this mutation are discussed along with response to high dose testosterone in three cases of MAIS across a six-generation family pedigree with a missense AR exon 8 mutation (nucleotide **a**ga --> **g**ga, p. R872G arginine to glycine). All three cases of MAIS displayed consistent gynaecomastia and micropenis but variable fertility. High dose testosterone treatment for 3 years in one young man caused increased virilisation and height growth but was ineffective for micropenis. Genetic counselling allowed for effective prediction of MAIS risks in progeny for carrier and non-carrier sisters. This AR mutation, previously shown to display increased ligand dissociation rate from the mutated AR in binding assays, was shown by *in silico* structural modelling to demonstrate weakened closure energy of the "lid" of the ligand binding pocket allowing for easier ligand dissociation from binding site. An *in vitro* yeast-based androgen bioassay demonstrated unimpaired androgen bioactivity. **Conclusion:** The molecular mechanism of the p. R8729G mutation in exon 8 of the AR ligand binding domain demonstrated increased ligand dissociation from its binding site due to weakened closure of the binding pocket "lid" but without impact on androgen bioactivity. This novel molecular mechanism may be present in other cases of MAIS. Discrepancy between MAIS genotype and phenotype in those carrying the same AR mutation is known and may be present within our cohort.

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Molecular Mechanism of Androgen Receptor Mutation in Multigenerational Mild Androgen Insensitivity Syndrome

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Objective Androgen insensitivity syndrome (AIS) due to androgen receptor (AR) mutations create a spectrum of clinical presentations based on residual AR function. The mildest impairment of this condition is known as mild AIS (MAIS), whose undefined molecular mechanism and subtle clinical features leave it little understood and underdiagnosed. **Methods and Result** The clinical features of