Functional and structural analysis of R607Q and R608K androgen receptor substitutions associated with male breast cancer.

Poujol N, Lobaccaro JM, Chiche L, Lumbroso S, Sultan C.

Institut National de la Sante et de la Recherche Medicale, INSERM U439, Pathologie Moleculaire des Recepteurs Nucleaires, Montpellier, France.

We previously described an androgen receptor (AR) point mutation located in the DNA-binding domain (DBD), adjacent to another AR substitution. Both were observed in two unrelated families with male breast cancer (MBC) and partial androgen insensitivity syndrome. This work was designed to determine the potential role of these two residues by in vitro study of the consequences of these two substitutions on biological functions and their structural impact at the atomic level. Mutant ARs revealed normal androgen-binding affinities and weaker DNA binding to an isolated androgen-responsive element. In cotransfection assays the mutant ARs displayed a reduced transactivation efficiency at 0.3 x 10(-10) M. Neither binding to an estrogen-responsive element nor transactivation efficiency of an ERE reporter gene was observed. Molecular modeling revealed that Arg607 and Arg608 were partially surface-exposed and located in adjacent areas in the AR-DBD complex with DNA. This is in favor of a protein-protein interaction. It is conceivable that such an interaction could be affected by mutation of one of these twoarginies.

PMID: 9220020 [PubMed - indexed for MEDLINE]