Human Genomics

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Multigenerational evidence of X-linked adrenal hypoplasia congenita due to a novel *NR0B1* frameshift

Lang Tian[1†], Jie Mei[2†], Xi Zheng[3] and Hong-Mei Dai[1*]

Abstract

Backgroud Pathogenic *NR0B1* variants, encoding DAX-1, are a major cause of X-linked adrenal hypoplasia congenita (AHC), yet genotype–phenotype variability persists.

Results In a Chinese four-generation pedigree, two affected males carried a novel *NR0B1* frameshift, c.573_576dup4 (p.T193Gfs*13). Segregation showed wild-type fathers and heterozygous carrier mothers, and unaffected male relatives lacked the variant. The duplication shifts the reading frame from residue 193 and introduces a premature stop at residue 205, truncating DAX-1. Pedigree analysis supports *NR0B1* c.573_576dup4 (p.T193Gfs*13) as a novel AHC-causing variant.

Conclusions This maternally inherited frameshift underlies AHC in this family, expanding the *NR0B1* mutational spectrum and underscoring genetic testing.

Keywords Adrenal hypoplasia congenita, X-linked recessive inheritance, *NR0B1*, Alphafold

Introduction

Adrenal hypoplasia congenita (AHC) is a rare but clinically life-threatening endocrine disorder characterized by underdevelopment of the adrenal cortex leading to primary adrenal insufficiency, and it exhibits hereditary characteristics [1]. Common presenting features include vomiting and diarrhea, feeding difficulties, dehydration, hypoglycemia, hyponatremia with hyperkalemia, and cutaneous hyperpigmentation [2].

AHC requires early recognition. Infants with hyperpigmentation, vomiting/diarrhea, and poor weight gain or feeding difficulty should have electrolytes and adrenal steroids tested. Infants and young children exhibiting biochemical features such as hyponatraemia with hyperkalaemia, low cortisol/elevated adrenocorticotropic hormone (ACTH), increased renin levels and/or insufficient aldosterone should undergo prompt comprehensive endocrinological assessment [3]. Given the familial inheritance of AHC, individuals with suggestive manifestations or from high-risk families should undergo early gene-centered screening and aetiological confirmation, primarily through genetic testing, in addition to clinical suspicion, hormone assessment, and imaging studies [4]. Consequently, genes closely linked to AHC have become priority targets in diagnostic workflows.

Pathogenic mutations in *NR0B1* (*DAX1*), an X-linked recessive gene, are the principal cause of AHC, with a marked predominance in males [5]. *NR0B1* mutation types correlate with AHC clinical phenotypes, and distinct

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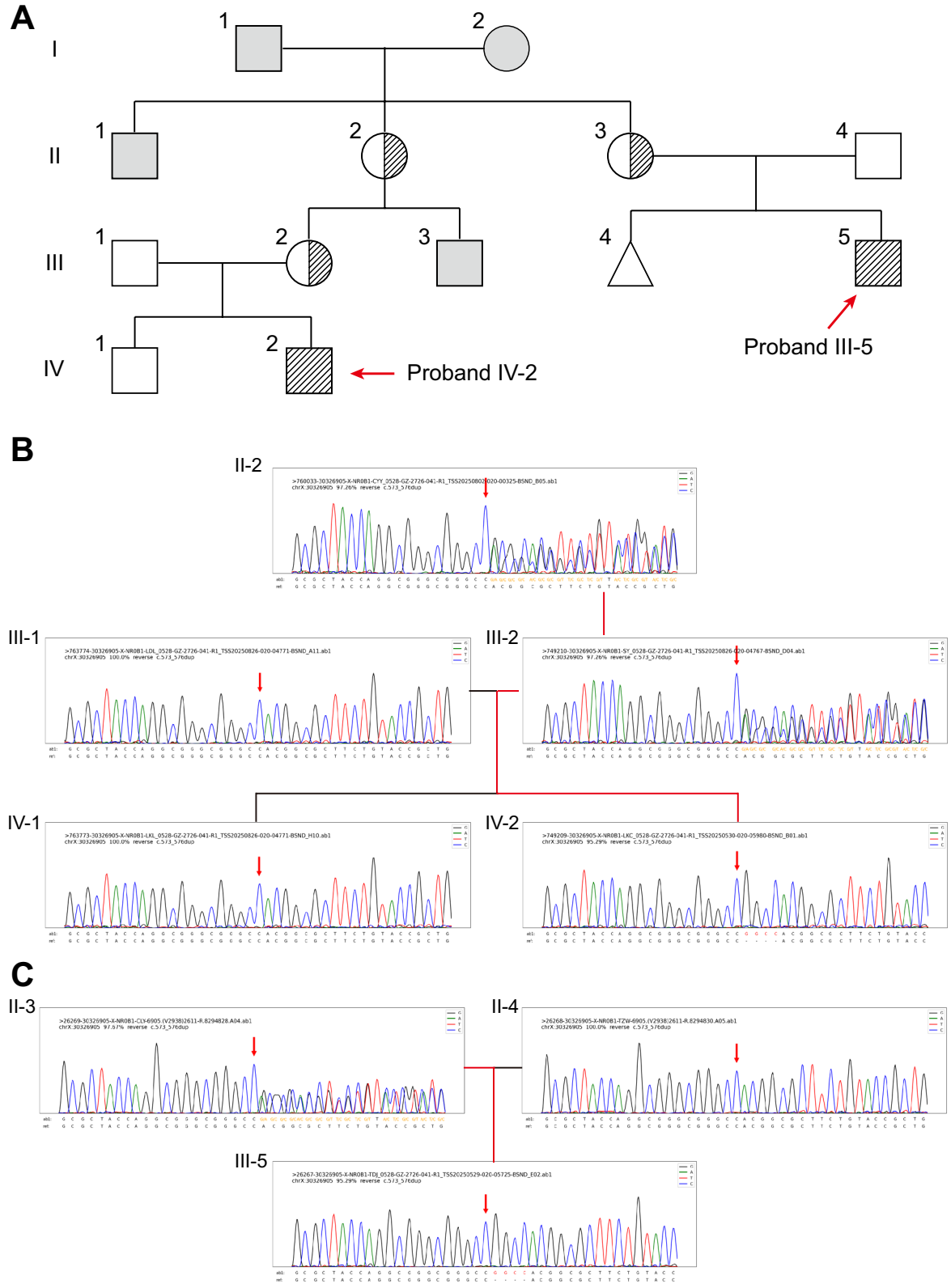

Fig. 1 (See legend on next page.)

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Fig. 1 Pedigree of the family and *NR0B1* mutation testing. **A** Proband III-5 and proband IV-2, diagnosed with AHC, carry the same *NR0B1* mutation inherited through the maternal line. Individuals III-2 and II-3 are heterozygous carriers, each with a 1/2 (50%) risk of transmitting this X-linked recessive mutation to male offspring. The pathogenic *NR0B1* mutation in this family traces to I-2. Squares denote males, circles denote females. Individual III-4 was a stillborn fetus with unknown sex and genotype. White symbols indicate *NR0B1* wild-type genotype, shaded symbols indicate carriers of the *NR0B1* mutation, half-shaded symbols (II-2, II-3, III-2) indicate heterozygous carriers, gray symbols indicate genotype not tested. **B***NR0B1* mutation testing in the family of Proband IV-2. The hemizygous *NR0B1* c.573_576dup4 (p.T193Gfs*13) identified in Proband IV-2 was inherited from his mother (III-2) and can be traced to his maternal grandmother (II-2). **C***NR0B1* mutation testing in the family of Proband III-5. The hemizygous *NR0B1* c.573_576dup4 (p.T193Gfs*13) identified in Proband III-5 was inherited from his mother (II-3). His father (II-4) is *NR0B1* wild type

mutation patterns influence prognostic guidance. From a therapeutic perspective, patients harboring nonsense/frameshift mutations generally require lifelong steroid replacement, while certain missense mutations may retain partial function. However, existing therapeutic approaches cannot restore normal adrenal or gonadal development. Although gene-editing approaches (e.g., CRISPR-Cas9-based correction) represent a potential future avenue, the immediate clinical priority remains early genetic mutation screening to address pressing diagnostic needs [6].

In summary, the association between *NR0B1* and AHC is well established. However, novel mutation types and pedigree characteristics remain incompletely described. We report a four-generation family in which two of four surviving males exhibit inherited AHC (Fig. 1A). The clinical features of this family were delineated, and genomic sequencing was performed on the two affected individuals and additional relatives within the pedigree, particularly maternal relatives, through which a novel hemizygous *NR0B1* frameshift mutation was identified as the pathogenic cause. Consequently, our findings provide additional evidence that *NR0B1* c.573_576dup (p.T193Gfs*13) is a pathogenic, familial etiology of AHC and contribute new information to *NR0B1* mutation catalogs, thereby facilitating optimized diagnosis and management in future patient populations.

Methods

Clinical data

This case series involved patients managed at Hunan Children's Hospital (Hunan, China) and the Third Xiangya Hospital of Central South University (Hunan, China). Proband IV-2, a 7-year-old male, was admitted to the Third Xiangya Hospital of Central South University in 2025. Proband III-5, an 11-year-old male, was evaluated and followed at Hunan Children's Hospital during 2019–2020. After written informed consent was obtained from the legal guardian/participant and institutional ethics approval was granted, general information, initial symptoms, and key physical findings were collected according to routine clinical procedures. Baseline biochemical and endocrine assessments were performed, including electrolytes and cortisol/ACTH, with renin/aldosterone, 17-hydroxyprogesterone (17-OHP), and hypothalamic–pituitary–gonadal (HPG) axis hormones as indicated. Abdominal ultrasonography and/or MRI were obtained. Testing platforms and interpretive standards followed the hospital's routine practice. This study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (Approval No.: Kuai 25575). Following written informed consent from the patients and their relatives, peripheral blood samples were collected from probands and family members for subsequent sequencing analyses.

Genomic sequencing

To detect *NR0B1* mutations in the probands, targeted sequencing of the gene/locus was performed and analyzed. Genomic DNA was extracted from peripheral blood collected from participants using a standardized protocol. Targeted libraries were prepared (random-endonuclease method) Indexed libraries were sequenced on the AmCare-Seq-2000 platform. Reads were processed with an in-house pipeline using GATK HaplotypeCaller to call single-nucleotide variants and small insertions/deletions. PCR validation was performed for the *NR0B1* locus using the following primers (5′→3′): 0528-GZ-2726-041-F1: TAGGCGTAC TCCTTGGTACTGA; 0528-GZ-2726-041-R1: CATCCT CTACAGCTTGCTCACT. The expected amplicon spans chrX:30,326,342–30,327,049 and is 708 bp in length.

Protein structure modeling and visualization

The full-length human DAX-1 protein model was obtained from the AlphaFold Protein Structure Database (entry AF-P51843; https://alphafold.ebi.ac.uk/). Coordinates for the human DAX-1 peptide in complex with LRH-1 (PDB ID: 4RWV) and the mouse Dax-1 in complex with LRH-1 (PDB ID: 3F5C) were downloaded from the RCSB Protein Data Bank (https://www.rcsb.org/). Protein sequences for DAX-1 (*NR0B1*), LRH-1 (*NR5A2*), and SF-1 (*NR5A1*) were retrieved from UniProt (https://www.uniprot.org/). AlphaFold Server (https://alphafoldserver.com/) was used to generate DAX-1–LRH-1 and DAX-1–SF-1 complex models for structural visualization. The truncated amino-acid sequence corresponding to *NR0B1* c.573_576dup (p.T193Gfs*13) was generated by applying the variant described in Human Genome Variation Society (HGVS) nomenclature to the NM_000475.5 coding DNA sequence and translating it to protein. The resulting ~ 205-aa product (residues 1–192 identical to WT, followed by a 13-residue frameshift tail) was modeled with ColabFold (https://github.com/sokrypton/ColabFold) for illustrative structural depiction.

Results

Proband IV-2 presented to the Department of Pediatrics, Third Xiangya Hospital of Central South University in May 2025. He was the product of a third pregnancy and second live birth (G3P2), delivered vaginally at term (40 weeks) with a birth weight of 3.4 kg. The skin was mildly dark at birth and external genitalia were normal. Postnatally, he occasionally experienced vomiting and diarrhea during colds, though no hospitalisation or investigation occurred. Progressive generalized hyperpigmentation was noted, with particularly prominent gingival and scrotal darkening. On evaluation, stretched penile length was 4 cm and testicular volumes were 3 mL bilaterally. Parental heights were 163 cm (father) and 158 cm (mother), with a genetically predicted height of 167 ± 5 cm. At age 7 years 2 months, the proband measured 137.7 cm in height, weighed 31 kg, with a BMI of 16.4 kg/m^2. Bone age by the Greulich–Pyle atlas was 11.5 years. By Tanner–Whitehouse 3 (TW3), the RUS (R) bone age was 11 years 1 month and the carpal (C) bone age was 10 years 10 months. During assessment, it was ascertained that Proband III-5 (the son of the proband IV-2's maternal great-aunt) had been diagnosed with AHC with an *NR0B1* mutation (Fig. 1A). Given this family history, AHC-related testing was pursued for IV-2. Initial laboratory results showed ACTH 1,780.77 pg/mL, cortisol 10.87 μg/dL, Na^+ 137.7 mmol/L, and K^+ 4.83 mmol/L (Table 1). Targeted genetic testing of proband IV-2 revealed a hemizygous *NR0B1* mutation, c.573_576dup4 (p.T193Gfs*13) (Fig. 1B), confirming an X-linked AHC diagnosis. Hydrocortisone replacement was initiated for proband IV-2 at 5 mg doses administered at 07:00, 12:00, 18:00, and 23:00. Vitamin D and calcium were supplemented as appropriate. Proband III-5 was delivered by cesarean section as a G2P1 infant. Routine antenatal care during G2 was unremarkable until late gestation, when fetal hypoxia was suggested. Birth weight was 3.35 kg, skin tone at birth was fair, and external genitalia were normal. Feeding was normal during the first year. From age 1 year onward, proband III-5 experienced frequent colds with recurrent respiratory infections requiring intravenous therapy. Progressive skin hyperpigmentation began after age 6, without genital abnormalities. In January 2019 (age 11 years), proband III-5 developed postprandial vomiting, with intermittent recurrent emesis over more than 3 months, diffuse cutaneous hyperpigmentation, and violaceous lips. Laboratory testing indicated electrolyte disturbances (hyponatremia, hypochloremia), plasma renin activity and aldosterone were within reference ranges, cortisol 5.43 μg/dL, ACTH > 2,000 pg/mL, luteinizing hormone (LH) 0.36 mIU/mL, follicle stimulating hormone (FSH) 1.89 mIU/mL, testosterone 0.81 ng/dL, sodium 120.8 mmol/L, chloride 88.90 mmol/L, and carbondioxide combining power (CO_2-CP) 16.6 mmol/L (Table 1). Accordingly, supportive inpatient management was initiated, including hydrocortisone supplementation, gastric mucosal protection with omeprazole and cimetidine, and intravenous fluid therapy. Genetic testing was subsequently performed. After genetic analysis, a diagnosis of X-linked adrenal hypoplasia congenita was established. Neither parent exhibited relevant clinical features. Following the diagnosis, regular follow-up of electrolytes was recommended. After discharge, oral hydrocortisone acetate was continued at 10 mg before breakfast, 5 mg before lunch, and 5 mg before dinner, together with calcium carbonate/vitamin D3 administered orally twice daily. The sequencing panel for proband III-5 encompassed 1,691 endocrine-related genes across 22,966 coding exons (total 3,805,128 bases). Subsequent comparison with the genetic testing report of proband IV-2 revealed an identical c.573_576dup4 (p.T193Gfs*13) mutation in both individuals, characterised by a duplication of the GGCC sequence following positions 573–576 in the reference gene sequence. Recognizing the complexity of genomic disease, diversity of inheritance modes, and variant mechanisms, we note that single-individual testing has limitations for inferring inheritance patterns and de novo status. Moreover, results reflect current knowledge of disease genes and do not exclude pathogenic variants outside the tested range. Additional variants detected in proband III-5 are summarized in Table 2. While some have been reported in internal or population databases or occur at very low frequencies consistent with evolutionary conservation and in silico predictions, none provided strong evidence for an AHC association. Collectively, these data support NR0B1 c.573_576dup4 (p.T193Gfs*13) as a previously unrecognized pathogenic mutation. Further follow-up of affected and at-risk relatives will be undertaken.

Extended family testing was performed to determine the origin of the mutation. Proband IV-2's father (III-1) did not carry the alteration, and the mutation was inherited from the mother (III-2), who was heterozygous. The older brother (IV-1) inherited the mother's non-variant allele and is *NR0B1* wild type. Consequently, IV-1 did not display the pathological phenotype of AHC until the

Table 1 Partial clinical test results at initial presentation for proband IV-2 and proband III-5

	Na^+ mmol/L (135–145)	K^+ mmol/L (3.5–5.5)	Cortisol μg/dL (6.7–22.6)	ACTH pg/mL (7.2–63.6)	17-OHP nmol/L (0–30)	Testosterone ng/dL (3–68)
Proband III-5	120.8	5.39	5.43	> 2000	0.83	0.81
Proband IV-2	137.7	4.83	10.87	1480.77	0.47	16.03

Table 2 Predicted additional risk variants in proband III-5

Gene	CCDC40	EYS	FRAS1	USH2A
OMIM	613,799	612,424	607,830	608,400
Inheritance	AR	AR	AR	AR
HG19 position	chr17:78,073,509	chr6:65,532,543	chr4:79,296,891	chr1:215,987,206
Transcript	NM_017950	NM_001142800	NM_025074	NM_206933
Nucleotide and amino acid change(s)	c.3364C > T (p.Q1122*)	c.3164 + 1G > T	c.3152–2A > G	c.9611A > G (p.H3204R)
Zygosity	Heterozygous	Heterozygous	Heterozygous	Heterozygous
Population frequency	–	< 0.001	–	0.003 (East Asian)
ACMG classification	Class 2—Likely pathogenic	Class 2—Likely pathogenic	Class 2—Likely pathogenic	Class 3—Uncertain significance
Associated disease / Reference	Primary ciliary dyskinesia type 15	Retinitis pigmentosa type 25	Fraser syndrome	Retinitis pigmentosa type 39 / Usher syndrome type 2A

age of 14 (Fig. 1B). For proband III-5, the mutation was inherited from the mother (II-3; heterozygous), whereas the father (II-4) was wild type (Fig. 1C). Tracing the familial origin indicated that II-2 and II-3 are sisters who both carry the same *NR0B1* mutation, which likely originated from their mother (I-2). These findings support classification of *NR0B1* c.573_576dup4 (p.T193Gfs*13) as a novel frameshift underlying X-linked AHC. Male carriers are hemizygous and manifest the disease phenotype.

Discussion

The molecular pathology of AHC primarily arises from loss-of-function mutations in genes essential for adrenal development, among which *NR0B1* has been the most extensively studied. The pathogenic gene in male patients is transmitted from a carrier mother. If the mother is not a carrier, the pathogenic gene may originate from a de novo mutation or result from maternal germline mosaicism. In the pedigree analyzed here, the clinical genetic features were concordant with XR inheritance. Males constituted the primary affected group, and both probands (III-5 and IV-2) harbored the same hemizygous *NR0B1* mutation inherited from their mothers. Broader pedigree analysis indicated that the third-generation maternal uncle (III-3) and the fourth-generation older brother (IV-1) were unaffected, consistent with heterozygous carrier status for the *NR0B1* mutation and further supporting the XR transmission of hemizygous *NR0B1* mutations in AHC.

NR0B1 is a key regulator of endocrine development, located on Xp21, and it encodes the 470-amino-acid protein DAX-1, a member of the nuclear receptor superfamily. DAX-1 is an orphan nuclear receptor (no known endogenous ligand) with a distinctive N-terminal domain, and a C-terminal ligand-binding–like (LBD-like) domain [7]. Physiologically, DAX-1 is required for normal adrenal formation and regulates expression of enzymes involved in cortisol and aldosterone biosynthesis [8]. Frameshift *NR0B1* variants typically create premature termination codons, triggering nonsense-mediated decay (NMD) or yielding truncated DAX-1 that lacks essential segments, markedly reducing transcriptional repression. Nonsense variants act similarly: upstream changes are removed by NMD, whereas distal 3′ events may escape NMD and produce truncated proteins missing nuclear-localization signals or corepressor-binding interfaces [9]. By contrast, many missense variants cluster near the nuclear-receptor–like domain, impairing folding, stability, nuclear import, or SF-1/coregulator interactions and thus causing partial loss of repression. The aforementioned mutations ultimately converge on adrenal cortical cell differentiation disorders and defects in steroidogenic enzymes expression. However, the extent of functional damage varies by mutation class and position, constituting a molecular basis for clinical heterogeneity in AHC. This underscores the close relationship between *NR0B1* mutation architecture and phenotype, highlighting the need to comprehensively map the *NR0B1* mutational landscape and its disease associations.

Several relatively common *NR0B1* mutations with pathogenic characteristics in AHC have been reported to date. In this study, a previously undescribed hemizygous frameshift, *NR0B1* c.573_576dup4 (p.T193Gfs*13), is reported. The affected region is an essential segment of the protein with high cross-species conservation, and the duplication is predicted to introduce a PTC. An AlphaFold-based full-length human *NR0B1* (DAX-1) model shows that the DAX-1 C-terminus (~aa 256–470) forms a compact multi-helical bundle consistent with a nuclear receptor LBD, whereas the N-terminus is relatively extended (Fig. 2A). Previous studies indicate that DAX-1 relies on its C-terminal LBD-like domain to form inhibitory complexes with NR5A family receptors (e.g., LRH-1/*NR5A2* and SF-1/*NR5A1*), thereby negatively regulating target-gene transcription [10]. Consistent with this, PDB entries for human DAX-1 peptide bound to LRH-1 (PDB ID: 4RWV) and mouse Dax-1 bound to LRH-1 (PDB ID: 3F5C) reveal a continuous DAX-1–LRH-1 interface (Fig. 2B, C). We additionally generated AlphaFold3-based DAX-1–LRH-1 and DAX-1–SF-1 complex models as schematic visualization (Fig. 2D, E). Protein-level predictions for the patient mutation

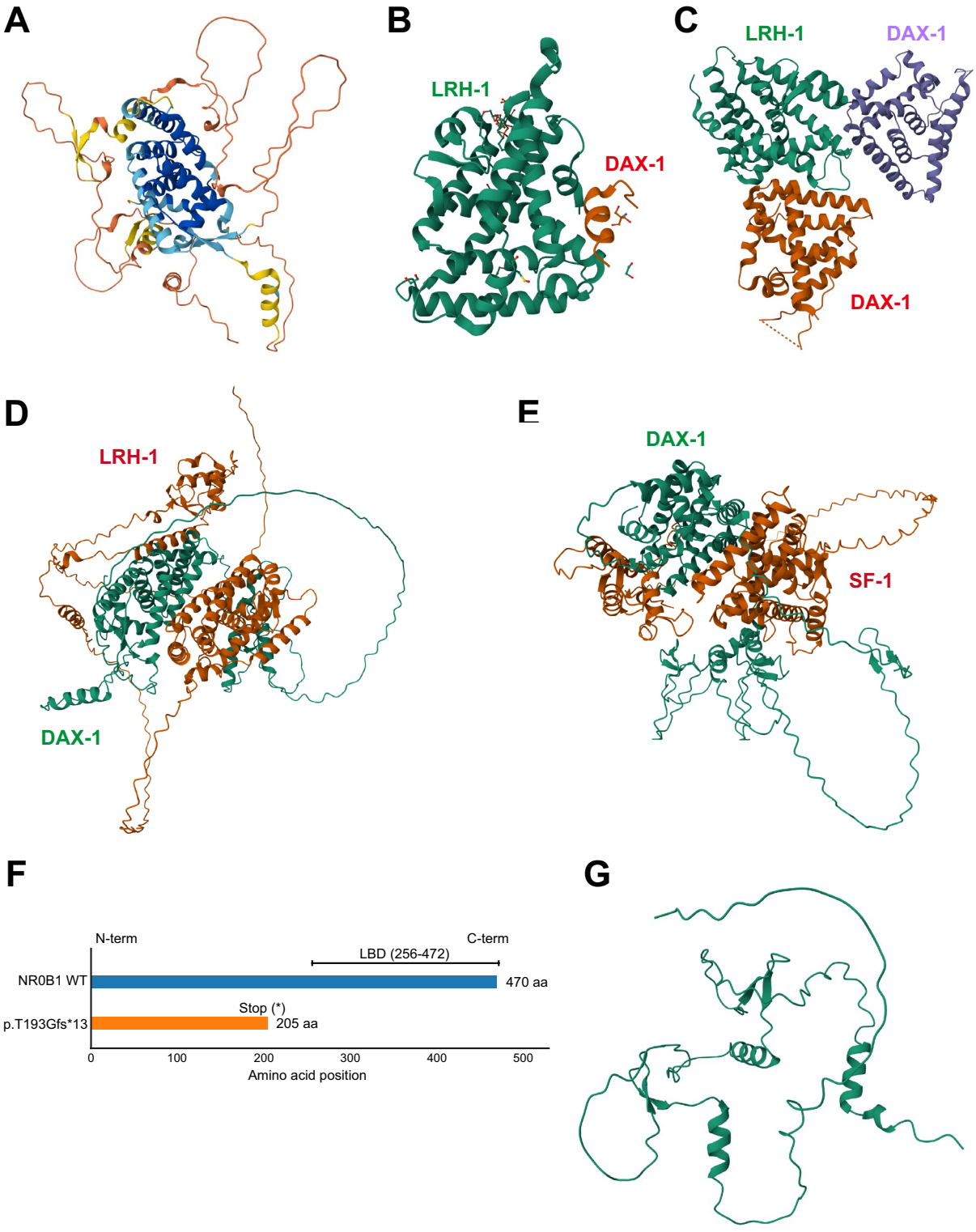

Fig. 2 Structural illustration of DAX-1 and *NR0B1* c.573_576dup4 (p.T193Gfs*13). **A** Schematic of the three-dimensional structure of wild-type human DAX-1. **B** Three-dimensional structure of the human LRH-1–DAX-1 peptide complex (PDB ID: 4RWV), with the DAX-1 peptide in red and LRH-1 in green. **C** Three-dimensional structure of the mouse LRH-1–Dax-1 complex (PDB ID: 3F5C), with Dax-1 shown in red and purple, and LRH-1 in green. Dax-1 participates as two copies to form a (Dax-1)_2: LRH-1 heterotrimer. **D** AlphaFold-predicted three-dimensional model of human DAX-1 with LRH-1, with DAX-1 in green and LRH-1 in red. **E** AlphaFold-predicted three-dimensional model of human DAX-1 with SF-1, with DAX-1 in green and SF-1 in red. **F** Schematic comparison of amino-acid sequences for wild-type *NR0B1* and *NR0B1* c.573_576dup4 (p.T193Gfs*13). **G** Predicted three-dimensional structure of the *NR0B1* c.573_576dup4 (p.T193Gfs*13)

NR0B1 c.573_576dup (p.T193Gfs*13) indicate truncation of DAX-1 at ~ 205 aa, introducing a premature termination codon and therefore predicting loss of function primarily via NMD. If a truncated product were produced, it would lack the entire C-terminal LBD-like region (aa 256–470) (Fig. 2F). Modeling of the truncated protein (aa 1–205) suggested retention of only the N-terminal segment without the secondary-structure and geometric features corresponding to the C-terminal LBD-like domain (Fig. 2G). Collectively, the predicted truncation removes the C-terminal LBD-like domain of DAX-1, which is consistent with an *NR0B1* loss-of-function mechanism in X-linked AHC. However, several limitations should be acknowledged. The AlphaFold3-based DAX-1–LRH-1 and DAX-1–SF-1 complex models presented in Fig. 2 are computational, schematic visualizations and should not be interpreted as functional evidence of protein expression or in vivo interaction changes for the frameshift allele. In particular, because this variant introduces a premature termination codon, loss of function is most plausibly mediated by NMD, and the presence of a stable truncated DAX-1 protein in patient tissues was not assessed in this study. Therefore, the structural depiction is intended to provide context for expected domain loss rather than to establish molecular interactions. Future work using experimental approaches will be required to validate the predicted consequences of this variant and to further delineate the mechanistic link between the mutation and the clinical phenotype.

Conclusions

In summary, under current ACMG/AMP criteria, the *NR0B1* c.573_576dup4 (p.T193Gfs*13) mutation is provisionally classified as likely pathogenic (Class 2). To date, this mutation has not been reported in clinical case series and is absent from the reference population databases queried. Integrating the pedigree analysis with genetic findings from both probands (III-5 and IV-2) and their paternal/maternal relatives, *NR0B1* c.573_576dup4 (p.T193Gfs*13) is concluded to be a novel AHC-causing hemizygous mutation. This frameshift introduces a premature termination codon and is therefore predicted to result in *NR0B1* loss of function, consistent with the established molecular mechanism of X-linked AHC.

Abbreviations

AHC	Adrenal hypoplasia congenita
ACTH	Adrenocorticotropic hormone
17-OHP	17-Hydroxyprogesterone
HPG	Hypothalamic–pituitary–gonadal
ACMG/AMP	American College of Medical Genetics and Genomics and the Association for Molecular Pathology
HGVS	Human Genome Variation Society
LH	Luteinizing hormone
FSH	Follicle stimulating hormone
CO_2-CP	Carbondioxide combining power
LBD-like	Ligand-binding–like
PTC	Premature termination codons
NMD	Nonsense-mediated mRNA decay
PAE	Predicted aligned error

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Author contributions
HMD conceived and designed the study. HMD, LT, and XZ collected and curated the clinical data. JM analyzed the sequencing data and drafted the initial manuscript. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this work are available on request from the corresponding author. The data are not publicly available due to privacy/ethical restrictions.

Declarations

Ethics approval and consent to participate
Informed consent was obtained by the authors. This study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (Approval No.: Kuai 25575). Written informed consent was obtained from patients and relatives.

Consent for publication
Consent for publication was provided by patients and relatives.

Competing interests
The authors declare no competing interests.

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