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LETTER TO THE EDITOR

Five-alpha-reductase type 2 deficiency in Spain

Déficit de 5-alfa-reductasa tipo 2 en España

Dear Editor,

We have read the scientific letter "5-alpha-reductase type 2 deficiency. A new case in the Spanish population".[1]

In the letter, the authors present a new case of 5-alpha-reductase type 2 deficiency, clinically, biochemically and molecularly diagnosed in Spain, in a person with karyotype 46,XY who, unlike other cases diagnosed at pubertal age, has maintained a female gender assigned at birth. It is very interesting to be able to have a record of the diagnoses molecularly confirmed in people with "different sexual development" (DSD), as they are included within the so-called "rare diseases". In this case, the authors have detected the previously described homozygous mutation c.271T>G/p.Tyr91Asp in the *SRD5A2* gene. The parents were carriers and the family came from Almeria.

We were surprised to read that, according to the authors, it is the first case of Spanish origin reported with a molecular diagnosis, with only one previous clinical and biochemical diagnosis reported in 1995.[2]

We should clarify that, since it became possible for us to reach a molecular diagnosis, we have tried to confirm the clinical and biochemical diagnoses of patients with DSD and karyotype 46,XY molecularly. Among these, we were able to confirm the diagnoses of 5-alpha-reductase type 2 deficiency in patients studied at various hospitals in Spain, most of whom were born in our country, as well as in families of Spanish origin. Two patient studies were published as individual cases in 2004,[3,4] and a total of 10 case studies (eight new patients) were published in 2011.[5]

The first published case was that of a patient[3] who was a compound heterozygous carrier of the mutations (hereinafter referred to as 'variants') c.344G>A/p.Gly115Asp and c.736C>T/p.Arg246Trp (NM_000348.4), with the mother, originally from Granada, being a carrier of c.344G>A/p.Gly115Asp, and the father, originating from Trieste, Italy, being a carrier of c.736C>T/p.Arg246Trp. Both variants had been described in other non-Spanish populations. The second patient[4] was an adopted girl of Chinese origin, who was a compound heterozygous carrier of c.680G>A/p.Arg227Glu and c.656del/p.Phe219SerfsTer60, with the c.680G>A/p.Arg227Glu variant having been reported in Asia, while the c.656del/p.Phe219SerfsTer60 variant was new.

In the studies of the eight (8) new patients (two of them sisters) published in 2011,[5] six (6) variants were presented, and the frequency of two (2) *SRD5A2* gene polymorphisms in the ten (10) patients with 5-alpha-reductase type 2 deficiency was also analysed and compared with patients with 46,XY DSD without a molecular diagnosis, or with a molecular diagnosis in other genes and in normal controls with 46,XY karyotype.

These eight (8) new patients were born in Spain and had parents of Spanish origin (except one father of Italian origin). The most commonly detected variant was c.377A>G/p.Glu126Arg (previously reported) in six (6) patients: homozygous in two sisters from Granada and in another non-related girl; heterozygous combined with c.578A>G/p.Asn193Ser in a girl from Lleida, and with c.620C>A/p.Ala207Asp in a boy studied in Málaga (with carrier parents), while it was the only variant detected in a boy from Madrid, born very premature and with low weight, but homozygous for the combination of the two polymorphisms in *SRD5A2*. The other two patients were compound heterozygotes: one for c.344G>A/p.Gly115Asp and c.513G>C/p.Arg171Ser (born in Mallorca, whose mother, of Spanish origin, was a carrier of c.344G>A/p.Gly115Asp, and father, of Italian origin, was a carrier of c.513G>C/p.Arg171Ser), and the other for c.271T>G/p.Tyr91Asp and c.563_564del/p.Tyr188CysfsTer9 (born in Valencia, whose mother was a carrier of c.271T>G/p.Tyr91Asp and the father was a carrier of c.563_564del/p.Tyr188CysfsTer9). It is interesting to note that the c.271T>G/p.Tyr91Asp variant detected in this last mother and daughter from Valencia is the one that has just been reported as homozygous by the authors of the scientific letter[1] in a patient from Almeria.

In summary, the variant in *SRD5A2* c.271T>G/p.Tyr91Asp recently reported in Spain[1] and previously reported in other populations had already been previously reported in Spain.[5] All the sporadic variants in *SRD5A2* that predict an amino acid change that we have detected in Spain have also been described in other populations, with the c.377A>G/p.Glu126Arg variant being prevalent in Spanish patients without common family origins. Among the variants reported in ten (10) patients, only two (2) nonsense variants were new: c.656del/p.Phe219SerfsTer60 in a patient of Chinese origin[4,5] and c.563_564del/p.Tyr188CysfsTer9 in a patient and her father from Valencia.[5]

All the variants in *SRD5A2*[3–5] that we have reported are recognised in the genomic databases (The Human Gene Mutation Database [HGMD®]), in which our publications on previously unreported variants are referenced.[4,5] For this reason, it is essential to refer to them when analysing new patients in order to obtain a correct description of the incidence and distribution of molecular diagnoses.

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Mónica Fernández-Cancio[a,b], Laura Audí[c,*], Diego Yeste[b,c,d]

[a] *Grupo de Investigación sobre Crecimiento y Desarrollo, Instituto de Investigación Vall d'Hebron, Hospital Universitario Vall d'Hebron, Barcelona, Spain*
[b] *CIBER de Enfermedades Raras (CIBERER), Instituto de Salud Carlos III (ISCIII), Madrid, Spain*
[c] *Sección de Endocrinología Pediátrica, Hospital Universitario Vall d'Hebron, Barcelona, Spain*
[d] *Universidad Autónoma de Barcelona, Barcelona, Spain*

* Corresponding author.
E-mail address: 6620lap@gmail.com (L. Audí)
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