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Novel (60%) and Recurrent (40%) Androgen Receptor Gene Mutations in a Series of 59 Patients with a 46,XY Disorder of Sex Development

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Background: Androgen receptor (AR) gene mutations are the most frequent cause of 46,XY disorders of sex development (DSD) and are associated with a variety of phenotypes, ranging from phenotypic women [complete androgen insensitivity syndrome (CAIS)] to milder degrees of undervirilization (partial form or PAIS) or men with only infertility (mild form or MAIS).

Objective: The aim of the study was to characterize the contribution of the AR gene to the molecular cause of 46,XY DSD in a series of Spanish patients.

Setting: We studied a series of 133 index patients with 46,XY DSD in whom gonads were differentiated as testes, with phenotypes including varying degrees of undervirilization, and in whom the AR gene was the first candidate for a molecular analysis.

Methods: The AR gene was sequenced (exons 1 to 8 with intronic flanking regions) in all patients and in family members of 61% of AR-mutated gene patients.

Results: AR gene mutations were found in 59 individuals (44.4% of index patients), of whom 46 (78%) were CAIS and 13 (22%) PAIS. Fifty-seven different mutations were found: 21.0% located in exon 1, 15.8% in exons 2 and 3, 57.9% in exons 4–8, and 5.3% intronic. Twenty-three mutations (40.4%) had been previously described and 34 (59.6%) were novel.

Conclusions: AR gene mutation is the most frequent cause of 46,XY DSD, with a clearly higher frequency in the complete phenotype. Mutations spread along the whole coding sequence, including exon 1. This series shows that 60% of mutations detected during the period 2002–2009 were novel.

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