Isolated persistent pubertal gynecomastia in three adolescent males as the only phenotypic expression of PAIS with androgen receptor gene mutations

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Background:
Pubertal gynecomastia is observed during pubertal period in up to 65% of adolescent males. It is usually idiopathic and tends to regress within 1 to 2 years, although sometimes pubertal gynecomastia persists. Its pathogenesis is not known, but a frequent evoqued mechanism of glandular breast tissue is the result of transient imbalance in testosterone and estradiol ratio. Most of time, pubertal gynaecomastia disappears within 6 to 12 months. In adolescent boys with persistant gynaecomastia, other clinical findings such as body proportions, testicular size and hormonal pattern should orientate additional diagnostic explorations (Klinefelter syndrome, Kennedy's disease or PAIS).

Case Presentation and Methods
We investigated three adolescent males with isolated persistent pubertal gynecomastia: twin brothers and an unrelated adolescent boy. The twins (17 yrs) had normal male external genitalia. Biological testing showed normal testosterone concentration (4.1 and 3.8 ng/ml, respectively) and normal response to the HCG stimulation test (10.3 and 13 ng/ml, respectively). The gonadotropin level was normal. Spermatogenesis investigations revealed azoospermia in one of the brothers and oligospermia in the other. The third adolescent boy (16 yrs) presented normal male external genitalia. Biological investigations showed normal testosterone level (3.6 ng/ml) and no other sign of alteration. No evidence of spermatogenesis failure was documented.
Direct sequencing has been performed using DNA extracted from peripheral blood leucocytes.

Results
For the twins, genetic analysis of the AR gene revealed a c.1937C>A mutation in the hinge region leading to a substitution of an alanine by aspartic acid: p.Ala646Asp. This mutation was transmitted by their mother. She presented no sign other than very sparse pubic hair. The molecular impact of this mutation has been shown to be closely related to the Exon 1 polymorphic regions [1]. We thus analyzed the two length polymorphism regions in the exon 1 of AR gene. The poly(Gln) region was 25 Glutamine long while the poly(Gly) was only 10 Glycine long. This result is in accordance with the aggravation of p.Ala646Asp mutation functional impact in the context of long Poly(Gln) and short poly(Gly) For the third adolescent, genetic analysis of the AR gene identified the c.134C>G substitution resulting in a p.Ala45Gly change in amino acid. This mutation was transmitted by his mother. The maternal family history revealed a first cousin with bilateral mastectomy for persistent and prominent bilateral gynecomastia.

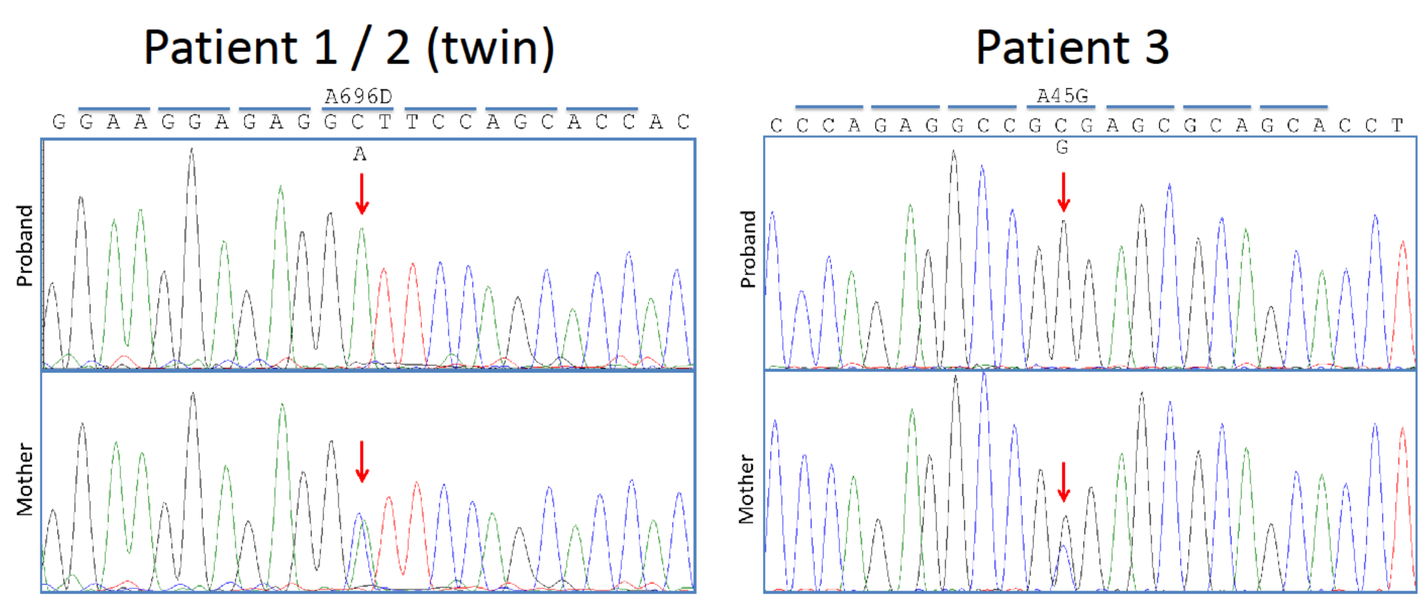

Figure: AR gene sequences for proband and their mothers.

	Twin Brother 1		Twin Brother 2		Third Patient
Biological parameters	Basal	After HCG test	Basal	After HCG test	Basal
Testosterone (ng/ml)	4.05	10.28	3.76	13.03	3.6
FSH (UI/L)	1.2	0.2	2.2	0.5	1.6
LH (UI/L)	3.4	1.2	5	1.7	2.8
Estradiol (pg/ml)	18	63	22	107	ND
Prolactine (µg/L)	16.4	21.9	16.4	34.1	ND
Progesterone (µg/L)	0.7	0.5	0.4	0.3	ND
D4-androstenedione (ng/ml)	2.8	3.4	2.9	3.5	ND
DHEA-Sulfate (µmol/L)	9.34	10.55	4.4	5.66	ND
17-OH-progesterone (ng/ml)	2.2	2.2	1.4	2.17	1.9

Table. Hormonal and clinical features of the 3 persistent gynecomastia patients.

Conclusions
These data suggest that isolated persistent pubertal gynecomastia should be investigated to identify a possible defect of the AR gene.

References
1 – Werner R., Holterhus PM et al. The A645D Mutation in the hinge region of the human androgen receptor (AR) gene modulates AR activity, depending on the context of the polymorphic Glutamine and Glycine repeats. JCEM. 2006. 91 (9):3515-3520

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