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Partial Androgen Insensitivity Syndrome Caused by a Novel Mutation

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Abstract

The spectrum of androgen insensitivity syndrome (AIS) is well characterized, ranging from complete androgen insensitivity (CAIS) to varying degrees of partial and mild insensitivity (PAIS). There is evidence correlating loss of androgen receptor function caused by mutations with the clinical phenotype. We present a patient with phenotypic and biochemical evidence of partial androgen insensitivity who has a c.2746 T>C base pair substitution causing a p.Tyr916 His sequence variant in the androgen receptor that has not been previously reported. Furthermore, this mutation is in an atypical site, and the phenotype does not correspond with previous reports of complete androgen insensitivity caused by mutations in this region. This highlights potential deficiencies in our molecular understanding of this syndrome, and re-enforces that it is not appropriate to consider all patients with partial androgen insensitivity as a single cohort; we should instead consider different sub-groups when considering the molecular basis and subsequent therapy.

Keywords: Androgens; Insensitivity; Mutation.

Introduction

Morris first described androgen resistance in a case series and coined the term 'testicular feminisation syndrome'. More recently, a spectrum of disorders has been defined varying from the original complete androgen insensitivity syndrome (CAIS) to varying degrees of androgen resistance as part of the partial androgen insensitivity syndromes (PAIS). Thus, we now recognize different pathological subtypes of varying degrees of androgen resistance.

Complete androgen insensitivity syndrome

The characteristic presentation is of apparently phenotypic females either developing inguinal swellings during infancy, or primary amenorrhoea as an adolescent [1]. Such patients have an XY karyotypes, biochemically demonstrate serum testosterone levels within or above the normal range, and have inappropriately elevated luteinizing hormone (LH) levels. This hormone profile is suggestive of resistance to androgens, which is borne out by genetic studies that demonstrate missense mutations in the coding regions for the androgen-receptor. The majority of these mutations occur in regions encoding the ligand-binding domain [2]. Furthermore, functional assays have even found complete loss of androgen receptor function in patients with this phenotype [3]. Hence, this is now classified as 'complete androgen insensitivity syndrome'.

Partial androgen insensitivity syndrome

A series of mainly case studies have also identified patients with a phenotype of a varying degree of under-masculinisation, ranging from mild reduction in penile size or infertility to appearances similar to the complete androgen insensitivity syndrome. However, despite also having a biochemical profile suggestive of hormone resistance, and mutations mostly clustered in the binding domains of the androgen receptor, functional assays indicate only a partial loss of androgen receptor function [4]. Correspondingly, in general the degree of functional loss of the androgen receptor correlates with the severity of the syndrome.

It is now generally possible to recognize these characteristic phenotypes and biochemical profiles, and suspecting the diagnosis to confirm it with genetic testing. Typically, patients with CAIS will have gonadectomy, followed by oestrogen replacement, although the optimal timing of gonadectomy remains unclear. By contrast, in cases of partial androgen insensitivity, high dose testosterone replacement, to provide excess substrate and thereby compensate for partial loss of function at the ligand binding domains of the receptor, forms the mainstay of treatment [5]. We present a case where the clinical and biochemical phenotype were characteristic of PAIS, but the genetic variant described was in an unexpected position within the receptor although molecular modelling was highly suggestive of pathogenicity.

Case Presentation

A 22-year-old Polish male presented to the Endocrinology Clinic primarily concerned about the small size of his penis. He was raised outside the UK and gave a history of hypospadias that was surgically corrected as a child, as well as gynaecomastia, which developed during adolescence and had also been surgically managed at the age of 19 years. He did not shave at all, but had good libido and was able to maintain sexual intercourse. He was not taking any medication. His principal complaint was that while sexual intercourse was possible and he was able to ejaculate, he was concerned that the size of the erect penis was inadequate.

Physical examination revealed a eunuchoid habitus with an arm span of 190.4 cm and a height of 180.9 cm and normal body mass index (24.2 kg/m^2). Genital examination showed a small penis and testes of 10ml bilaterally, no chest hair, scanty axillary hair, a female distribution of pubic hair with a few extra hairs towards the umbilicus, but moderate hair growth over the lower legs. A biochemical profile revealed high testosterone levels above the normal range with normal-high gonadotrophins, suggestive of androgen resistance (Table 1). On the basis of the phenotype and biochemical profile he was diagnosed with PAIS. The plan was to commence high dose testosterone replacement, testosterone undecanoate 1 g monthly. A genetic profile using Sanger PCR to analyse the androgen receptor gene detected a

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■	Testosterone 49.6 nmol/L (8.4-28.7)
■	LH 10 UI/L (1.5-9.3)
■	FSH 12.9 UI/L (2.0-20)
■	Prolactin 209 mU/L (45-375)
■	Oestradiol 181 pmol/L (0-191)
■	SHBG 37.3 nmol/L (13-71)

Table 1: Serum biochemical profile.

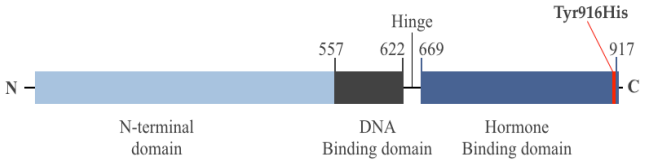

Figure 1: Location of the mutation in the androgen receptor gene.

mutation: however, the mutation was not in the coding region for the receptor ligand binding domain as expected and has not previously been reported, with a hemizygous base-pair substitution (c.2746 T>C) causing incorporation of an alternative amino-acid p.Tyr 916 His into the androgen receptor protein (Figure 1).

Discussion

The molecular pathogenesis of AIS is thought to be well characterised, with over 800 mutations identified in the androgen receptor gene and 95% of these being situated in the exons that encode the ligand-binding domain of the receptor protein [6]. The pathophysiological effects of these mutations have been further confirmed in rat models, which display a phenotype of androgen insensitivity when such mutations are induced [7].

Additionally, androgen-binding assays provide further evidence for the molecular basis of the different androgen insensitivity syndromes, by demonstrating a complete loss of androgen binding affinity in patients with CAIS, while in patients with PAIS there is a reduction rather than a complete loss of androgen-binding affinity [4].

However, in this particular case the mutation reported is in a particular region, which codes for a C-terminal tethering region rather than the ligand binding domains where most mutations have been identified. Although mutations have previously been reported within this region, such as the adjacent (H917R) mutation, they have only been reported to cause a phenotype of CAIS [8]. In this patient, the novel mutation induces PAIS rather than the expected CAIS as seen in all other patients with mutations in the same coding region. This poses important questions about the validity of our current understanding of the molecular basis of these androgen insensitivity syndromes, and also about their subsequent management.

Firstly, it is challenging to account for why a mutation in the receptor-tethering region can result in this partial as opposed to complete loss of receptor function. There have been studies into the effect of different mutations in the ligand binding domain, which can alter hydrogen bonding between the receptor and the androgen to different degrees and thereby the receptor affinity and the resulting phenotype [9]. However, there are currently no dedicated studies concerning the rarer mutations in the C-terminal tethering region, meaning that we have no irrefutable molecular evidence that could account for exactly how different mutations in this region could lead to differing phenotypes of complete or partial androgen insensitivity.

Furthermore, this potential deficiency in our molecular understanding of these conditions is particularly interesting when we also consider the reported proportion of patients who do not clinically respond to treatment with high-dose testosterone. If we were to assume that almost all of the cases of partial androgen insensitivity were attributable to mutations in the ligand-binding domain, reducing binding affinity, then we would expect that all patients should in theory respond to an increased level of ligand via this high-dose testosterone treatment. However, given that we know that many patients do not respond to the testosterone treatment [10], it is reasonable to assert that this may be due to their receptor mutation being in a different region as in this patient.

Therefore, the novel mutation found in this patient in association with a phenotype of PAIS raises questions as to how widely applicable our molecular understanding of partial androgen insensitivity syndrome is. We therefore must question whether patients with PAIS, who do not respond to testosterone treatment are actually another patient cohort; with a different mutation to those who respond to testosterone. This effectively highlights the need for genetic testing and patient-based rather than generic therapy in patients with PAIS.

References

1. Quigley CA, De Bellis A, Marschke KB, el-Awady MK, Wilson EM, et al. (1995) Androgen receptor defects: historical, clinical, and molecular perspectives. Endocr Rev 16: 271-321.
2. Matias PM, Donner P, Coelho R, Thomaz M, Peixoto C, et al. (2000) Structural evidence for ligand specificity in the binding domain of the human androgen receptor. Implications for pathogenic gene mutations. J Biol Chem 275: 26164-26171.
3. Evans BAJ, Jones TR, Hughes IA (1984) Studies of the androgen receptor in dispersed fibroblasts: investigation of patients with androgen insensitivity. Clin Endocrinol (Oxf) 20: 93-05.
4. Veiga-Junior NN, Medeats PAR, Petroli RJ (2012) Clinical and laboratorial features that may differentiate 46,XY DSD due to partial androgen insensitivity and 5a-reductase type 2 deficiency. Int J Endocrinol.
5. Hughes IA, Houk C, Ahmed SF, Lee PA; LWPES Consensus Group; ESPE Consensus Group (2006) Consensus statement on management of intersex disorders. Arch Dis Child 91: 554-563.
6. Matias PM, Donner P, Coelho R, Thomaz M, Peixoto C, et al. (2000) Structural evidence for ligand specificity in the binding domain of the human androgen receptor. Implications for pathogenic gene mutations. J Biol Chem 275: 26164-26171.
7. Yarbrough WG, Quarmby VE, Simental JA, Joseph DR, Sar M, et al. (1990) A single base mutation in the androgen receptor gene causes androgen insensitivity in the testicular feminized rat. J Biol Chem 265: 8893-8900.
8. Ahmed SF, Cheng A, Dovey L (2000) Phenotypic features, androgen receptor binding, and mutational analysis in 278 clinical cases reported as androgen insensitivity syndrome. J Clin Endocrinol Metab 85658-65.
9. Cheikhelard A, Morel Y, Thibaud E (2008) Long-term followup and comparison between genotype and phenotype in 29 cases of complete androgen insensitivity syndrome. J Urol 80: 1496-1501.
10. Weidemann W, Peters B, Romalo G, Spindler KD, Schweikert HU (1998) Response to androgen treatment in a patient with partial androgen insensitivity and a mutation in the deoxyribonucleic acid-binding domain of the androgen receptor. J Clin Endocrinol Metab 83: 1173-1176.