A novel breakpoint deletion within a CAG repeat causes complete androgen insensitivity syndrome: Report of its segregation in a large Czech family

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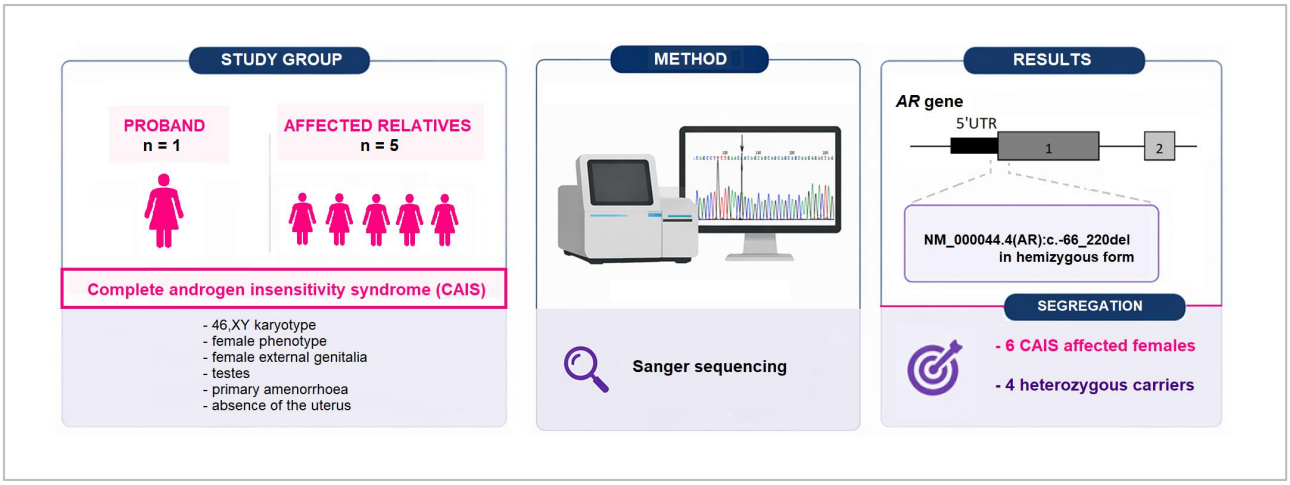
Background. Complete androgen insensitivity syndrome (CAIS) is one of the most prevalent conditions of disorders/differences of sex development (DSD), with an X-linked recessive inheritance. A hemizygous pathogenic variant in the *AR* gene causes the condition.
Case Report. We present a five-generation Czech family with several CAIS-positive relatives. The proband is a 27-year-old female patient with a 46,XY karyotype, who exhibits the typical CAIS phenotype. This includes female external genitalia, the absence of uterus, a blind-ending vagina, undescended testes, and almost missing axillary and pubic hair.
Methods and Results. We identified a novel pathogenic, hemizygous NM_000044.4(AR):c.-66_220del p.? variant using Sanger DNA sequencing with specifically designed primers. This *AR* deletion was 286 bp in length and initiated in the 5'-UTR, terminating within the polymorphic CAG repeats in exon 1 of the *AR* gene. The *AR* variant removed the original initiation codon ATG, resulting in a shortened AR transcript with an unknown effect on the translation.
Conclusion. We describe a unique *AR* deletion identified in a 46,XY female patient with CAIS. The variant segregates in the large CAIS family; it was detected in five affected relatives, while the four remaining family members were asymptomatic carriers.

A Novel Breakpoint Deletion Within a CAG Repeat Causes Complete Androgen Insensitivity Syndrome: Report Of Its Segregation In A Large Czech Family



This report presents a large, five-generation Czech family, where the novel, pathogenic *AR* variant was detected in six patients with CAIS, and four relatives were asymptomatic carriers.

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INTRODUCTION

Androgen insensitivity syndrome (AIS; MIM:300068) is one of the most prevalent causes of disorders/differences of sex development (DSD) (ref.[1,2]). The first mention of this syndrome dates back to 1817. However, the official term "testicular feminization syndrome" was described by Morris in 1953. The author reported 82 cases exhibiting the female phenotype and bilateral testes[3]. This syndrome is classified as 46,XY DSD, specifically as a defect in androgen action[4,5].

AIS is subdivided into three categories. Complete androgen insensitivity (CAIS), partial (PAIS; MIM:312300), and mild androgen insensitivity (MAIS). CAIS is characterised by the presence of a complete female phenotype with the presence of nondysplastic testes, absence of the uterus, and infertility. PAIS is an age-appropriate androgen-concentration-producing milder variant that exhibits certain female physical traits, micropenis, severe hypospadias (perineoscrotal), and a bifid scrotum. Finally, healthy men who exhibit normal testicular development, but who may exhibit adolescent gynecomastia, azoospermia, and infertility at a later age, represent the last group – mild androgen insensitivity (MAIS) (ref.[6]). The prevalence of CAIS ranges from 1:20,400 to 1:99,100 in 46,XY individuals[1,7,8], while for PAIS, the incidence is 1:130,000 (ref.[9]).

Human androgens, mainly testosterone and 5α-dihydrotestosterone (DHT), play a crucial role in male sexual differentiation, the development of secondary male characteristics, and the initiation and maintenance of spermatogenesis[10,11]. The biological functions of these steroid hormones are exerted through their association with the androgen receptor (AR). Compared with testosterone, DHT has a higher binding affinity for its receptor. Following synthesis, testosterone is transported to target tissues and converted to DHT by 5α-reductase[12].

Hemizygous pathogenic variants in the androgen receptor gene (*AR,* MIM:*313700) represent the primary cause of AIS (ref.[13]). The *AR* gene is located at Xq11–Xq12 on the X chromosome[14]. *AR* contains eight exons and spans more than 90 kb (Fig. 1A), encoding a 110-kDa AR protein containing 919 amino acids[15-17]. According to the reference sequence NM_000044.6, AR includes 920 amino acids. The difference is due to variability in CAG repeats. The AR protein contains four central functional regions, including the N-terminal *trans*-activation domain (NTD, encoded by exon 1), the central DNA-binding domain (DBD, encoded by exons 2 and 3), the C-terminal ligand-binding domain (LBD, encoded by exons 4–8), and a hinge region connecting the LBD and the DBD (ref.[12]). It has been determined that up to 30% of the causative *AR* variants are sporadic, *de novo* variants[1]. The current version of the Androgen Receptor Gene Mutations Database (http://www.androgendb.mcgill.ca) describes over 500 causal *AR* variants as of 2012 (ref.[13]), while the Human Gene Mutation Database (HGMD) has documented more than 700 *AR* variants (http://www.hgmd.cf.ac.uk). It has been observed that AIS phenotypic variability is frequent, even for the same variant[13].

In this case report, we present a familial segregation of another novel *AR* variant, unique in terms of its localisation, in a large, five-generation Czech family with CAIS.

CASE REPORT

The proband is a 27-year-old female (IV-9). She is an attractive woman, without apparent dysmorphic features, eutrophic, and above predicted height. She was born to non-consanguineous parents, from a second physiological pregnancy. A delivery was at term, uncomplicated, with standard postnatal measurements of 3300 g and 50 cm. Breasts began to develop normally around age thirteen. At the age of fifteen, she was diagnosed with primary amenorrhoea. Gynecological examination revealed a four-centimetre-long blind-ending vagina, the absence of the uterus, and almost missing axillary and pubic hair. Her sexual maturation, according to Tanner, was M3, P1, and A0. Subsequent ultrasound examination revealed undescended testes in her pelvic cavity. They were surgically removed after she reached puberty. Before surgery, sex hormone levels were as follows: 17-beta-estradiol 70 pmol/L (reference limit 73–147 pmol/L), follicle-stimulating hormone (FSH) 2.4 U/L (1.8–22 U/L), and luteinizing hormone (LH) 26 U/L (1.20–103.0 U/L). The level of testosterone (T) was 25.00 nmol/L, higher than the reference limit of 0.35–2.6 nmol/L. The karyotype 46,XY was detected by cytogenetic analysis, raising the possibility of AIS, which was later confirmed by genetic testing. Other family members were available for clinical assessment and molecular genetic testing.

MATERIAL AND METHODS

Genomic DNA was isolated from the proband and other family members from peripheral blood leukocytes using a standard extraction procedure with AutoGenFlex (AutoGen, Holliston, MA, USA) and MagCore® Super Automated Nucleic Acid Extractor (RBC Bioscience Corp., New Taipei City, Taiwan). Primer sequences for polymerase chain reaction (PCR) and Sanger sequencing were designed according to Lubahn et al.[18]. Unsuccessful attempts to amplify the 5' end of exon 1 led us to assume that the 5' end of exon 1 is deleted, with an unknown 5' breakpoint. This was confirmed using a specific primer pair: 5'-GAGCCTAGCAGGGCAGATCT-3'; AR_A1new2, forward located in the 5'-untranslated region (UTR), while the 5'-CACAACTCCTTGGCGTTGTC-3' sequence; AR_A4, reverse is located in exon 1. Sanger DNA sequencing was performed on an ABI 3130xl and an ABI 3130 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) using a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) in both directions, according to the manufacturer's protocol. Sequence data for the samples were collected using the 3130/3130xl Series Data Collection Software 4.0 with Sequencing Analysis Software (Applied Biosystems). The pathoge-

nicity of the variant was evaluated in accordance with the recommendations of the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (ref.[19]). Electropherogram analysis was conducted using the Chromas Lite MFC Application, version 2.6.6 (Technelysium, Australia). Familial segregation analysis was performed using targeted Sanger sequencing.

A multiplex ligation-dependent probe amplification (MLPA) was performed using the SALSA MLPA probe mix P074-A1 by MRC Holland (Amsterdam, The Netherlands) for the detection of copy-number variation (CNV) of *AR*. The amplified products were then separated using an ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). The resultant data were interpreted using Cofalyser.Net software (MRC-Holland; Amsterdam, The Netherlands).

Furthermore, we performed RT-PCR followed by Sanger DNA sequencing to determine the effect of the deletion on transcription and the presence of transcripts, respectively. RNA was extracted from patient's leukocytes using a PAXgene Blood RNA Kit (PreAnalytiX, QIAGEN, Germany) and treated with DNase I (RNase-free) (Thermo Fisher Scientific, Waltham, MA, USA). The DNA-free RNA was then reverse transcribed using a SuperScript™ III One-Step RT-PCR System with Platinum™ *Taq* DNA Polymerase (Thermo Fisher Scientific) with two primer pairs (annealing temperature 60 °C, following the manufacturer's recommendations. The primer pairs were designed to amplify the region of interest in the 5'-UTR part (5'-TCTTGTCCACCGTGTGTCTT-3'; forward) and exon 1 (5'-TACGATGGGCTTGGGGAGAA-3'; reverse) and the control region of exon 1 (5'-AATGGGCCCCTGGATGGATA-3'; forward) and exon 2 (5'-AGACCTTGCAGCTTCCACAT-3'; reverse) to confirm the presence of AR transcripts. Universal oligonucleotide sequences were added to custom primers (5'- TGTAAAACGACGGCCAGT-3'; forward primers and 5'-CAGGAAACAGCTATGACC -3'; reverse primers). Finally, the complementary DNA PCR products were purified by ExoSAP (protocol available on request) and bidirectionally sequenced as described above.

RESULTS

A novel hemizygous variant NM_000044.4(AR):c.-66_220del p.? in the 5'-UTR and the 5'-end of exon 1 of the *AR* gene was detected in the proband (IV-9) by Sanger DNA sequencing (Fig. 1B, 1C). The expected control amplicon length was 952 bp, whereas the proband's amplicon was only 666 bp. The coordinates in question are chrX:66 764 923-66 765 208, corresponding to the reference sequence NM_000044.4. The observed novel deletion (absent in ClinVar), spanning 286 bp, began within the 5'-UTR and ended within the polymorphic CAG repeat in exon 1. At the same time, the original initiation codon ATG was removed. In addition, the variant has not been documented in population databases (gnomAD Exomes, v.4.1; gnomAD Genomes, v.4.0). This deletion was classified as likely pathogenic by the Franklin platform (Genoox; http://www.franklin.genoox.com). Notably, this *AR* deletion cannot be detected by the current version of the MLPA assay (data not shown). The sequences of the probes X-066,681493 (12602-L13686) and X-066,682602 (12598-L13682) (hg18) on Xq12 were located in different regions of the 5'-UTR of *AR*, with the deleted region occurring between them. Subsequent RNA analysis revealed a shortened AR transcript carrying the deletion, with an unknown effect on translation (data not shown).

Familial segregation was performed in 15 family members of the proband (see Fig. 2). All subjects who tested positive for CAIS (III-1, III-10, III-26, IV-23, V-3) carried the same hemizygous *AR* variant. The unaffected relatives III-8, III-17, III-22, and IV-8 (Fig. 1D, 1E) were heterozygous carriers. Family members III-2, III-4, III-6, III-13, IV-28, and IV-29 were negative for the reported *AR* deletion. Further clinical information could be obtained from female patient III-19, who exhibited the CAIS phenotype. However, the female patient did not consent to genetic testing. The pedigree illustrates the transmission of the reported *AR* variant within a Czech family lineage, as depicted in Fig. 2. The *AR* variant was evaluated for pathogenicity and causality of the proband's phenotype, with familial segregation also considered. We assessed the aforementioned *AR* variant as pathogenic: PVS1, PM2, PP1, PP4, according to ACMG criteria[19].

DISCUSSION

In this case report, we present a patient with characteristic phenotypic features of CAIS that align with the typical phenotype described by Hughes et al.[6]. We also report the classification of androgen insensitivity grade 7 (complete AIS) by Quigley et al.[20]. A novel deletion, c.-66_220del p.?, was identified in a segment of the 5'-UTR and the 5'-end of exon 1 of the *AR* gene in ten family members. This included six CAIS-positive female patients with a 46,XY karyotype, including the patient presented here, and four other unaffected 46,XX female carriers of the *AR* variant. Initially, it proved impossible to detect an *AR* deletion using the standard Sanger DNA sequencing procedure, despite the use of the original primer set by Lubahn et al.[18]. The primers did not amplify the desired initiation codon sequence. Concurrently, the MLPA method (SALSA MLPA probe mix P074-A1) failed to detect this essential change because the area lacked probes. The sequence of the first probe X-066,681493 (12602-L13686) spans c.-206 bp to c.-183 bp, and the second probe X-066,68260 (12598-L13682) spans c.904 bp to c.927 bp. The latest version of P074-A4 also does not include a probe in this region. It is hypothesised that incorporating additional investigation(s) into the probe mix at the initiation of exon 1 (in proximity to the ATG initiation codon) could prove beneficial, as proposed. The creation of a new system required the use of experimental-specific primers,

placing the forward primer (AR_A1new2) from c.-233 bp to c.-214 bp before exon 1 to facilitate amplification and generate a PCR product of sufficient length.

The 5'-UTR of *AR* is of particular significance due to its structural elements, including the 5'-cap structure, RNA-binding protein motifs, upstream open reading frames (uORFs), internal ribosome entry sites (IRES), terminal oligopyrimidine (TOP) tracts, secondary structures, and G-quadruplexes. This region plays a critical role in translational regulation by influencing mRNA stability and translational efficiency[21]. The promoter region lacks the typical 'TATA' and 'CAAT' boxes but is located in a GC-rich region with two principal transcription initiation sites and contains a putative Spl protein binding site[22].

The *AR* deletion spans a substantial portion of the 5'-UTR and encroaches on the NTD region. The deletion

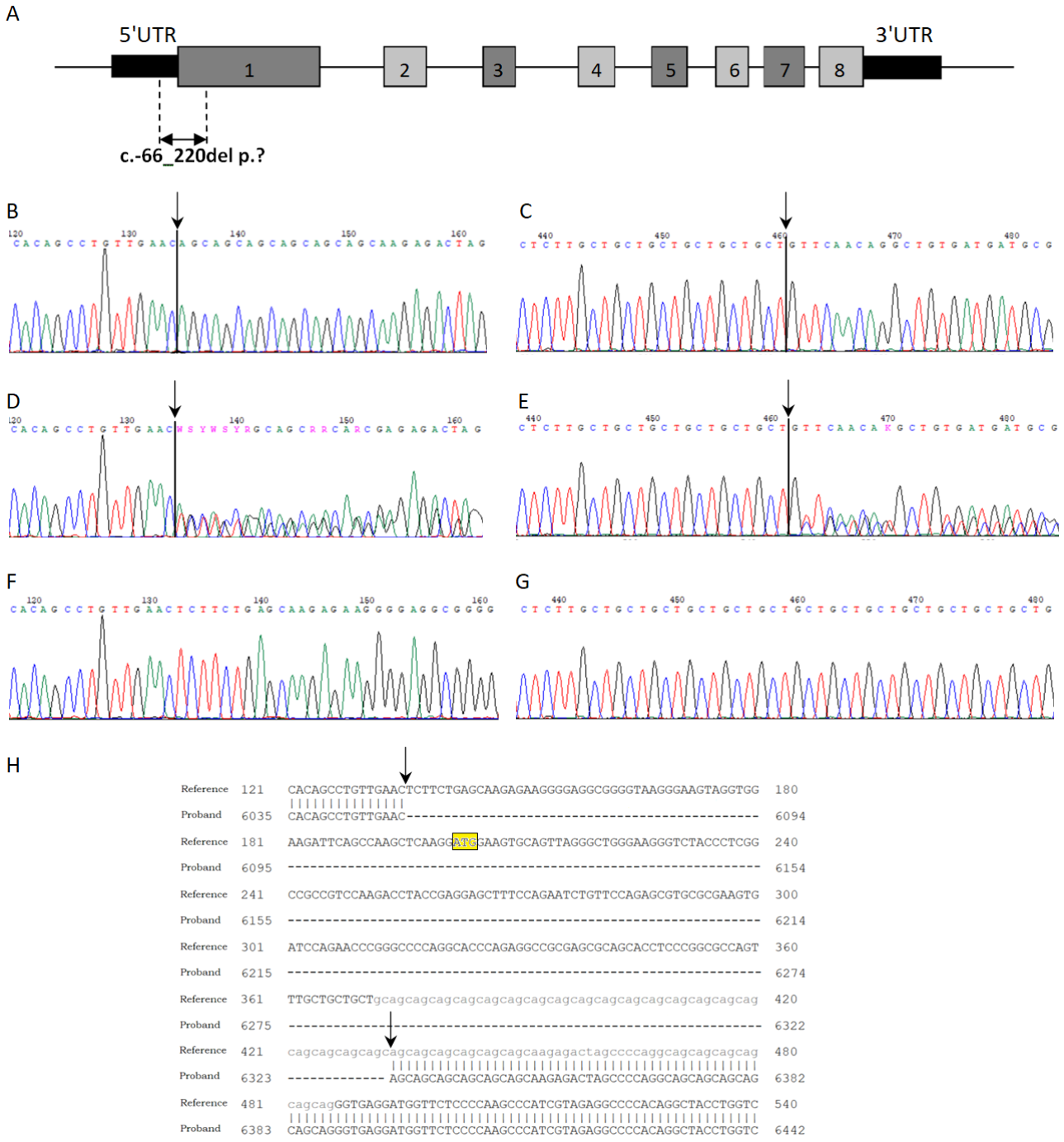

Fig. 1. A hemizygous variant NM_000044.4(AR):c.-66_220del p.? in the *AR* gene was identified. A scheme of the *AR* gene with the deleted region in part of the 5'-UTR and 5'-end of exon 1 of the *AR* gene **(A)**. A partial electropherogram of the hemizygous variant c.-66_220del p.? in the forward strand **(B)**, in the reverse strand **(C)**. A partial electropherogram of the same variant in heterozygous form in the forward strand (**D**), in the reverse strand **(E)**. A partial electropherogram of the control sequence in the forward strand **(F)**, in the reverse strand **(G)**. The localisation of the variant is indicated by the arrow (for B/C/D/E, and H). The BLAST visualisation of the pathogenic variant is shown in the forward strand (modified) **(H)**. The start codon ATG is shown in yellow, where exon 1 should begin (https://blast.ncbi.nlm.nih.gov/Blast.cgi).

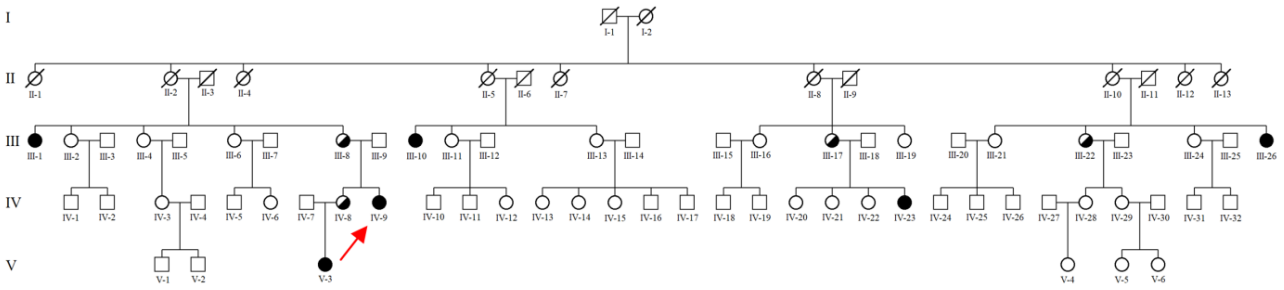

Fig. 2. A five-generational pedigree of the family with the segregation of NM_000044.4(AR):c.-66_220del variant. The proband is marked with the arrow (IV-9). Full-darkened symbols represent the 46,XY affected family members (III-1, III-10, III-26, IV-23, V-3), and half-darkened symbols indicate clinically unaffected 46,XX family members carrying a heterozygous deletion (III-8, III-17, III-22, IV-8). Family members III-2, III-4, III-6, III-13, IV-28, and IV-29 tested negative using targeted Sanger sequencing for the *AR* variant.

removes the initiation codon ATG, with *a priori* unknown consequences, and is predicted to disrupt regulatory elements within the 5'-UTR/exon 1 region, including RNA secondary structures, G-quadruplexes, cap-proximal regulatory sequences, and RNA-binding protein motifs. According to the *AR* sequence, another functional ATG initiation codon at position p.191 could be predicted (Ref. Seq. NM_000044.6). Similarly, as reported by Marino et al.[23] with *AR* variant type of start loss c.2T>C, with prediction of the next in-frame methionine start codon, resulting in a truncated protein missing the first 190 amino acids. Based on our RT-PCR analysis, we hypothesise that an alternative in-frame downstream ATG codon might be used to translate an abnormal AR transcript into an abnormal protein. Further research could help clarify the implications of this *AR* variant.

Despite several deletions in the *AR* gene, none have been identified in the 5'-UTR linked to CAIS. According to Gottlieb's updated McGill Androgen Receptor Gene Mutations Database, somatic mutations, minor duplications, and deletions of 3 or fewer nucleotides are the most frequent causal *AR* variants (http://www.androgendb.mcgill.ca) (ref.[13]).

As posited by Mizokami and Chang[24], the 5'-UTR appears indispensable for translation initiation but not for transcription. The researchers hypothesise that *AR* variants in the 5'-UTR could contribute to AIS by impairing AR translation without altering *AR* mRNA levels. This hypothesis was corroborated by Hornig et al.[25], who reported a germline single nucleotide pathogenic variant in two CAIS patients. In both *in vitro* and *in vivo* experiments, the *AR* variant was shown to introduce a translated uORF in the 5'-UTR of *AR*, resulting in reduced AR protein expression without affecting *AR* mRNA accumulation.

On the other hand, an unstable trinucleotide repeat CAG in exon 1 of the human *AR* gene could be a pathogenic determinant[26]. Two polymorphic trinucleotide repeats, CAG and GGC, have been identified in exon 1's structure. The triplets CAG and GGC differ in terms of the number of repeats they include, which affects the length of the polyglutamine and polyglycine tracts, respectively. They play an essential role in the NTD. In a healthy population, the number of CAG repeats ranges from 8 to 33, and GGC repeats from 10 to 27 (ref.[27]). The results of our study demonstrated that the *AR* gene deletion has resulted in a substantial shortening of the polyglutamine tract of the CAG repeat, with only 6 repeats in the patient. However, the mechanism underlying this genetic instability in the CAG region is unclear. As demonstrated by *in vitro* and *in vivo* experiments utilising AR constructs harbouring 15, 20, and 31 CAG repeats[28], it has been established that increased CAG repeat lengths result in diminished AR transcriptional activity[28,29]. The expansion of the polyglutamine tract has been observed to induce a rare neuromuscular disease, spinal bulbar muscular atrophy, which is associated with low virilisation, reduced sperm production, testicular atrophy, and infertility. Thus, spermatogenesis is necessarily androgen-dependent[28]. Short repeats of polymorphic repeat segments have been associated with an increased risk of prostate cancer[30], an androgen-dependent tumour. Conversely, it has been hypothesised that changes in these two repeat segments may likely play a role in some cases of male infertility associated with impaired spermatogenesis in male patients[28]. If translation starts from an alternative initiation codon the p.Met191 would probably not affect the shortening of the polyglutamine tract.

This unique Czech family affected with CAIS across five generations represents one of the most prominent families with a molecularly confirmed pathogenic variant in *AR*. As posited by Kar et al.[31] and Imperato-McGinley et al.[32], and as molecularly confirmed in 1999 (ref.[33]), large families with CAIS and different *AR* variants have been previously reported. This case demonstrates the complexity of molecular analysis, even in a syndrome with a causal gene, which has been well described since the 1950s[3]. The identification of the *AR* variant was achieved only after a decade, thanks to the use of specific primers. It is noteworthy that the proportion of women in the second and third generations, whether 46,XY or 46,XX, was 100% (Fig. 2), which is inconsistent with the expected distribution.

CONCLUSION

A novel, unique deletion, c.-66_220del, was identified in the 5'-UTR and the 5'-portion of exon 1 of the *AR* gene in ten family members, including six CAIS-positive individuals (one of whom was a 46,XY female patient and the focus of this report) and four other 46,XX unaffected carriers. This *AR* variant was not detected by standard DNA analysis. The *AR* deletion has a substantial impact on a significant segment of the 5'-UTR. Consequently, the *AR* variant removed the start codon, resulting in a shortened AR transcript with an unknown effect on translation. This results in a distinctive repetitive sequence of a substantial polyglutamine tract of CAG repeats. In the patient, only six repeats were observed. The *AR* variant was responsible for the typical CAIS phenotype in a large Czech family over five generations. We hope this information will help expand genetic testing for the *AR* gene and enable accurate, timely diagnosis of CAIS. Moreover, it may be beneficial in the context of informed reproduction and, eventually, for preimplantation diagnostics.

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Conflict of interest statement: All authors declare no competing interests.
Declaration of generative AI and AI-assisted technologies: Grammarly and DeepL (free versions) were used to improve the article's linguistic structure and language editing.
Ethics statement: The Ethics Committee of the Motol University Hospital, Prague, Czech Republic, approved this article. All procedures were performed in accordance with the tenets set out in the World Medical Association Declaration of Helsinki. The patient underwent molecular genetic analysis after obtaining written informed consent from the patient's parents.
Informed consent statement: Informed written consent was obtained from parents of the proband for the publication and other clinical information relating to this case to be reported for academic purposes.
Data availability statement: The reported *AR* gene variant was added to the Leiden Open Variation database (LOVD v.3.0) under the database ID: AR_000765 (https://databases.lovd.nl/shared/variants/0001068415#00002740). The data that support the findings of this study are available from the corresponding author upon reasonable request.

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