Identification of a Novel Androgen Receptor Mutation in a Family With Multiple Components Compatible With the Testicular Dysgenesis Syndrome

Context: Androgen signaling via the androgen receptor (AR) is essential for normal testis development and male reproductive functions. We describe a rare family with 3 males affected by a mild disorder of sex determination compatible with testicular dysgenesis syndrome (TDS), including subfertility, cryptorchidism, hypospadias, and testicular cancer, caused by a novel AR mutation. The aim of this study was to describe the phenotype of the affected males, characterize functionally the novel AR mutation, and discuss the significance of partial androgen insufficiency in the pathogenesis of TDS.

Participants: The proband, his first cousin, and a nephew underwent a detailed clinical investigation including genetic tests, whereas four female members of the family were tested for the specific AR mutation. Results: A novel AR mutation, c.2214T>G;p.Ile738Met, was identified in the affected family members. Functional analysis of the mutation in a gene-reporter assay showed a 50% reduction in AR-induced transcriptional activity. The affected males had elevated LH and T in accordance with decreased AR signaling. The histology and immunohistochemical profile of the testis tissue from the 2 patients with testicular cancer showed features consistent with insufficient testis development and TDS.

Conclusion: The presence of all hallmarks of TDS, including germ cell cancer, in a family with a novel AR mutation causing a partial decrease in AR function is in line with the concept that reduced androgen signaling may contribute to the development of TDS. It also seems consistent with the hypothesis that environmental factors interfering with this pathway can play a role in the pathogenesis of TDS.