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Disrupting DNA-binding Domain Dimerization In The Androgen Receptor In Mice Results In a Partial Androgen Insensitivity Model

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The androgen receptor (AR) plays a crucial role in the development and maintenance of the male phenotype, as shown in patients with androgen insensitivity syndrome (AIS). The AR is a nuclear receptor that needs to homodimerize to execute its role as transcription factor. Dimerization can occur through three different modes: via the DNA-binding domain (DBD), via the ligand-binding domain and via an interaction between the LBD and the aminoterminal domain. Dimerization via the DBD is very well known and occurs through the D-box located in the second zinc finger. DBD dimerization is generally accepted for all steroid receptors, but some of them show that D-box mutations do not inactivate them completely. However, for the AR, no monomeric transactivation capacity was described yet. To study the role of D-box independent activity of the AR, we introduced a double point mutation in the D-box that is predicted to disrupt DBD dimerization (ARDmon). These two point mutations were found in separate patients suffering from partial AIS. In vitro studies with this mutant suggest that the remaining activity depends on the androgen response element under investigation. We show that ligand binding was not affected by the D-box mutation. Furthermore, BioID assays indicated no

changes in coregulatory interactions. When introducing the corresponding mutation in mice, this led to a phenotype that is intermediate between global ARKO and wild type (WT) males. Based on their anogenital distance (AGD) and the absence of nipples at early age, the ARDmon/Y mice were identified as males. Follow-up of their AGD and body weight, however, revealed clear differences with both WT males and females. Furthermore, hypospadias was observed in the ARDmon/Y mice. Testes were smaller in size compared to the WT males and first analysis showed almost no expression of well-known AR regulated genes. Reminiscent structures of the epididymis were found.

In summary, the ARDmon mouse model shows an intermediate AIS phenotype. Via orchidectomy in combination with androgen replacement therapy, we will now investigate remaining androgen responses in the ARDmon/Y mice and elucidate response elements on which the AR can act in a D-box independent way. Additionally, we generated the first rodent PAIS model with a genetic cause of hypospadias.

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