

A SHARED BIOLOGY: SEX DETERMINATION AND THE ADRENAL GLAND

Background

The adrenal gland and gonads have a common embryonic origin, and so many aspects of their development and regulation are shared. Likewise, disorders of the two systems are often, though not always, interlinked. For example, the nuclear receptor transcription factor steroidogenic factor-1 (SF-1) is a key regulator of both adrenal development and sex determination; mice lacking SF-1 have no adrenal glands, no gonads, and appear female even if they have XY sex chromosomes.

In humans, adrenal complaints are often difficult to diagnose and are potentially life threatening, but can be treated with life-long steroid replacement therapies. Some of these conditions result from underdevelopment of the adrenal gland.

Disorders of sex development can lead to problems such as ambiguous genitalia in neonates, a failure to enter puberty or menstruate in teenage girls, or infertility in adult life. These conditions can be caused by disorders that affect the sex chromosomes, the development of the gonads, or the synthesis or response to androgens.

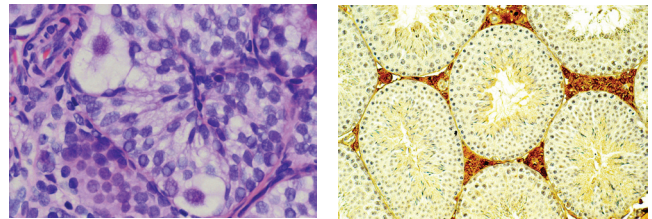
Dr John Achermann at the Institute of Child Health, University College London, has established his research career by studying the role of SF-1 and the associated nuclear receptor DAX-1 in human adrenal and reproductive development in both normal and disease conditions.

Advance

During postdoctoral research at the Centre for Endocrinology and Molecular Medicine at Northwestern University, Chicago, USA, Dr Achermann characterised mutations in DAX-1 in patients with an X-chromosome linked form of adrenal deficiency. He was the first to identify mutations in the SF-1 gene in patients with complex disorders of the adrenal gland and gonads. These mutations disrupt the DNA-binding domains of SF-1, and cause chromosomally male individuals to have female external genitalia and a uterus, as well as adrenal failure.

Dr Achermann's more recent work is also revealing the importance of dose-dependent effects of DAX-1 and SF-1 in human adrenal and gonad function. For example, while almost 60 per cent of boys with severe adrenal underdevelopment have mutations in the DAX-1 gene, less severe disruption of the DAX-1 protein can result in a milder form of this condition that first presents in adulthood. Similarly, less disruptive changes in SF-1 can cause poor development of the testes and reduced production of androgen hormones, but with normal adrenal function. Recent work suggests that around 15 per cent of patients with these features have SF-1 changes, making this one of the most common causes of disordered sex development currently known.

Dr Achermann's group is also studying other genes known to be involved in sex development and adrenal function, and has identified and characterised non-classical phenotypes in humans associated with mutations in several of these genes. This work aims to extend the understanding of how these disorders present so as to enhance diagnosis and inform scientific studies of these syndromes.



Germ cells (left) and testis cells (right), which are being studied by Dr John Achermann in his research on disorders of sex development.

How it's making a difference

Understanding the biology underlying disorders of the adrenal gland helps patients manage their disorder, helps doctors monitor patients for the development of associated features over childhood or in adulthood, and helps in the counselling of relatives about the risk of other children being affected. Dr Achermann's work has contributed to the molecular diagnosis and counselling for several complaints. The high frequencies of DAX-1 mutations in cases of childhood adrenal deficiencies and of SF-1 mutations in disorders of sex development are allowing these findings to be applied to genetic screening. DAX-1 screening is now available in several genetics clinics around the UK; as DAX-1 mutations are X-linked and women in patients' families may be carriers, genetic counselling for these families is now possible.

Dr Achermann has established patient and clinic networks through the European Society for Paediatric Endocrinology and EuroDSD consortium, thus increasing the numbers of patients who can be studied. He has also been involved in a consensus working group for disorders of sex development in Chicago, which has published statements from clinicians, patients and support groups for policy makers in healthcare provision. One of the most important outcomes of these meetings has been a revised nomenclature, which is more scientifically accurate and more acceptable to individuals with these conditions.

Dr Achermann's work has been presented at many invited lectures at international meetings and in publications in peer-reviewed journals. In 2002 he was awarded the European Society for Paediatric Endocrinology Young Investigator Award and in 2007 was awarded the SPARKS Young Investigator Medal from the Royal College of Paediatrics and Child Health.

Next steps

Dr Achermann's current research programme is exploring further the mechanisms of reproductive and adrenal development in humans. This will allow him to investigate how mutations in the key molecules contribute to human disorders. Based on his observation of a dose-dependency in SF-1 action, Dr Achermann also intends to understand milder changes in these factors within the general population. His development of collaborations around the EU means that he can focus on larger patient series in his clinical studies.

References

Lin L et al. Heterozygous missense mutations in steroidogenic factor-1 (SF1/AdBP4, NR5A1) are associated with 46,XY disorders of sex development with normal adrenal function. *J Clin Endocrinol Metab.* 2007 Mar;92(3):991–9.

Kohler B et al. Five novel mutations in steroidogenic factor-1 (SF1, NR5A1) in 46,XY patients with severe underandrogenization but without adrenal insufficiency. *Human Mutation* 2007; in press.

Achermann JC et al. A mutation in the gene encoding steroidogenic factor-1 causes XY sex reversal and adrenal failure in humans. *Nat Genet.* 1999 Jun;22(2):125–6.

Table of achievements

Inputs

- Endocrine Fellows Foundation Fellowship (1999)
- Fletcher Bequest Lectureship in Endocrinology, Department of Medicine, UCL (2001)
- GOSH/ICH Science Development Initiative Pump-Prime Award (2002)
- Wellcome Trust Clinician Scientist Fellowship (2002)
- Research Unit Grant from the European Society for Paediatric Endocrinology (in collaboration with primary investigator Dr Tuilpakov at the Endocrinological Research Centre, Moscow; 2005)
- Wellcome Trust Senior Research Fellowship in Clinical Science (2006)

Key activities/outputs

- Many invited lectures at international meetings and publications in peer-reviewed journals
- Member of the European Society for Paediatric Endocrinology Collaborative Research Unit and EuroDSD, establishing clinical and patient research networks within the EU
- Served on the editorial boards of several scientific publications
- Work with patient advocacy groups, research participants and consensus working groups to define standards of healthcare provision
- Involved in postgraduate clinical sciences teaching in UK and Europe
- Annual Meeting Steering Committee of The Endocrine Society (USA)
- Practising paediatrician at Great Ormond Street Hospital NHS Trust, London

Outcomes

- SPARKS Young Investigator Medal from the Royal College of Paediatrics and Child Health (2007)
- European Society for Paediatric Endocrinology Young Investigator Award (2002)
- European Paediatric Endocrinology Meeting prize for new research (2007)
- Constance Campbell Prize in Reproductive Science, Northwestern University, Chicago, USA (1999, 2001)

Timeline of Dr John Achermann

