Prediction of germ cell cancer occurrence in postpubertal individuals with androgen insensitivity based on pathological findings and cancer predisposition SNPs

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1. Introduction

Gonadectomy is generally postponed until early adulthood in complete androgen insensitivity syndrome (CAIS) and close surveillance of gonads *in situ* proposed in males with partial AIS (PAIS). Delaying gonadectomy (further) is controversial given the lack of data regarding germ cell cancer (GCC) development in adulthood and the absence of biomarkers for noninvasive GCC screening.

2. Aims and Objectives

To study the prevalence of GCC, carcinoma *in situ* (CIS), or signs of pre-malignancy (combined aberrant OCT3/4 and KITLG expression) in genetically confirmed AIS cases at a (post)pubertal age and study the correlation with a genetic predisposition for GCC based on allele profiling of 14 GCC-associated SNPs.

3. Methods

Immunohistochemical study of 97 samples (CAIS: 73 gonadectomy, 7 biopsy; PAIS: 10 gonadectomy, 7 biopsy). All surgical procedures were performed at or after the age of 14 years (median 17.5, range 14-54), either prophylactically or in case of suspicion of a mass. Allele sequencing of 14 GCC-associated SNPs was performed in 33/52 cases.

Gene	SNP ID	per allele OR (95% CI)	
		non-risk/risk allele	non-risk/risk allele
TERT	rs2736100	1,35	G/T
DMRT1	rs755383	1,49	C/T
KITLG	rs995030	2,69	A/G
ATF7IP	rs2900333	1,23	T/C
SPRY4	rs4624820	1,47	G/A
HPGDS	rs17021463	1,19	G/T
PPM1E	rs7221274	1,2	G/A
RFWD3	rs4888262	1,26	T/C
TEX14	rs9905704	1,27	G/T
MAD1L1	rs12699477	1,21	T/C
KITLG	rs1508595	2,56	T/C
UCK2	rs4657482	1,31	G/A
CENPE	rs4699052	1,27	T/C
KITLG (p53bs)	rs4590952		A/G

$$RR = \Sigma_{1\text{-}13}\, p_i G_i \, X \, OR_i$$

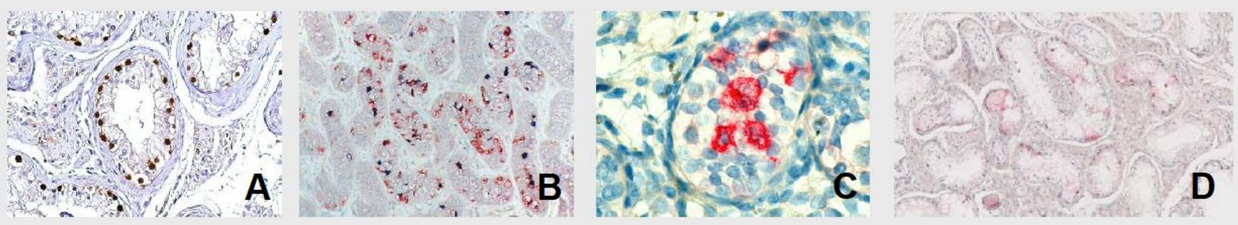


***Figure 1**: Invasive GCC / CIS (A, D) / pre-CIS (B) / maturation delay (C) of germ cells, based on HE, OCT3/4, TSPY and KITLG staining*

4. Results

CAIS	PAIS
No GCC or CIS	No invasive GCC
Premalignant changes in 9/80 samples **(11.25%)**	CIS in 1/17 samples **(5.9%)**
Premalignant changes in 6/42 women **(14.2%)**	CIS in 1/10 individuals **(10%)**
Mean age 17.5 years (14 – 21)	15 years

Preliminary SNP analysis in 33 patients (4/6 GCC cases): RR differs significantly in GCC versus no GCC cases (p 0.01) (Mann Whitney U)

***Figure 2: Relevant staining results**. A-D: CIS in 15y old PAIS case. A: TSPY; B: OCT3/4; C: OCT3/4-TSPY; D: KITLG. E-G: pre-CIS in 14y old CAIS case. E: TSPY; F: OCT3/4; G: KITLG.*

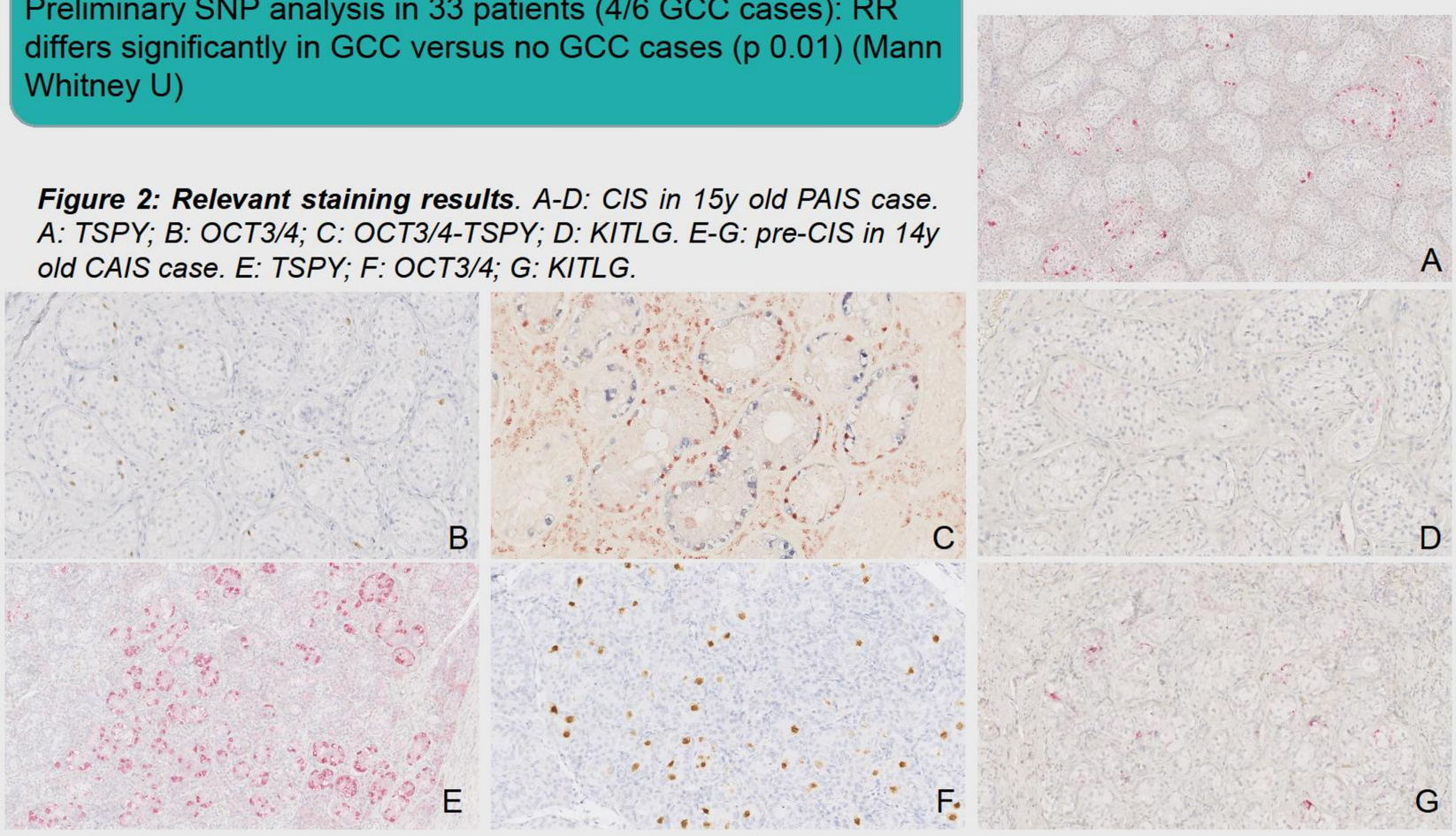
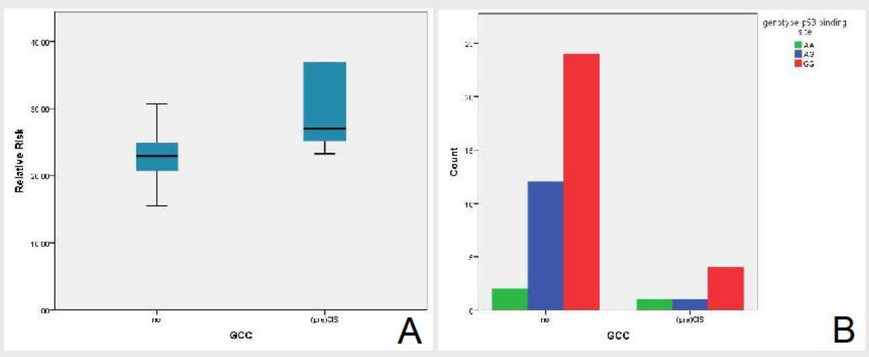


***Figure 3:** A: Box-plot of RR in GCC and no GCC cases.*

*B: Genotype frequencies of the KITLG p53 binding site (*rs4590952) in GCC and no GCC cases.



5. Conclusions

The **prevalence** of premalignant lesions in CAIS women in this cohort was **14%.** Lesions are already present during adolescence and often bilateral. No prospective data exist regarding progression of such lesions to GCC, however, available evidence suggests that malignant progression will only occur in a minority. A comparable prevalence of (pre)CIS was seen in PAIS, with possibly a higher risk of malignant progression given the residual AR activity. Preliminary data suggest a significantly higher risk of (pre)malignancy in individuals with a **genetic susceptibility** for GCC. This study represents the first step towards a **genomics based individualized management** of DSD patients.

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