Genetic and phenotypic continuum of *HOXA* genes: A case with double *HOXA9*/*HOXA13* mutations

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Abstract. The *HOXA* genes cluster plays a key role in embryologic development. Mutations in *HOXA* genes have been linked to different human phenotypes, including developmental delay, limb anomalies, and urogenital malformations. The present study reported a clinical and genetic investigation of a female patient with polymalformative syndrome including left arm agenesis, bicornuate uterus and bicuspid aortic valve. Using whole exome sequencing, two heterozygous missense variants were identified. Of these, one was a novel variant in the *HOXA13* gene [p.(Tyr290Ser)] and the second a heterozygous variant in the *HOXA9* gene [p.(Ala102Pro)]. To the best of our knowledge, this is the first association of *HOXA9*/*HOXA13* point mutations linked to a syndromic case. In conclusion, the present study suggested that the phenotypic spectrum of vertebral anomalies, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies and limb abnormalities/hand-foot-genital syndrome may be attributable to the combination of different *HOXA* variants, particularly in patients with a severe clinical presentation. The current report contributed as well to the molecular understanding of *HOXA* genes-related phenotypes via the identification of novel variant and genes associations.

Introduction

The *Hox* genes are a set of transcriptional factor genes that play a crucial role in controlling the body plan along the craniocaudal axis and specifying the segment identity of tissues within the embryo. Hox genes are involved in early developmental morphogenetic processes and remain expressed into adulthood (1).

Hox genes are highly expressed within the developing mesonephric duct, specifically *Hoxa9*, *Hoxd9*, *Hoxa10*, *Hoxd10*, *Hoxa11*, *Hoxa13*, and *Hoxd13* (1-3). The Hox proteins family is highly conserved among species. In vertebrates, there are 39 members organized into four tightly clustered gene arrays (*HOXA-HOXB-HOXC* and *HOXD*) (4).

In humans, the gene clusters are organized in a 3' to 5' orientation with paralog group 1 genes at the 3' end of the cluster (e.g., *HOXA1*, *HOXB1*, *HOXD1*) and higher number groups located at the 5' end. A cluster's temporal and spatial collinearity is represented as a pattern of expression along the anterior-posterior axis corresponding to the order of Hox gene in its cluster within the 3' to 5' direction. Thus, during the development, *HOX* genes located at the 3' end, are firstly expressed in the anterior regions and later on the 5' genes posteriorly (2-4). The role of mammalian *HOX* genes in regulating segmental patterns of the hindbrain, skeleton axis, and limb axis is extensively studied and well-known (5).

A total of 10 *HOX* genes have been linked to human conditions (*HOXA1*, *HOXA2*, *HOXA11*, *HOXA13*, *HOXB1*, *HOXB13*, *HOXC13*, *HOXD4*, *HOXD10*, and *HOXD13*) (4). Different patterns of inheritance and variable penetrance and expressivity have been reported.

The most reported syndrome associated with *HOXA* mutations is the Hand-foot-genital syndrome (HFGS; OMIM# 140000). HFGS is a rare autosomal dominant condition characterized by distal limb and genitourinary malformations and caused by *HOXA13* mutations (6-9). Limb abnormalities include first-digit hypoplasia, comprising short, proximally placed thumbs with hypoplastic thenar eminences and short, medially deviated halluces and fusion or delayed ossification of the wrist bones. These deformities appear to be bilateral and symmetrical, with variable severity (10,11). *HOXA13* mutations are fully penetrant for limb defects with variable expressivity and partially penetrant for genitourinary tract anomalies with different fertility implications. Of note, females with HFGS do not suffer systematically from infertility (8-10,12). Guttmacher (1993) reported a family with an HFG-like syndrome. The particularities noted in this family include uniphalangeal second toes with absent nails and postaxial polydactyly (13).

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Despite these distinct features, the genetic investigation of the family reported by Guttmacher revealed a missense mutation (p.Gln50Leu) in the *HOXA13* gene, indicating the phenotypic variability of the mutations (14).

The features of HFGS are found in another clinical association with a broad spectrum of congenital malformations: the VACTERL association (OMIM #192350). VACTERL is an acronym for vertebral anomalies, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities (15).

Thus, VACTERL association is typically defined by the presence of at least three of its features (15). Although HFGS was associated only with *HOXA13* genetic variations, many non-Hox genes have been linked to VACTERL association and other overlapping conditions (15-17). Solomon *et al* have listed more than 30 conditions with features in common with VACTERL and their genetic etiology. From the *HOX* genes family, only *HOXA13* and *HOXD13* genes are implicated in these disorders (15). As an example, clinical entities comprising cardiac defects such as Holt-Oram syndrome, CHARGE syndrome, Andersen syndrome, and Alagille syndrome are linked to *TBX5*, *CHD7*, *KCNJ2*, *JAG2*, and *NOTCH2* genes respectively (15).

The molecular basis of VACTERL is poorly known. Nevertheless, *HOXD13* mutation has been associated with this condition (18). The co-occurrence of the VACTERL association and Müllerian duct defects has been reported (19-22).

It should be noted that many of the overlapping syndromes include specific features that tend to help a clinical diagnosis of exclusion. Thus, a good clinical investigation is crucial to rule out overlapping diagnoses.

Here, we report a female patient with a syndromic clinical presentation including mainly arm agenesis, bicornuate uterus, and bicuspid aortic valve (BAV).

Materials and methods

A peripheral blood sample was collected after obtaining the written informed consent. Genomic DNA was extracted by standard techniques.

Subsequently, whole-exome sequencing (WES) was carried out using the Agilent Sure Select All Exon v4 kit (Agilent, Santa Clara, CA, USA), and the sequencing was performed on an Illumina HiSeq2000 sequencing apparatus (Illumina, SanDiego, CA, USA). Raw fastQ files were aligned to the hg19 reference human genome (University of California Santa Cruz, UCSC) using BWA software. Variant calling workflow was performed according to the GATK best practices. The output files were annotated using ANNOVAR software. Variant annotation and prioritization process were performed with the Variant Annotation and Filtering Tool (VarAFT), version 2.17-2 (http://varaft.eu/).

To pinpoint putatively pathogenic and causal variants we adopted the following filtering strategy: we first excluded variants with a minor allele frequency (MAF) >1% in the gnomAD database (http://gnomad.broadinstitute.org/). Then, we removed non-coding and synonymous variants. Subsequently, the remaining variants were filtered based on their *in silico* pathogenicity prediction and clinical relevance.

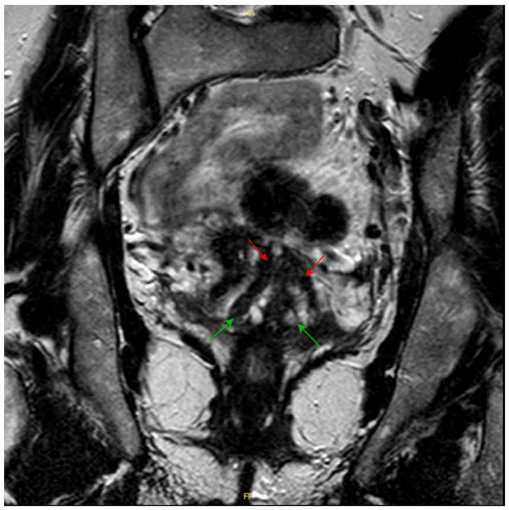

Figure 1. Pelvic magnetic resonance imaging of the patient at 40 years old: Axial T1 weighted sequences showing double uterine cavities (red arrows) with double cervix (green arrows).

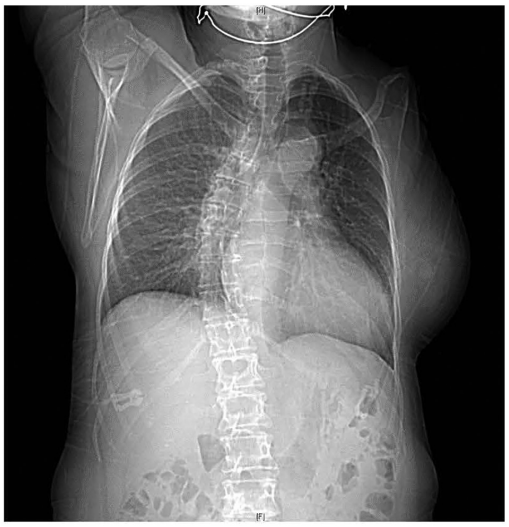

Figure 2. Computerized tomography scan of the patient at 50 years old showing scoliosis associated with agenesis of the left arm.

Amino acids conservation was assessed by sequence alignments using ClustalW (https://www.genome.jp/tools-bin/clustalw).

Results

Clinical and genetic findings. The patient is a female born to non-consanguineous parents. Her clinical presentation comprises features of VACTERL/HFGS syndrome including bicornuate uterus (double uterine cavities, double cervix), left arm agenesis, scoliosis, and BAV (Figs. 1 and 2). The patient was delivered at term with an upper left arm agenesis. Any imperforate anus nor anal atresia or tracheoesophageal fistula were noted in the patient's birth.

The patient had a history of normal intellectual developmental milestones without over-susceptibility to childhood diseases.

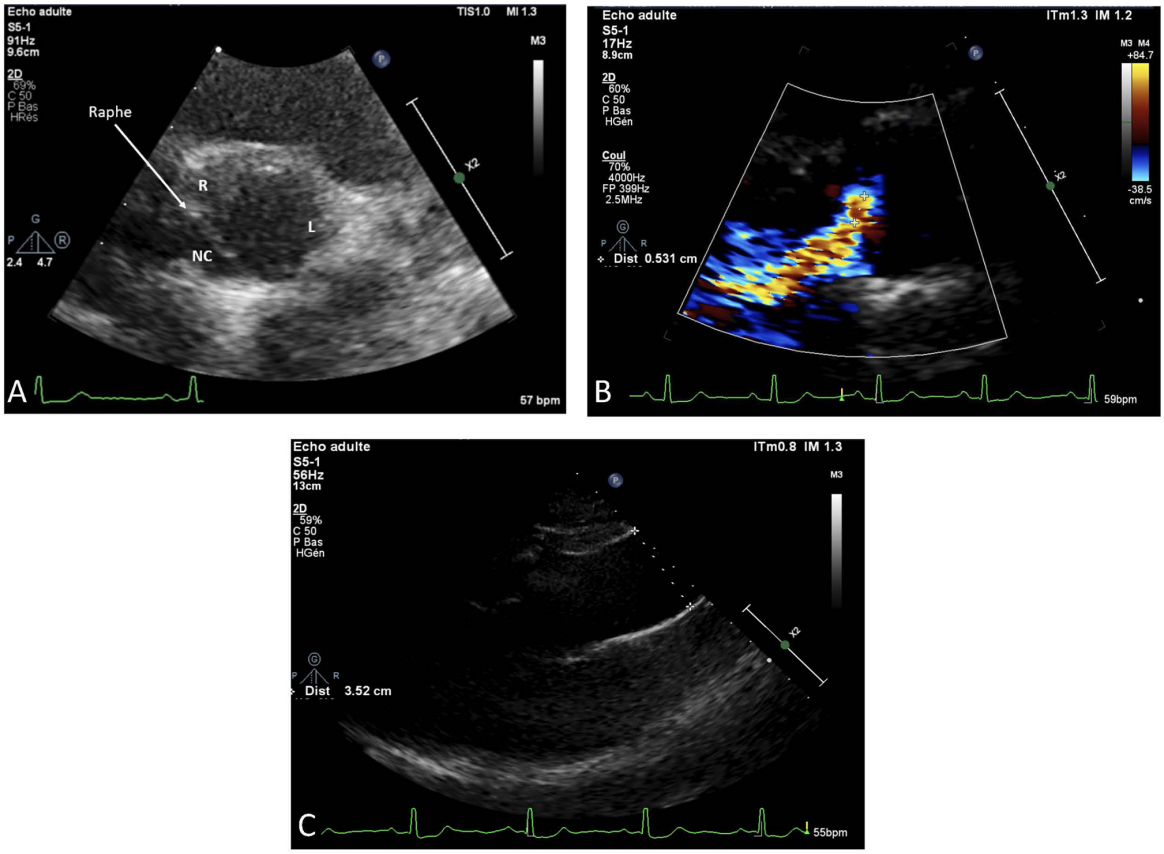

Figure 3. 2D-TTE of the patient. (A) 2D TTE parasternal short axis view showing a type 1 BAV with a raphe between the non-coronary and the right coronary cusps corresponding to a type I, NC-L, of the Sievers classification. (R=right cusp; NC=non-coronary cups; L=left cusp). (B) 2D TTE parasternal long axis view showing a moderate aortic regurgitation due to a prolapse of the fused leaflets. (C) 2D TTE parasternal long axis view ruling out any BAV-related aortopathy. TTE, transthoracic echocardiogram; BAV, bicuspid aortic valve.

Pelvic MRI showed two uterine cavities and a double cervix. On the T1-weighted sequence, there is no hematic retention in the right or left side of the uterine horns. No anomalies in the junction zones or the myometrium. Both appendages are of normal size and regular outline (Fig. 1). Of note, the patient did not have frequent pelvic pain or miscarriage history due to her bicornuate uterus.

Her cardiac evaluation revealed a type 1 non-calcified BAV. Transthoracic echocardiography showed a normal left ventricular ejection fraction (LVEF=70%) with a slight diastolic LV dilation (Indexed end-diastole volume=108 ml/m^2) and a raphe between the non-coronary and the right coronary cusps corresponding to a type I, N-L, according to the Sievers classification (Fig. 3A). A moderate aortic regurgitation was noted (ERO=20 mm^2) due to a prolapse of the fused leaflet and a restriction of the left coronary cusp (Fig. 3B). The aortic valve leaflets were thin and un-calcified. There was neither BAV-related aortopathy nor mitral regurgitation (Fig. 3C). Systolic pulmonary arterial pressure was normal (25 mmHg).

The patient's parents were not examined but were reportedly unaffected. The patient's mother did not accept to participate in the genetic study by reason of iatrophobia.

Whole exome sequencing data analysis allowed us to identify two missense variants in *HOXA9* and *HOXA13* genes.

The *HOXA13*: c.869 A>C: p.(Tyr290Ser) variant is novel, located upstream of the homeodomain, and predicted deleterious by SIFT, probably damaging by PolyPhen, pathogenic by UMD-predictor and has a CADD_phred score=31.

The *HOXA9*: c.304 G>C: p.(Ala102Pro) variant is located in the HOX9 activation region and predicted tolerated by SIFT, benign by PolyPhen, probably pathogenic by UMD-predictor, and has a CADD_Phred score=22.8.

Both amino acids are conserved among species (Fig. S1). Furthermore, the variants were absent from our in-house database gathering 300 exomes.

In order to assess the impact of the variants on the protein level, we used VarMap to retrieve protein structural annotations (23). VarMap output includes the predicted consequence of the variant and a mapping to the residue in the closest 3D protein structure in the Protein Data Bank. Both variants in *HOXA9* and *HOXA13* genes have a high disease propensity value, 1.58 and 1.67 respectively (Fig. 4). The propensities quantify how much more often a variant is observed in diseases than in the natural variant data obtained from gnomAD. Values range from the lowest (Ile->Val, propensity=0.25) to the highest (Cys->Arg, propensity=3.27).

Sanger sequencing of the father's patient showed the absence of both variants (Fig. 5).

As no familial history of limb or genitourinary abnormalities was reported by the patient and the absence of the variants in the father, the variants may have occurred *de novo*.

Furthermore, no variants were found in genes related to VACTERL and HFG syndromes with features in common

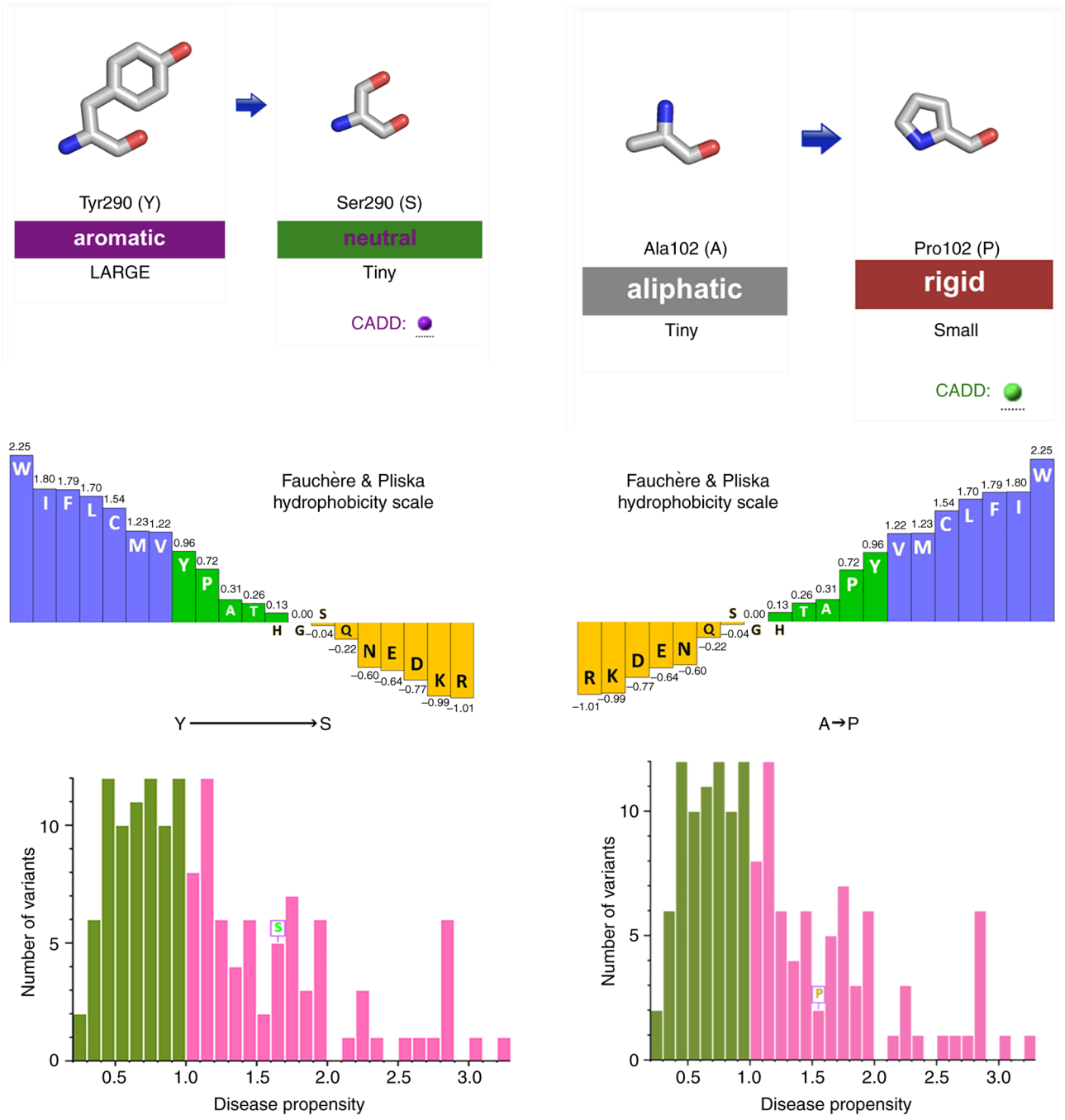

Figure 4. Histogram showing the distribution of disease propensities for different amino acid variants. Green bars correspond to variants that are less often associated with disease, while pink ones correspond to variants more often associated with diseases. Variants of interest are marked on the histogram with a boxed label. Differences in hydrophobicity are indicated in the hydrophobicity plot. Amino acids are marked by a one-letter code.

with the clinical presentation of our patient. The list of genes checked includes *JAG1*, *NOTCH1*, *NOTCH2*, *WNT7A*, *FBN2*, *LRP4*, *FOXF1*, *TBX3*, *TBX5*, *HOXD13*, *MID1*, *RBM8A*, *SALL1* and *ZIC3* genes.

Discussion

Here, we report a female patient with two missense variants in *HOXA9* and *HOXA13* genes, which may explain her clinical condition characterized by a complete arm agenesis, bicornuate uterus, and BAV. According to the *in silico* prediction, the novel *HOXA13*: p.(Tyr290Ser) is highly pathogenic with a CADD score=31. The *HOXA9*: p.(Ala102Pro) is predicted probably pathogenic by UMD-predictor with a high CADD score as well (22.8). Moreover, *HOXA9*: p.(Ala102Pro) is located in the activation domain of HOX9 protein (Fig. 6).

HOX genes are essential for reproductive tract development and for adult function. During embryonic development, *HOXA* genes play a key role in determining the segmental identity of the female genital tract (5). *HOXA9* and *HOXA13* genes are part of the A cluster on chromosome 7 and encode a DNA-binding transcription factor that may regulate gene expression, morphogenesis, and differentiation (5,24).

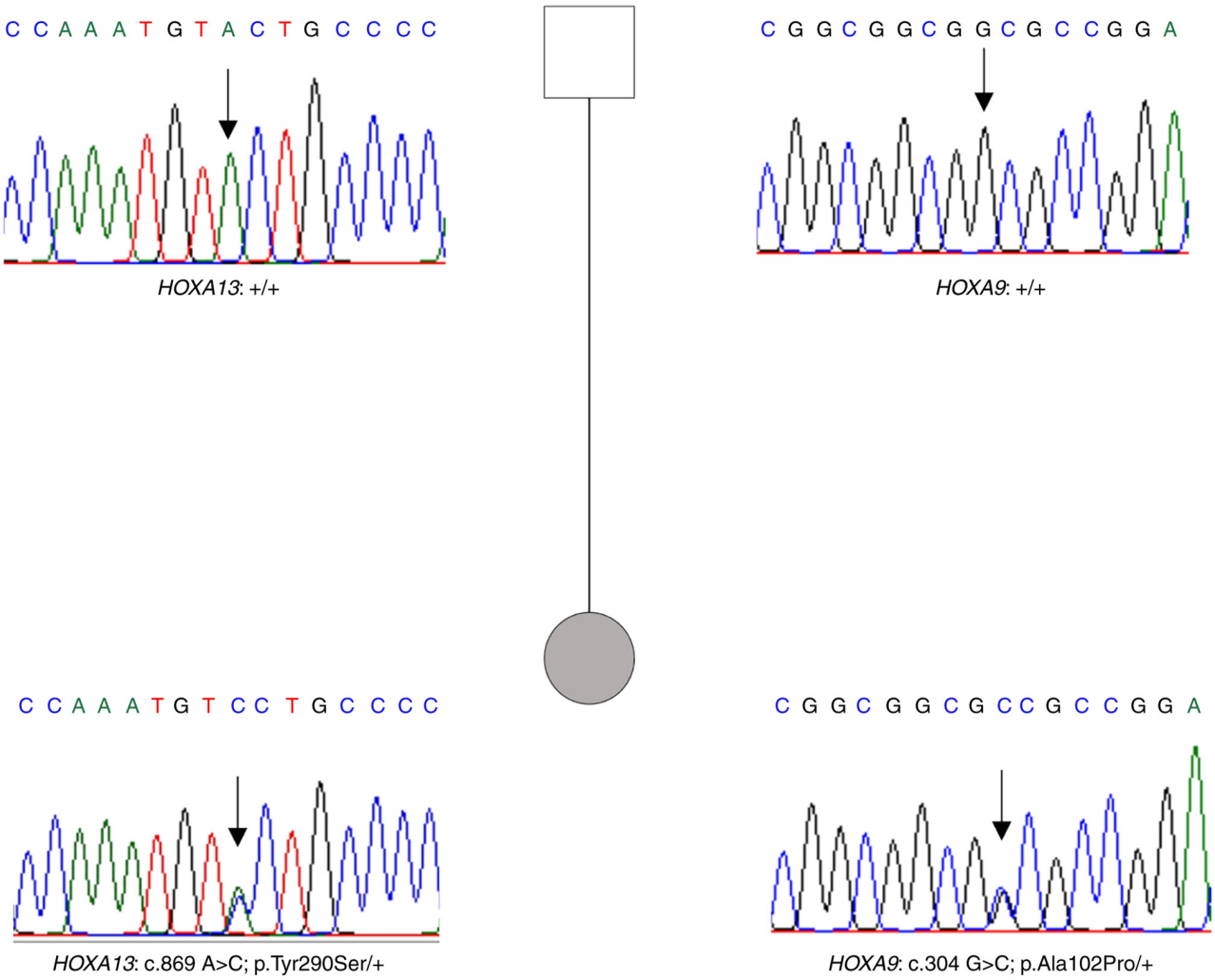

Figure 5. Sanger electropherograms and genotypes are shown below symbols: (+) indicates the wild-type allele and the arrow indicates the position of the mutation.

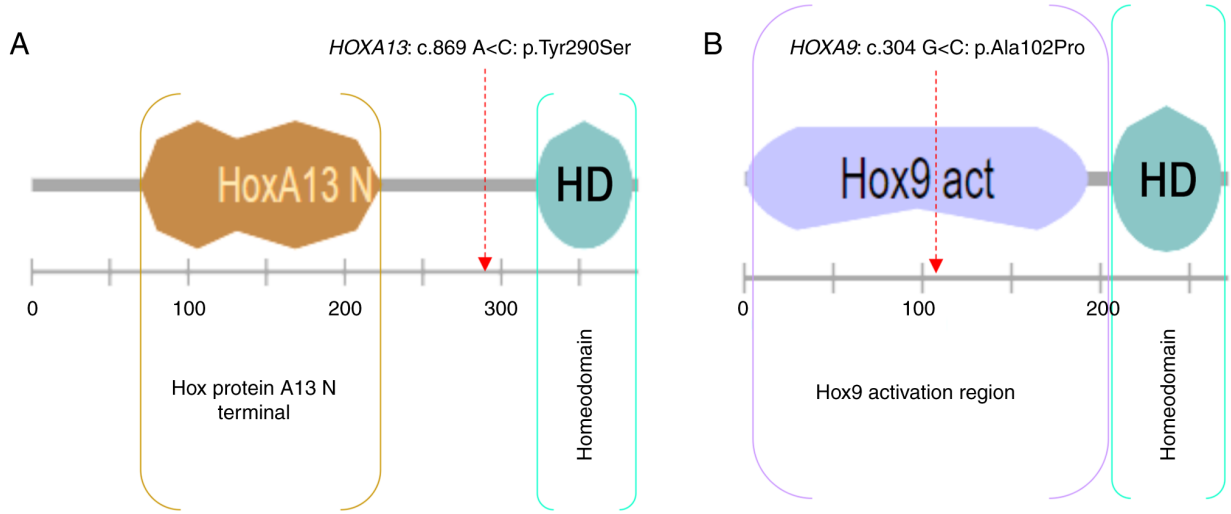

Figure 6. Schematic representation of HoxA13 and Hoxa9 proteins. (A) HoxA13 protein; (B) Hoxa9 protein. The identified variants are indicated by the red arrow.

In adults, *HOXA* genes contribute to maintain the developmental plasticity of reproductive tissues (5,25,26). *HOXA9* is highly expressed in areas destined to give rise to the oviduct. *HOXA10*, *HOXA11,* and *HOXA13* are expressed in the developing uterus, the lower uterine segment and cervix, and in the upper vagina, respectively (https://gtexportal.org/) (25).

Interestingly, *HOXA* genes expression persist in the adult tissues which continue to undergo developmental processes,

such as hematopoiesis (bone marrow), menstrual cycle, and pregnancy (reproductive tract) (5,25). In this line, *HOXA9* and *HOXA13* genes have been associated, respectively, with human myeloid leukemia and Müllerian defects (8,27,28). Indeed, the *HOXA13* gene plays a crucial role in Mullerian ducts fusion and ureter remodeling by the elimination of the common caudal nephric duct. *Hoxa13* mutant mice develop megaureters, hydronephrosis, and malformations of the uterus (8).

Patients with *HOXA13* mutations present several digit anomalies including short thumbs, short middle phalanges of the fingers, clinodactyly of the fifth fingers, and the fusion of distal and middle phalanges of the toes (6,7,11,29). The first *HOXA13* mutation was identified in a large family with HFGS reported originally by Stern *et al* 1970 (9,30). The nonsense mutation identified in this family is located in the HOXA13 homeodomain and leads to the truncation of 20 amino acids which likely abolishes or reduces the protein's ability to bind to DNA (9).

Thereafter, different mutations have been reported in patients with HFGS including protein truncating variants and missense variants (6,7,31,32). Interestingly, missense mutations in *HOXA13* have been correlated to a severe limb phenotype (10,14). The clinical presentation of the patient harboring the first missense mutation in the human *HOX* protein, *HOXA13*: p.(Asn51His), has been described as very severe. He had extremely short thumbs, absent halluces, marked hypoplasia of all middle phalanges, and granular hypospadias (10).

Both gain of function and dominant negative mechanisms have been reported as the genetic basis of *HOXA13*-related phenotypes. Indeed, missense mutations are likely to perturb the DNA-binding properties of HOXA13, leading to both loss and specific gain of function (11,14).

The association *HOXA13*/*HOXD13* and *HOXA11* has been reported in patients with amegakaryocytic thrombocytopenia and radio-ulnar synostosis. Furthermore, the association *HOXD13*/*HOXA13* has been as well reported as linked to triphalangeal thumb brachyectrodactyly syndrome (29,33). Moreover, patients double mutated in *HOXD13* and *HOXA13* showed more severe digital abnormalities than patients harboring monogenic mutations (29).

To our knowledge, congenital heart defects have not been reported in syndromes linked to *HOXA13* mutations. However, a de novo 7 alanine deletion (Ala55-Ala61 del) in the polyalanine tract of the *HOXD13* gene has been identified in a patient with VACTERL association (18). Her clinical presentation included: anal atresia, tetralogy of Fallot, bilateral vesicoureteral reflux, and fusion of the distal interphalangeal joints of 4th and 5th toes (18). Of note, missense mutations in the *HOXA13* gene have been described as more pathogenic than protein-truncating mutations or polyalanine expansion leading to a more severe phenotype (11).

Overall, compared to the cases published previously, our patient distinctively has a complete arm agenesis and BAV making the association *HOXA9*/*HOXA13* clinically interesting.

According to the *in silico* prediction, the literature, and ACMG classification, *HOXA13*: p.(Tyr290Ser) is the most relevant variant that may explain the patient's phenotype. Indeed, the *HOXA13* variant meets the ACMG pathogenic criteria: PS3 (Well-established *in vitro* or *in vivo* functional studies supportive of a damaging effect on the gene or gene product), PM6 (Assumed de novo but without confirmation of paternity and maternity), PP2 (Missense variant in a gene that has a low rate of benign missense variation and in which missense variants are a common mechanism of disease) and PP4 (Patient's phenotype or family history is highly specific for a disease with a single genetic etiology).

Although the novel *HOXA13* variant is more clinically relevant in the present case, the contribution of the *HOXA9*/*HOXA13* genes in BAV needs to be investigated.

Our case study provides new insights into the likely implication of the *HOXA* genes not only in limb and genitourinary anomalies but also in cardiac defects found in patients with *HOXA* morphopathies.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JFA and SZ conceived and designed the study. AT, GN, JFA performed the clinical investigation of the patients and family members. SZ and JFA confirm the authenticity of all the raw data. HJ analyzed and interpreted the data, performed the molecular investigation and wrote the original draft preparation. AT, JFA and SZ critically reviewed and edited the manuscript. SZ supervised and validated the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient and family members included in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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