[10]	7	1 (14)
Trobs et al (2004)[11]	4	1* (25)
Mazzanti et al (2005)[12]	10	2 (20)
Brant et al (2006)[13]	7	3 (43)
Cools et al (2011)[8]	23	1 (4)
Present study	8	4 (50)

* Dysgerminoma; remainder of gonadal tumors were gonadoblastomas.

Dendrinos ML et al. 2015. J Pediatr Adolesc Gynecol; 28:192-195.

Aims of study

- To evaluate growth hormone response in Turner girls (TS) and 45,X/46,XY females

- To explore gonadoblastoma risk in 45,X/46,XY females

Methods

- Ethics approval from SCHN Ethics Committee
- Audit of patient records and endocrine database over last 30 years
- Final height data using database or GHAC data
- Comparisons made between TS and 45,X/46,XY groups
  - Mann-Whitney U test
- Independent review of all histopathology

Study population

198 females aged ≤30 years with TS or mixed gonadal dysgenesis

51 Turner syndrome
(with final height available)

- 45,X (n=26)
- Mosaic without Y material (n=25)

19 45,X/46,XY females
(final height available in 10)

- 45,X/46,XY karyotype with TS phenotype (n=17)
- Other cytogenetic abnormalities (n=2)
  - isochromosome Yq
  - 45,XO/48,XYY +12

Presenting features

- All 45,X/46,XY patients assigned female gender of rearing
- Age at diagnosis from pre-natal to 13 years

PRESENTING FEATURE	NUMBER	AGE AT PRESENTATION
Atypical genitalia	8 • Clitoromegaly (8) • Labial fusion (2) • Absent or small uterus (5)	Birth-3yo
Short stature	8	3-13yo
Dysmorphic features of Turner syndrome	3	Birth-11yo
Incidental antenatal karyotype finding	3	Antenatal

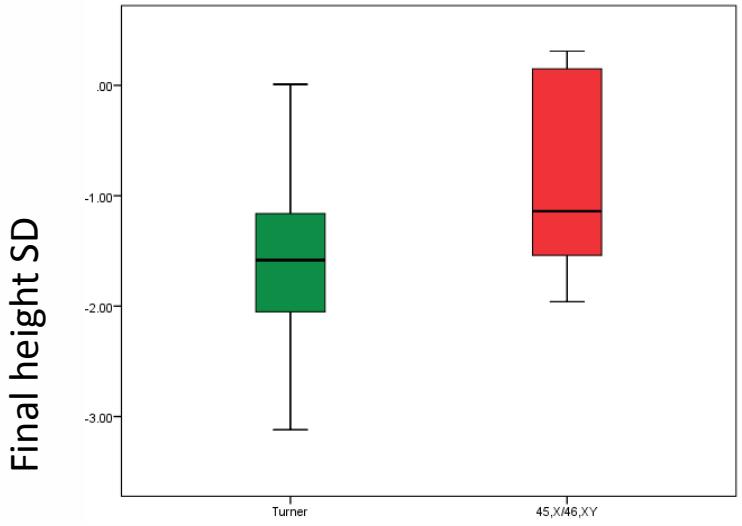
Baseline characteristics at GH commencement

	TOTAL GROUP N=198	TURNER SYNDROME N=50 (95% CI)	45,X/46,XY FEMALES N=10 (95% CI)	P value
Age (years)	9.1 (7.2 to 8.1)	8.1 (7.1 to 9.1)	7.7 (4.9 to 10.4)	0.37
Height SD	-2.4 (-2.6 to -2.2)	-2.5 (-2.7 to -2.2)	-2.3 (-2.8 to -1.9)	0.82
Mid-parental height SD	-0.14 (-0.4 to 0.1)	0.0 (-0.2 to 0.2)	-0.7 (-1.2 to -0.1)	**0.04**
GH dose (mg/m2/week)	7.1 (6.6 to 7.6)	7.1 (6.5 to 7.7)	7.0 (5.2 to 8.7)	0.59
Duration of growth hormone (years)	6.9 (5.9 to 7.9)	6.8 (5.8 to 7.8)	8.2 (4.6 to 11.7)	0.35

Height and growth hormone response

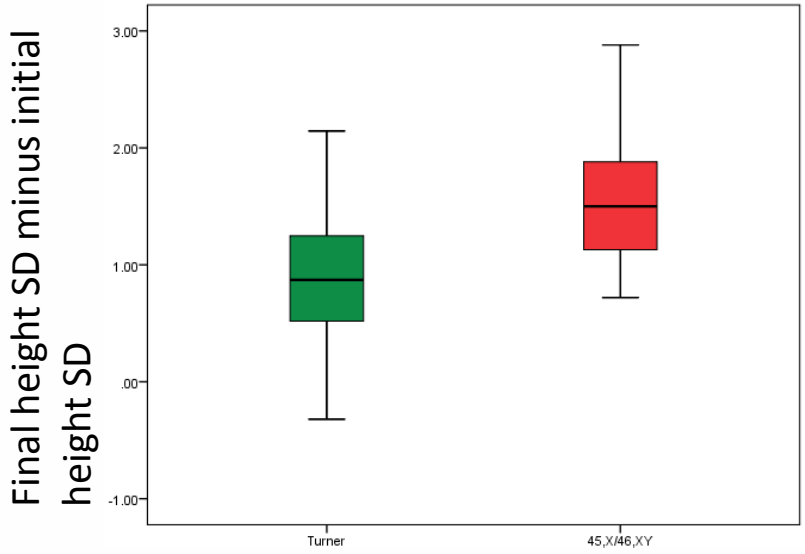
	TURNER SYNDROME N=50 (95% CI)	45,X/46,XY FEMALES N=9 (95% CI)	P value
Height SD at 12 months	-2.0 (-2.3 to -1.8)	-1.9 (-2.3 to -1.5)	0.95
Change in height SD at 12 months	0.4 (0.3 to 0.5)	0.4 (0.2 to 0.7)	0.81
Final height SD	-1.6 (-1.8 to -1.4)	-0.8 (-1.4 to -0.1)	**0.02**
Final height SD minus initial height SD	0.9 (0.7 to 1.0)	1.5 (1.1 to 2.0)	**0.01**
Final height SD minus MPH SD	-1.6 (-1.8 to - 1.4)	-0.3 (-1.3 to 0.7)	**<0.01**

Comparison of final height SD



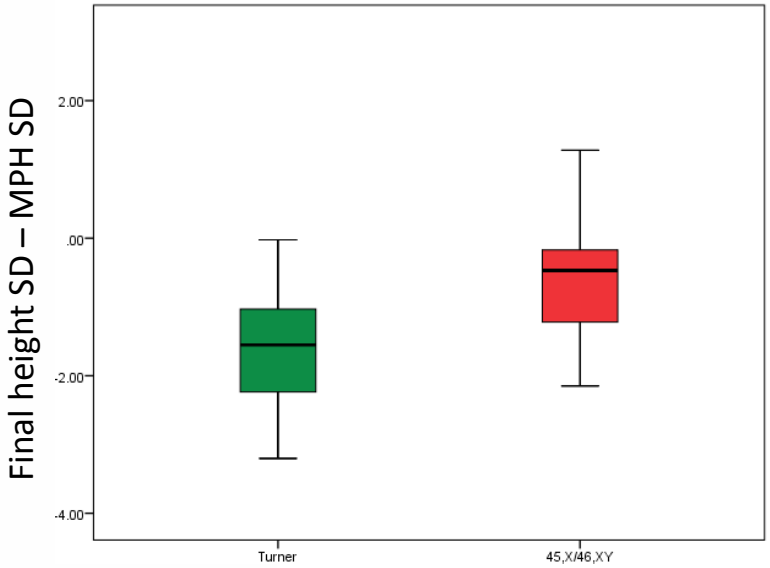
Turner vs 45,X/46,XY Females

Comparison of final minus initial height SD



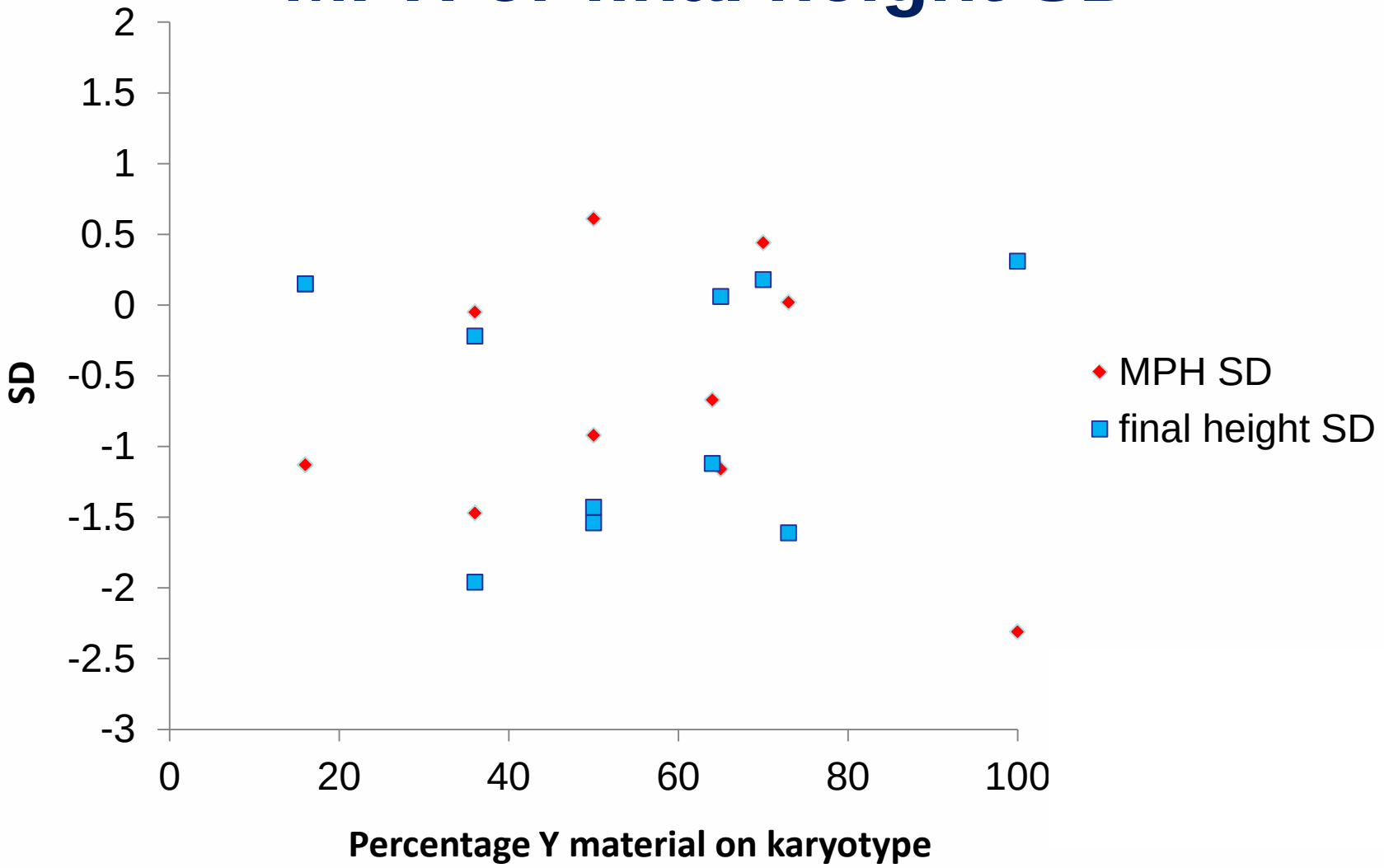
Turner vs 45,X/46,XY Females

Comparison to target height SD



Turner vs 45,X/46,XY Females

Percentage of Y material on karyotype is not associated with MPH or final height SD



Conclusions re growth

- 45,X/46,XY females respond better to growth hormone treatment over time than Turner girls

Study population for gonadal pathology analysis

- Across SCHN
- **19 45,X/46,XY females aged ≤30 years**
  - 45,X/46,XY karyotype with TS phenotype (n=17)
  - Other cytogenetic abnormalities (n=2)
    - » isochromosome Yq
    - » 45,XO/48,XYY +12

Gonadal differentiation in 45,X/46,XY girls (SCHN)

45,X/46,XY females (19 pts, 38 gonads)

Atypical genitalia at birth (n=8 patients, 42%)

8 pts (16 gonads) gonadectomy (at 1-34mo)

1/16 normal ovary
3/16 streak gonads
3/16 streak ovaries
5/16 ovotestis
4/16 testes

Y material 16-70%

Female phenotype at birth (n=11 patients, 58%)

11 pts (22 gonads) gonadectomy (at 1mo-14yo)

4/22 streak gonads
16/22 streak ovaries
2/22 ovotestis

Y material 12-100%

Genitalia appearance at birth is significantly associated with presence of testicular parenchyma (χ^2= 10.0, p<0.01)

Gonadoblastoma risk in 45,X/46,XY girls (SCHN)

45,X/46,XY females (19 pts, 38 gonads)

Atypical genitalia at birth (n=8 patients, 16 gonads)

1/16 ovary
3/16 streak gonads
3/16 streak ovaries
5/16 ovotestis
4/16 testes

3/16 gonads (18.8%) gonadoblastoma (2 definite, 1 equivocal)

1/3 gonads also Stage 1 dysgerminoma (2mo)

Female phenotype at birth (n=11 patients, 22 gonads)

4/22streak gonads
16/22 streak ovaries
2/22 ovotestis

11/22 gonads (50%) gonadoblastoma

3/9 gonads also Stage 1 dysgerminoma (11 and 13yo)

No significant association between genitalia appearance and gonadoblastoma risk (χ^2= 3.9, p=0.05)

No significant association between presence of testicular parenchyma and gonadoblastoma risk (χ^2= 0.6, p=0.4)

Gonadoblastoma risk in 45,X/46,XY girls (SCHN)

45,X/46,XY females (19 pts, 38 gonads)

Atypical genitalia at birth (n=8 patients, 42%)

cf. Cools 2011 study 37%

Female phenotype at birth (n=11 patients, 58%)

8 pts (16 gonads) gonadectomy (1-34mo)

1/16 ovary
3/16 streak gonads
3/16 streak ovaries
5/16 ovotestis
4/16 testes

Mean age gonadectomy 0.6yrs
cf. Cools 2011 2.2 yo

3/16 gonads (18.8%) gonadoblastoma

cf. Cools 2011 study 52% risk

1/3 gonads also Stage 1 dysgerminoma (2mo)

11 pts (22 gonads) gonadectomy (at 1mo-14yo)

4/22 streak gonads
16/22 streak ovaries
2/22 ovotestis

Mean age gonadectomy 7.3 yrs
cf. Cools 2011 12.2 yo

11/22 gonads (50%) gonadoblastoma

cf. Cools 2011 study 2.2% risk

3/9 gonads also Stage 1 dysgerminoma (11 and 13yo)

Conclusions

- Phenotype at birth or gonadal differentiation pattern is not associated with risk of gonadoblastoma

- Difficult to predict risk of gonadoblastoma in females with 45,X/46,XY karyotype
  - Recommendation for early gonadectomy in all girls

Future work

- Australia and NZ wide study looking at gonadal pathology in 45,X/46,XY females is currently underway

Acknowledgements

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- Dr Grahame Smith, Dr Kim Matthews
  - Urology and Gynaecology
- Dr Nicky Graf
  - Histopathology
- CHW Radiology, Histopathology Medical Records

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