Precocious/early and accelerated puberty in a boy with a homozygous R192C mutation in *CYP19* (aromatase) gene

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Introduction

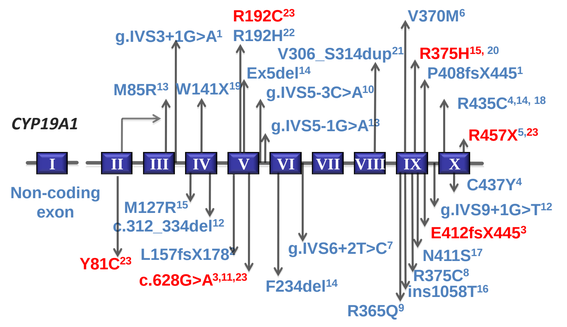
Aromatase deficiency is a rare autosomal recessive disorder produced by ***CYP19*** gene mutations. This enzyme is essential for the biosynthesis of estrogens from androgen precursors. The biological relevance of this enzyme is not only related to its role in estrogen biosynthesis, but also to its potential influence on the androgen-estrogen ratio in different tissues (1)

Disordered sexual development (DSD) has been reported in 46,XX affected patients. In these girls, a resetting of central gonadotropin feedback resulting in moderate-high increases of serum FSH, and occasionally mild increments in serum LH has been reported (1-3).

Most 46XY affected patients presented with normal external genitalia and the condition often remains undiagnosed until late puberty. In adult affected males,. slight increment of basal serum FSH (and in some cases also basal serum LH) despite normal or even high serum testosterone and normal inhibin B levels were reported. These findings support the important role of estrogens either from peripheral origen or locally synthesized on the regulation of gonadotropin secretion (3-5)

There is scarce information about clinical and biochemical findings in affected boys during prepubertal and pubertal years, since only 2 patients, younger than 4 ys of age, without a long-term follow-up, have been reported (6-7).

Reported mutations in the human *CYP19 (cP450arom)* gene are featured in this schematic representation



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[22]Bouchoucha et al. (2014)
[23]Marino et al (2014)

Argentinian origen

AIM

We report the clinical phenotype and hormonal studies of a 46,XY aromatase deficient boy

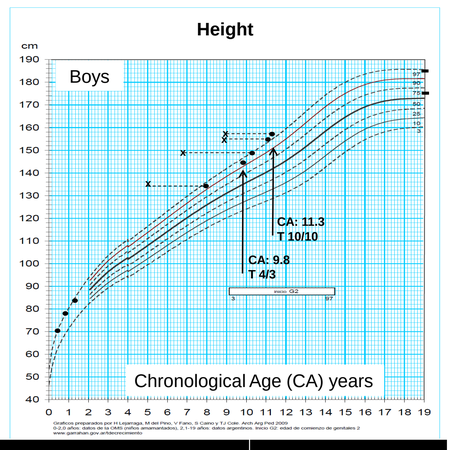
Clinical Material

The patient is the older brother of a 46,XX affected sister (2). Maternal virilisation was present during both pregnancies.

Coding exons of the *CYP19* gene and the flanking intronic regions were PCR amplified from patient, parents and control cDNA.

Results

Chronological age (years)	7.9	9.8	11.3
Bone age (G&P)	5		9
Height (cm)	134.2	144.5	157.5
SDS	1.63	1.51	2.38
Weight (kg)	28.3	31	46.5
SDS	0.95	0.95	0.95
BMI (kg/m2)	15.7	14.8	18.7
SDS	-0.03	-1.00	0.98
Tanner stage (TS)			
G	I	I	IV
PH	I	I	III
Testicular volume	2/2	4/3	10/10



Chronogogical Age	8 years			Normal basal RV (8 ys)	11.3 ys		Normal basal RV(TS IV)
Condition	Basal	LHRH test	After hCG		Basal	LHRH test	
LH (MIU/ml)	<0.10	<0.10 / 0.83 / 1.14		0.13 ± 0.32	3.8	3.8 /17.2/ 18.9	0.79 ± 0.99
FSH (MIU/ml)	0.47	0.82 / 2.14 / 4.08		1.10 ± 0.82	2.8	2.8 /3.9 / 4.7	2.26 ± 0.96
Testosterone (ng/ml)	<0.05	<0.05	2.94	<0.30 / 1.5	5.99		1.05-5.45
Androstenedione (ng/ml)	<0.10	0.18	1.31	0.05 – 0.55	1.20		0.2-1.03
Estradiol (pg/ml)	< 9	< 9	< 9		<9		
SDHEA (ng/ml)	331	319	452	45-530	808		610-1390
AMH (pmol/l)	829			350-1885	104.9		45-225
Inhibin B (pg/ml)	90.7			30-150	369.7		90-290

OGTT / Time (min)	0	30	60	90	120
Glucose (mg/dl)	76	136	108	99	94
Insulin (IU/ml)	4.3	53.8	22.7	14.5	15.1

Bone Mineral Density (DXA)	L2-L4	Whole body
g/cm^2(Z score)	0.64 (0.53)	0.53 (0.09)

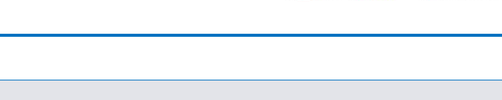
RV: reference values, TS IV, Tanner stage IV

Laboratory tests at 8 ys of age showed normal prepubertal basal serum gonadotropin (including an adequate GnRH stimulation test), inhibin B, AMH, testosterone and androstendione levels. OGTT was normal as well as bone mass, assessed by DEXA.

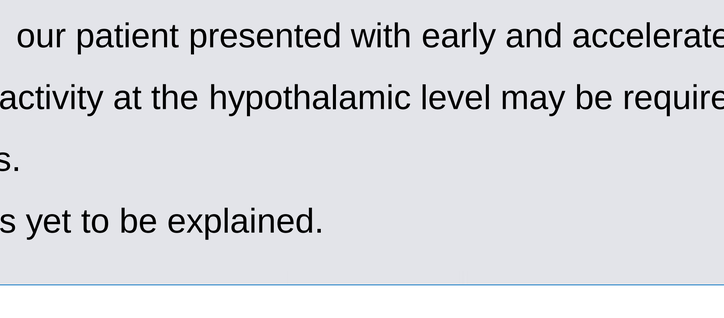
Laboratory tests at 11.3 ys of age revealed normal pubertal basal and GnRH stimulated gonadotropin levels and increased serum testosterone and inhibin B levels

Molecular studies

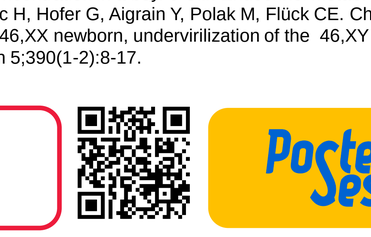
Pedigree of the family



Schematic representation of the genomic structure of the *CYP19A1* gene showing the C-to-T transition in exon 5



Sequence alignment: mutated arginine at position 192 is highly conserved in homologues of P450arom from many species analyzed.



Discussion

Normal pubertal development has been assumed in adult men with aromatase deficiency. Estrogen restrain on gonadotropin secretion has been demonstrated in animal and human models of estrogen deficiency acting from the early phases of puberty in males. Interestingly, our patient presented with early and accelerated puberty and apparently normal pituitary gonadal function. This human model of nature suggests that aromatase activity at the hypothalamic level may be required to define pubertal tempo and/or the time of puberty onset in boys.

The presence of increased basal inhibin B levels in this aromatase deficient patient is yet to be explained.

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DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS 10-12 SEPTEMBER