Functional Impact of Novel Androgen Receptor Mutations on the Clinical Manifestation of Androgen Insensitivity Syndrome

Abstract
Androgens are responsible for the development and maintenance of male sex characteristics. Dysfunctions in androgen action due to mutations in the androgen receptor gene (AR) can lead to androgen insensitivity syndrome (AIS) that can be classified as mild (MAIS), partial (PAIS), or complete (CAIS). We have analyzed functional effects of p.Ser760Thr, p.Leu831Phe, p.Ile899Phe, p.Leu769Val, and p.Pro905Arg mutations and the combination p.Gln799Glu + p.Cys807Phe that were identified in patients with PAIS or CAIS. The p.Leu769Val and p.Pro905Arg mutations showed complete disruption of AR action under physiological hormone concentrations; however, they differed in high DHT concentrations especially in the N/C terminal interaction assay. Mutations p.Ser760Thr, p.Leu831Phe, p.Ile899Phe presented transactivation activities higher than 20% of the wild type in physiological hormone concentrations and increased with higher DHT concentrations. However, each one showed a different profile in the N/C interaction assay. When p.Gln799Glu and p.Cys807Phe were analyzed in combination, transactivation activities <10% in physiologic hormone conditions indicated an association with a CAIS phenotype. We conclude that the functional analysis elucidated the role of mutant ARs, giving clues for the molecular mechanisms associated with different clinical AIS manifestations. Differences in hormone-dependent profiles may provide a basis for the response to treatment in each particular case. (C) 2017 S. Karger AG, Basel (AU)