



Genital anomalies and gonadoblastoma in females with WAGR syndrome

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WAGR syndrome

- A contiguous gene childhood cancer syndrome caused by interstitial deletion of the distal portion of chromosome 11p13
- Wilms tumor in ~40%: led to the localization of the WT1 gene at 11p13
- Aniridia (sporadic): Readily diagnosed in a neonate.
 - * 2/3 of all aniridia is AD due to PAX 6 gene mutation/deletions
- Genital anomalies in males
- Retardation of growth and development

Phenotype & Cytogenetics of WAGR

- This section could not be reproduced. It contains a picture of an aniridic eye, male genitalia and a picture of chromosome 11, specifically 11p13 with the distance between WT1 and PAX 6 of 700 kb

Genital anomalies/tumors in WAGR

- Wide range of external and internal genital anomalies in XY individuals, ranging from severe ambiguity with vagina/uterus prompting female gender assignment, to normal male.

- Male genital anomalies are hypothesized to be due to deletion of one *WT1* allele, as *WT1* regulates male gonadal & genital development.
- Gonadoblastomas are reported in XY females with intra-abdominal
- dysgenetic gonads – i.e. typical setting.

***What about genital development & tumors
in XX females with WAGR?***

- Virtually unknown – a few observations buried in case reports
- Literature regarding gonadoblastomas sometimes difficult to interpret because of inclusion of XY females

***Genital development & tumors
In 7 XX females with WAGR***

- This report will describe 7 individuals who have internal genital anomalies and/or tumors, in order to raise awareness of these findings in females and suggest pathogenetic mechanisms.
- 4 new cases from the WAGR network and 3 literature cases
- WAGR network: total 19 XX females, 10 with “Genital” anomalies, but details on these 4 only

***7 XX females with WAGR
External genitalia normal***

		gonads	menarche	menses	uterus	tumor
1	18 yo	streak	nl	irreg	nl	L luteal cyst
2	18 yo	small	nl	irreg	nl	
3	33 yo		nl		septate/dup vagina	
4	17 yo		nl		bicornuate	
5	21 mos autopsy	streaked gonads				
6	4 yo MRI	“absent” gonads		and	absent uterus	
7	22 yo	Small gonads			Hypopl/unicornuate	

7 XX females with WAGR

- 5/7 with small/streak /non imageable gonads
- 4/7 with uterine “absence” or fusion anomalies
- 1/7 with benign luteal cyst
- 1/7 with early-onset bilateral gonadoblastoma
- 2/5 post-pubertal patients with irregular menses
- 5/7 had Wilms tumor
- None had radiotherapy, which can cause ovarian failure

***Small, streak and/or non-detectable gonads are frequent
when looked for in WAGR:
a hypothesis for pathogenesis***

- High levels of *WT1* expression are observed in the developing genital ridges and fetal gonads and in mature gonads persist only in the Sertoli cells of the testis, and granulosa and epithelial cells in the ovaries.
- Perhaps haploinsufficiency of *WT1* leads to poor ovarian formation or maintenance.

Gonadoblastoma Pathology

- Gonadoblastoma is a rare ovarian tumor that is composed of primordial germ cells intimately mixed with sex chord elements that resemble Sertoli and granulosa cells. The tumor cells are surrounded by nests of ovarian stroma containing Leydig or lutein type-cells. In 50% of cases, there is overgrowth of germ cells with progression to dysgerminoma, the ovarian homologue of a seminoma of the testes.

Gonadoblastoma: X's and Y's

- Gonadoblastoma occurs almost exclusively in persons with gonadal dysgenesis associated with the presence of a Y chromosome or a Y fragment.

- There is a proposed gonadoblastoma locus on the Y chromosome (*GBY*). One candidate gene is *TSPY*.

Gonadoblastoma in WAGR

- All but one report are XY individuals with ambiguous genitalia and intra-abdominal dysgenetic gonads – the usual setting.
- The one 21 month old case died of post-measles pneumonia - the findings were incidental.
- Bilaterality and early age at onset suggests intrinsic predisposition to gonadoblastoma.
- The Gonads were streak, as reported in other XX WAGR individuals.

Gonadoblastoma in XX WAGR: Hypothesis

- Haploinsufficiency of *WT1* appears to cause not only small ovaries, but streak ovaries as well.
- Perhaps *TSPX* interacts with *WT1* such that *WT1* haploinsufficiency leads to *TSPX* dysfunction in cell cycle regulation or conversion to a *TSPY*-like function in promoting gonadoblastoma development.

Pathogenesis of uterine anomalies: Unknown, but there is an Association with Wilms tumor

- ~10% of girls with WT have uterine anomalies
- Population study of 2,065 women using pelvic u/s found 1/250 women had uterine anomaly
- Concluded that girls with WT are 22 times more likely to have uterine anomaly

- Small number, 1 WT patient had WAGR
- Recommended that all girls with WT have pelvic u/s after puberty
Byrne & Nicholson (2002)

Proposed medical recommendations for XX individuals with WAGR

- Bases on the occurrence of uterine anomalies, streak gonads and gonadoblastoma, screen WAGR females with periodic pelvic ultrasound or MRI.
- Consider gonadectomy if streak gonads are identified.
- Be aware that menstrual irregularities are common and provide anticipatory guidance.

Role of WT1 in gonadal development

- The complex role of WT1 in gonadal development is far from being understood and a number of gene targets for WT1 have been suggested, including the sex determining gene SRY and steroidogenic factor 1 (Sf1)

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