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BRIEF COMMUNICATION



Chromatin assembly factor subunit *CHAF1A* as a monogenic cause for oculo-auriculo-vertebral spectrum

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Oculo-auriculo-vertebral spectrum (OAVS) is characterized by abnormal development of the 1st and 2nd branchial arches. Despite arguments against a monogenic condition, a few genes have been involved in a minority of cases. We now report heterozygous, presumably loss-of function variants in the *CHAF1A* gene in 8 individuals, including 3 members of the same family. Four cases fulfill stringent diagnostic criteria for OAVS, including asymmetric ear dysplasia, preauricular tags, mandibular asymmetry +/- vertebral malformations. Two patients also presented with kidney malformations. *CHAF1A* encodes a subunit of CAF-1 (chromatin assembly factor-1), a heterotrimeric protein complex responsible for the deposition of newly synthesized histones H3-H4 onto the newly synthesized DNA strand during replication. The identification of loss-of-function variants in *CHAF1A* is consistent with the hypothesis of early developmental genes dysregulation driving OAVS and other associations recently lumped under the acronym Recurrent Constellations of Embryonic Malformations (RCEM).

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INTRODUCTION

Oculo-auriculo-vertebral spectrum (OAVS), encompassing Goldenhar syndrome, hemifacial microsomia, and facio-auriculo-vertebral spectrum, includes an abnormal development of the 1st and 2nd branchial arches and remains loosely defined with no consensual minimum clinical diagnostic criteria [1, 2] (MIM#164210, 620444). The incidence ranges from 1/3500 to 3.8/100 000 according to selected minimal criteria [3, 4]. Distinctive -although inconsistent- features include facial asymmetry (the anomalies being uni or bilateral), macrostomia due to commissural cleft, jugal tags and upper eyelid clefts. Frequent extra craniofacial anomalies include cardiac, vertebral and genitourinary malformations [5]. OAVS is classified as one of the “recurrent constellations of embryonic malformations” (RCEM), possibly occurring during blastogenesis or gastrulation [6]. The observation of an OAV-VATER association supports the hypothesis of a shared pathogenic mechanism among recurrent malformation associations [6, 7]. The molecular basis of OAVS remains largely unknown and recurrence risk in sibs and descendants is estimated to be low (2 to 3%) although variable according to definitions. Discordance in monozygotic twins, a higher incidence in pregnancies conceived via assisted reproductive technologies

and in twin gestations and, environmental factors such as maternal diabetes or vasoactive drugs, also argue against a monogenic condition [2]. However, vertical transmissions, recurrent CNVs and heterozygous variants in a few genes have been identified in a minority of OAVS cases ([2] for review), the most robust being Chr14q22.3 duplications including *OTX2* [8] and variants in *SF3B2* and *FOXI3* [9–11]. Here we report heterozygous variants in the histone assembly gene *CHAF1A* as a novel cause of OAVS, expanding the molecular landscape of disease and our understanding of its pathophysiology.

METHODS

All patients underwent exome or genome sequencing in solo, duo or trio, through their respective institutions. Cases were identified through the Genematcher (<https://genematcher.org/>) and Decipher (<https://www.deciphergenomics.org/>) exchange platforms (Table 1). Segregation analysis was done by Sanger sequencing in families A and B using standard techniques. RNA was extracted from blood samples on PAXgene tubes using the Nucleomag RNA kit (Macherey Nagel). RT-PCR was performed using the superscript II and Second Strand cDNA synthesis kits (Invitrogen), then libraries were enriched by an Agilent XT HS2 custom panel before sequencing.

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Table 1. Clinical and molecular findings.

Case	Case A / II.2, father	Case A / III.1, son	Case A / III.3, son	Case B	Case C	Case D	Case E	Case F	Nb/total (%)
Ethnicity / Country	European / France	European / France	European / France	European / Spain	European / The Netherlands	Martinique, Reunion Island, Madagascar / France	Caucasian / USA	European/Irish	
Variant gDNA (GRCh38)	19:g.4428891G>A	19:g.4428891G>A	19:g.4428891G>A	19:4429522_4429523del	19:g.4409675del	19:g.4423875G>A	19:g.4409420_4409429dup	19:g.4432073G>A	
Variant cDNA (NM_005483.3)	c.1604+1G>A	c.1604+1G>A	c.1604+1G>A	c.1687_1688del	c.876del	c.1377+1G>A	c.621_630dup	c.2069G>A	
Variant p.(protein)	p.(?)	p.(?)	p.(?)	p.(Cys563*)	p.(Thr293Profs*29)	p.(?)	p.(Thr211Profs*20)	p.(Trp690*)	
Status	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	heterozygous	heterozygous	Heterozygous	
Testing method	WES in trio	WGS in trio	Sanger	WES, verified Sanger	WES in trio	WGS in trio	WES in trio	WES in trio	
Inheritance	de novo	Inherited from II.2	Inherited from II.2	Inherited from healthy father	de novo	de novo	de novo	de novo	
Array CGH	—	—	—	Normal	SNP array - Normal	SNP array - Normal	Normal	Normal	
Other molecular analysis performed	—	—	—	—	—	Gene panel deafness - Normal	MT-DNA - Normal	—	
Other candidate variant from WES or WGS	—	—	—	—	—	—	—	—	
Sex	M	M	M	F	F	M	M	M	
Pregnancy	Unknown	NIPT Normal (low PAPP-A)	Unilateral ear tag	Unknown	Normal	Pelvic kidneyNasal bone hypoplasia	Multicystic dysplastic left kidney at 20 weeksNIPT Normal	Normal	3/6 (50%)
Birth parameters	N/A	Normal	normal	Unknown	41 +5; weight: 4720g	Normal	Normal	Normal	
Age when last seen	39 years	5 years	2.5 years	22 years	17 years	23 months	4 years	7 years	
Feeding	Normal	Normal	Normal	Normal	Normal	Normal	Sensory issues with textures, abnormal gag reflex, slow eater	Early feeding issues	2/8 (25%)
Facial features									
Mandibular asymmetry	+	+	—	+	—	—	—	+	4/7 (57%)
Commisural cleft	—	+	—	—	—	—	—	—	1/8 (13%)
Cleft lip ± palate	—	—	—	—	Unilateral cleft lip and cleft palate	—	—	—	1/8 (13%)
Microretrognathia	—	—	—	—	—	—	—	+	1/8 (13%)
Preauricular tag	Unilateral	Bilateral	Unilateral	Bilateral	Unilateral (right)	—	—	—	5/8 (63%)
Other tag	—	Jugal, unilateral	—	—	—	—	—	—	1/8 (13%)
Abnormal ear shape	Unilateral dysplastic (surgery)	Bilateral dysplastic overfolded and anteverted	—	Left dysplastic	Small low implanted left ear with flat helix	Bilateral dysplasticTragus hypoplasia, protruding antitragus	Small	Unilateral anotia	7/8 (88%)
Asymmetric ears	+	+	—	+	+	+	+	+	7/8 (88%)
external auditory canal	Normal	Normal	Normal	Normal	Normal	bilateral narrow external auditory canal	Normal	Normal	1/8 (13%)
Ocular anomalies	—	—	—	retinal coloboma	—	Mild hypertelorism	—	—	2/8 (25%)
Teeth	Normal	Normal	Normal	Dental over crowding	N/A	Normal	Dental over crowding	Normal	2/7 (29%)
Other facial features	—	—	—	—	Synophrys, periorbital fullness, nose is asymmetric, long philtrum	—	—	—	1/8 (13%)
Audition	Normal	Normal but OM and tympanic aerators until 3.5 y	Normal	Normal	Normal hearing but tympanic aerators because of OME	Normal	Normal hearing but tympanic aerators	Right severe conductive hearing loss	hearing loss 1/8 (13%)OME 3/8 (38%)
vision	Normal	Normal	normal	normal	Wearing glasses	Normal	Normal	Normal	1/8 (13%)

Table 1. continued

Case	Case A / II.2, father	Case A / III.1, son	Case A / III.3, son	Case B	Case C	Case D	Case E	Case F	Nb/total (%)
Skeletal features									
Vertebral anomalies	Fusion of C2 C3	—	—	Fusion defect of the posterior arch of C1	—	N/A	N/A	—	2/6 (33%)
Costal anomalies	—	—	—	—	—	N/A	N/A	—	0
Other skeletal malformations	—	—	—	—	—	N/A	N/A	—	0
Other									
Kidney	N/A	Normal	N/A	normal	Normal	fused pelvic kidneys (S or L shape)	Unilat renal agenesis, vesicoureteral reflux grade 1	N/A	2/5 (40%)
Heart	Normal	Normal	Normal	normal	no murmur	normal	normal	normal	0/8
Neurodevelopmental disorder	Normal	Normal	Normal	Normal	Normal motor developmentCognitive low-normal	Normal motor developmentMild speech delay	Hypotonia, delayed motor development (1-2years delayed), uncoordinated running Normal cognition but delayed socially and articulation issues	Normal	1/8 (13%)
Brain imaging	not performed	not performed	not performed	not performed	not performed	not performed	Normal MRI	Normal MRI	0/2
Other	—	—	—	—	—	—	hypothyroidism on synthroid	—	1/8 (13%)

OM otitis media, OME otitis media with effusion, N/A not assessed, NIPT non invasive prenatal test, WES whole exome sequencing, WGS whole genome sequencing.

RESULTS

CHAF1A variants were identified in 6 families (8 patients), occurred de novo in all but one sporadic case and co-segregated with the disease in the familial case (Table 1). The nature of the variants (splice variant in canonical sites, nonsense or frameshift variants) predicted loss-of-function in a gene highly intolerant to loss-of-function (pLI = 1, LOEUF = 0.05, source: gnomAD v4.0, <https://gnomad.broadinstitute.org>). The variants were absent from all databases tested, including gnomAD v4.

The index case from family A presented with asymmetric microtia, preauricular tags, facial asymmetry and a commissural cleft and was diagnosed with OAVS. His father presented with asymmetric ear dysplasia, facial asymmetry and a cervical vertebral block between C2 and C3, and the proband's younger brother had a unilateral preauricular tag (Fig. 1A). We subsequently gathered 5 additional cases that extend the clinical spectrum with incomplete penetrance for each feature. The most common features included dysplastic and asymmetric ears (7/8 patients), preauricular tags (5/8) and mandibular asymmetry (4/8) (Table 1). External ear dysplasia ranged from isolated preauricular tag to anotia (Fig. 1B). 3/8 patients benefited from tympanic aerators for otitis media and 3/8 have overcrowded teeth. Other recurrent features included cervical vertebrae malformations (2/6; cervical vertebral block or fusion defect of the posterior arch of C1) and kidney malformations (2/5; renal agenesis or fused kidneys). Non-midline cleft lip and palate, mild neurodevelopmental delay and retinal coloboma were each reported once and it remains unclear whether these features are the consequence of *CHAF1A* loss-of-function.

The variation occurred de novo in 4 of the 5 of the sporadic cases. In family A, it occurred de novo in the affected father (Fig. 1A) that transmitted it to his 2 affected sons and not to his unaffected daughter. Concerning case B, the variation is inherited from an unaffected parent after clinical reassessment, indicating possible incomplete penetrance.

The variants are scattered along the gene (Fig. 2A). To evaluate the consequences of one splice variation, we performed cDNA sequencing in an affected case from family A carrying the c.1604+1 G > A variant in intron 8. We detected two abnormal transcripts compared to controls (Fig. 2B): one skipping exon 8 and the other using an intronic cryptic splice site located 16 bp 5' of the normal splice site, both resulting in a frameshift and a premature stop codon, supporting variant pathogenicity.

DISCUSSION

In accordance with numerous observations of isolated ear dysplasia or preauricular tag(s) in first degree relatives of patients with a full blown OAVS [12], phenotypic variability is observed within family A. Indeed, the younger son presented with a single preauricular tag and would not have been suspected of OAVS without his medical familial history. Worth noting, there is a correlation between the presence of preauricular tags and *CHAF1A* being included in chr19p13.3 deletions (while mandibular asymmetry is not mentioned but could be overlooked in patients presenting multiple congenital anomaly and intellectual disability) [13]. Regarding sporadic cases, a clinical diagnosis of OAVS was made prior to molecular studies for patients B and F (2/5) but such was not the case for sporadic cases C, D and E (3/5), who presented atypical features, including bilateral and symmetric ear dysplasia, absence of mandibular asymmetry and/or preauricular tags, and presence of a cleft lip and palate in 1 proband. Furthermore, 1 among 12 asymptomatic parents being a carrier, incomplete penetrance could be observed.

The occurrence of nonsense, frameshift or canonical splice sites variants in 8 patients argues for loss-of-function. *CHAF1A* is highly intolerant to loss-of-function, with very few standing variations in gnomAD v4 (LOEUF [0.02–0.11], i.e. more intolerant than other OAVS genes: *SF3B2* [0.12–0.25], *FOXI3* [0.16–0.73] where mono and

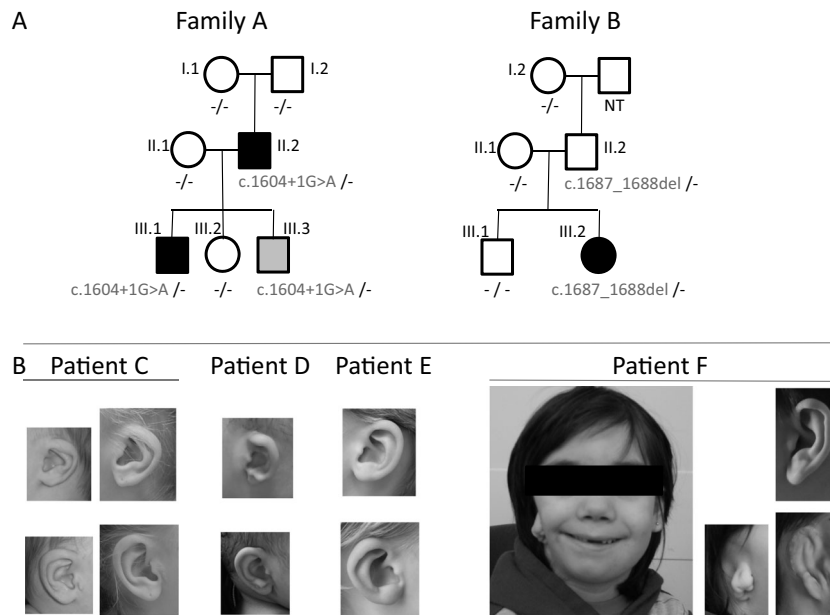


Fig. 1 Familial and clinical findings of patients. **A** Simplified family tree for familial cases. Black circles or squares: affected. Gray: mild phenotype. NT: not tested. **B** Photographs of patients. Left and right ears of patient (C) at 2 months and 11 years of age, patient (D) at 2 years, patient (E) at 6 years, patient (F) frontal view and right profile view at 7 years and at 13 years after reconstruction surgery of right ear. The patients are labeled as in Table 1.

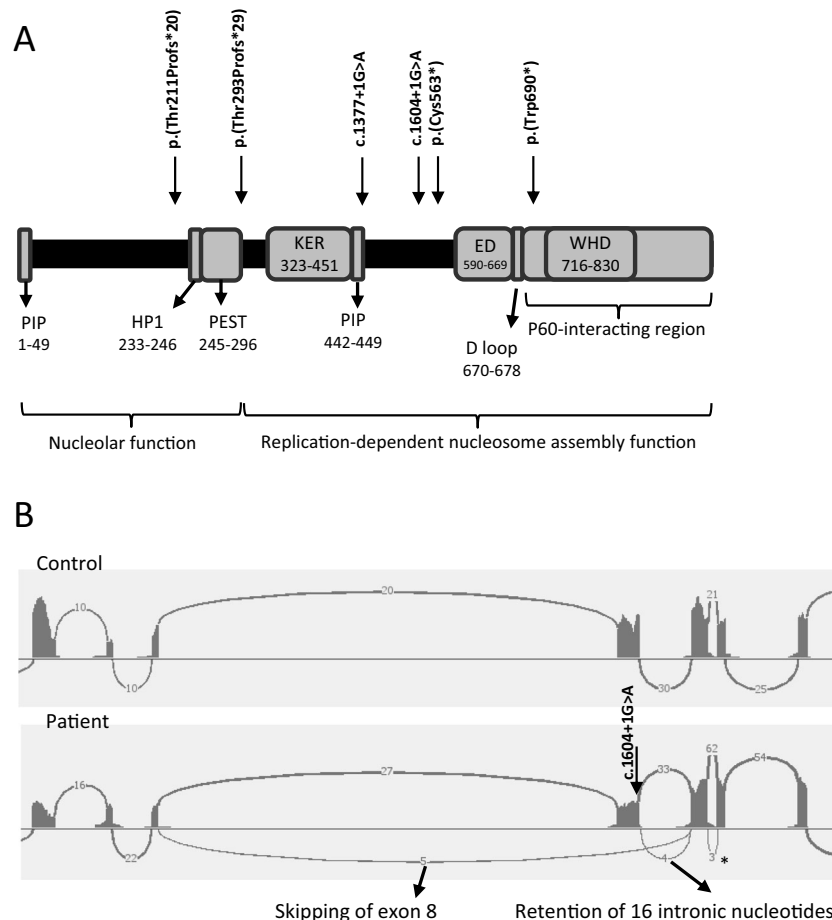


Fig. 2 Molecular findings. **A** Representation of CHAF1A domains along with the variants identified in this study. The protein domains are indicated according to Gopinathan Nair 2022 [17]. **B** Sashimi plot of the CHAF1A cDNA sequencing in a control and a patient from family A, showing two different aberrant splicing isoforms resulting in a frameshift (arrows). Junctions supported by a single read have been filtered. The junction labeled with * was found on a few reads in several controls and is not predicted pathogenic.

biallelic variants have been reported in patients—note that LEUF does not apply to *OTX2* due to triplosensitivity as the disease-causing mechanism). The canonical splice site variant tested showed aberrant transcripts presumably leading to synthesis of truncated proteins in addition to NMD presumed with a canonical splice site variant.

CAF-1 (chromatin assembly factor-1, MIM 601246) is part of an evolutionarily conserved heterotrimeric protein complex made of p48 (encoded by *RBBP4*), p60 (encoded by *CHAF1B*) and p150 (encoded by *CHAF1A*) subunits. CAF-1 is responsible for the deposition of newly synthesized histone H3-H4 dimers onto the newly synthesized DNA strand during replication and repair [14, 15]. CAF-1 is also involved in the maintenance of heterochromatin domains through cell division and in asymmetric cell division [16]. Within the complex, p150 is the subunit that recognizes the DNA strand through binding to PCNA via its PIP (PCNA Interaction Protein) motif. p150 also binds p60 to carry H3-H4 histones to the assembly fork for the formation of nucleosomes [14]. Structural resolution of the human CAF-1 complex in nucleosome formation shows that p150 binds p60 by its C terminus and p48 by its middle. In addition, its ED-loop secures binding of the H3-H4 heterodimer to p48 and p60 [15]. Apart from PIP motifs and the ED loop, p150 also contains a KER domain (rich in lysine, glutamic acid, and arginine) that forms a long helix and is involved in DNA binding, a SUMO-interacting domain, an HP1 (heterochromatin 1 protein) interacting domain, and a WHD (Winged helix domain) in the C-terminal region that mediates interaction with the p60 subunit (Fig. 2B). A Proline, Glutamic acid, Serine and Threonine-rich (PEST) domain present in both p150 and p60 is presumed to regulate the degradation of unbound subunits of the complex (p150 structure is reviewed in [17]).

Homozygous loss of *Chaf1a* in mouse model leads to severe alterations in heterochromatin organization in pluripotent embryonic cells and developmental arrest at the 16-cells stage. The phenotype has not been evaluated in heterozygotes beyond viability ([18] and M. Gerard, personal communication). In yeast, depletion of individual CAF-1 subunits does not affect cell viability but induces de-repression of silenced genes as a consequence of abnormal heterochromatin organization [19]. RNA-seq analyses showed that induced degradation of p150 in yeast leads to upregulation of ~2500 genes and downregulation of ~250 genes, which is consistent with a functional role for CAF-1 in gene silencing via heterochromatin organization [15]. The dysregulation of numerous genes due to *CHAF1A* loss-of-function likely participates to the phenotypic variability observed in patients. As with *OTX2* and *FOXI3* (transcription factors; regulation of gene expression) and *SF3B2* (component of the spliceosome; mRNA maturation), this is consistent with the hypothesis of RCEMs being the consequence of early, possibly epigenetic dysregulation of gene expression considering *CHAF1A* function.

We propose that *CHAF1A* be added to the list of rare monogenic causes of OAVS with variable expression and possibly incomplete penetrance. Molecular testing in a larger series of patients will further define the clinical spectrum of *CHAF1A*-related disease.

DATA AVAILABILITY

The variants have been submitted to ClinVar, accession number SCV005061834 to 1839. Other data generated or analyzed during this study are included in the published article. Details are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

VP, JDE, NMG, ALA, BC, IMML, EARN, RS, PJ, TD, HZE, AS, SH, AP, PB, JA conducted molecular and clinical evaluation of the patients. FO revised the manuscript according to CAF-1 function. VP set up the study and collected the data. JA and VP wrote the manuscript that was reviewed and edited by all authors.

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COMPETING INTERESTS

There is no competing interest. HZE is an employee of GeneDx, LLC, USA.

ETHICAL APPROVAL

These studies have been approved by institutional committees in each country when performed on a research basis. Ethical approval was not required for case reports based on analysis performed in diagnostic conditions. Consent for publication of photos was obtained.

ADDITIONAL INFORMATION

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