

CASE REPORT

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A novel c.64G > T (p.G22C) *NR5A1* variant in a Chinese adolescent with 46,XY disorders of sex development: a case report

Dan Zhang^{1†}, Dajia Wang^{1†}, Yajie Tong¹, Mingyu Li², Lingzhe Meng¹, Qitong Song¹ and Ying Xin^{1*}

Abstract

Background Adolescents with 46,XY disorders of sex development (DSD) face additional medical and psychological challenges. To optimize management and minimize hazards, correct and early clinical and molecular diagnosis is necessary.

Case presentation We report a 13-year-old Chinese adolescent with absent Müllerian derivatives and suspected testis in the inguinal area. History, examinations, and assistant examinations were available for clinical diagnosis of 46,XY DSD. The subsequent targeting specific disease-causing genes, comprising 360 endocrine disease-causing genes, was employed for molecular diagnosis. A novel variation in nuclear receptor subfamily 5 group A member 1 (*NR5A1*) [c.64G > T (p.G22C)] was identified in the patient. In vitro functional analyses of the novel variant suggested no impairment to *NR5A1* mRNA or protein expression relative to wild-type, and immunofluorescence confirmed similar localization of *NR5A1* mutant to the cell nucleus. However, we observed decreased DNA-binding affinity by the *NR5A1* variant, while dual-luciferase reporter assays showed that the mutant effectively downregulated the transactivation capacity of anti-Müllerian hormone. We described a novel *NR5A1* variant and demonstrated its adverse effects on the functional integrity of the *NR5A1* protein resulting in serious impairment of its modulation of gonadal development.

Conclusions This study adds one novel *NR5A1* variant to the pool of pathogenic variants and enriches the adolescents of information available about the mutation spectrum of this gene in Chinese population.

Keywords 46,XY disorders of sex development, *NR5A1*, Anti-Müllerian hormone, Adolescent

Background

46,XY disorders/differences of sex development (DSD) occur with a frequency of approximately 1:20,000 [1] and encompass complete or partial gonadal dysgenesis, undervirilisation or under-masculinisation of an XY

male due to genetic variation, abnormal hormone secretion, or abnormal changes in peripheral sensitivity to testosterone [2, 3]. A great proportion of 46,XY is caused by mutations in key transcription factors required for sex differentiation and androgen biosynthesis or action [2]. Compared with other age stages, adolescents with 46,XY DSD face additional medical and psychological challenges, which are particularly prominent and difficult for newly diagnosed adolescents [3]. To optimize management and minimize hazards, correct and timely diagnosis is necessary [3]; however, the diagnosis rate of 46,XY DSD with gonadal hypoplasia is exceptionally low [4], with > 50% of patients not receiving a molecular diagnosis [5, 6]. Clinical, biochemical, and imaging tests

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Sex In Development Foreword By N D C Lewis

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The I and Being Human Norman Holland, 2017-07-05 The I in the title pertains to the core of self that persists over time. These are challenges that elude people like social scientists, philosophers or critics of literature and the arts who would chronicle or explain humanity's doings. This informative, engaging and joyous book by Norman N. Holland offers a usable model for the aesthetics, psychology, history and science of the human subject. Holland begins by modeling the self as a theme and variations, constant yet constantly changing. He shows how symbolization, perception, cognition and memory all contribute to the sense of I; hence how any one I grows out of a specific history and culture but also out of experiences all humans share. Holland proposes a scientific psychology based on his model, fusing the experiments of academic psychology with the insights of psychoanalysis. He illustrates his theory by the lives of George Bernard Shaw, Scott Fitzgerald and other writers as well as Freud's patient Little Hans in adulthood, a famed stage director at the Metropolitan Opera. The I and Being Human attempts nothing less than to draw together aspects of the self such as objectivity and subjectivity that have eluded connection. In so doing, Norman Holland offers a rereading of psychoanalysis as a theory of the I.

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