

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

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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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