Steroidogenic factor-1 (NR5A1): orphan nuclear receptor finds a home in human reproduction, and beyond

John C. Achermann

Genetics and Genomic Medicine Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, University College London, London WC1N 1EH, United Kingdom

The quest to discover a “master-regulator” of adrenal and reproductive function began in the late 1980s, when it became apparent that specific transcription factors often played key roles in the development and function of different organs. Subsequently, the research groups of Keith Parker and Ken-ichirou Morohashi independently cloned a nuclear receptor transcription factor that could have this master-regulator role, which was termed steroidogenic factor-1 (SF-1, also known as Ad4BP/FTZ-F1 and officially as NR5A1/NR5A1).

SF-1 is an “orphan” nuclear receptor (with no high-affinity ligand) that promotes the transcription of an array of different genes involved in endocrine development, steroidogenesis and metabolism. The generation of a knockout mouse model of Nr5a1 in 1994, which had impaired adrenal and gonad development and brain ventromedial hypothalamic (VMH) anomalies, soon provided conclusive proof that SF-1 was indeed an essential player in endocrine biology.

The next goal was to establish whether biologically important variants in SF-1/NR5A1 occurred in humans. Initial efforts understandably focussed on individuals with a similar phenotype to the mouse model; namely, primary adrenal insufficiency and complete gonadal (testicular) dysgenesis. This combination of clinical features is very uncommon, but a heterozygous change in individuals with a wider range of features is very uncommon, but a heterozygous change in...
developmental networks or in situations where pheno-
typic penetrance is variable.

Finally, from a developmental biology perspective, SF1Next really highlights the major role that SF-1/NR5A1 plays in human reproductive development, function and related conditions. Along with the androgen receptor (AR/NR3C4) and DAX-1/NR0B1, SF-1/NR5A1 is one of the most common nuclear receptor-related conditions in humans, with a large number of different variants and wide spectrum of clinical features emerging.8

This work also highlights future challenges and questions. Long-term follow up will be needed to establish: if there is any risk of adrenal insufficiency with age, or under stress; what the gonadal tumour risk might be; how likely ovarian dysfunction is with time in 46,XX individuals who harbour SF-1/NR5A1 variants; and whether assisted reproductive strategies have a role. Genetic counselling can be difficult, especially in the context of variable penetrance and – now – potential oligogenic effects in some situations. The American College of Medical Genetics and Genomics (ACMG) criteria for defining pathogenicity can be challenging in these contexts. This may be particularly true when the effects of SF-1 disruption may be “locked” in a dosage sensitive developmental time window, or influenced by other hard-
to-define mechanisms such as skewed allelic expression.

Despite these challenges, SF1Next clearly serves to further establish SF-1-associated conditions as a major entity, 25 years after the first report of a pathogenic variant in humans. We look forward to what the (SF1) next 25 years of clinical and basic research will bring.

Contributors
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