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CASE REPORT

Chung–Jansen syndrome can mimic Cornelia de Lange syndrome: Another player among chromatinopathies?

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Abstract

Cornelia de Lange syndrome (CdLS) is a rare multisystem congenital neurodevelopmental disorder (NDD) characterized by distinctive facial anomalies, short stature, developmental delay, hirsutism, gastrointestinal abnormalities and upper limb reduction defects. CdLS syndrome is associated with causative variants in genes encoding for the cohesin complex, a cellular machinery involved in chromatid pairing, DNA repair and gene-expression regulation. In this report, we describe a familial case of a syndromic presentation in a 4-year-old patient (P1) and in his mother (P2). Trio-based Whole Exome Sequencing (WES) performed on P1 was first negative. Since his phenotypic evolution during the follow-up was reminiscent of the CdLS spectrum, a reanalysis of WES data, focused on CdLS-related genes, was requested. Although no alterations in those genes was detected, we identified the likely pathogenetic variant c.40G > A (p.Glu14Lys) in the *PHIP* gene, in the meanwhile associated with Chung-Jansen syndrome. Reverse phenotyping carried out in both patients confirmed the molecular diagnosis. CHUJANS belongs to NDDs, featuring developmental delay, mild-to-moderate intellectual disability, behavioral problems, obesity and facial dysmorphisms. Moreover, as here described, CHUJANS shows a significant overlap with the CdLS spectrum, with specific regard to facial gestalt. On the basis of our findings, we suggest to include *PHIP* among genes routinely analyzed in patients belonging to the CdLS spectrum.

KEYWORDS
CdLS, CHUJANS, Chung–Jansen syndrome, Cornelia de Lange syndrome, PHIP, whole exome sequencing

1 | INTRODUCTION

Cornelia de Lange syndrome (CdLS, OMIM #122470) is a rare and genetically heterogeneous condition with multisystemic involvement and considerable phenotypic variability. The estimated prevalence varies between 1/10,000 and 1/30,000 individuals (Kline et al., 2007). CdLS is further characterized by prenatal and/or postnatal growth retardation, distinctive facial anomalies, short stature, developmental delay (DD) and intellectual disability (ID), behavioral problems, possible major malformations, upper limb defects and hirsutism (Deardorff

et al., 1993; Kline et al., 2018). In particular, craniofacial features of CdLS include micro-brachycephaly, synophrys, arched eyebrows, long eyelashes, depressed nasal bridge, anteverted nares, long philtrum, thin upper lip, high arched palate, late eruption of small widely spaced teeth, micrognathia (Beck & Fenger, 1985).

The genetic basis of CdLS was firstly recognized in genes encoding the cohesin complex, a cellular machinery involved in chromatid pairing, DNA repair and gene-expression regulation. In fact, most individuals affected from the CdLS spectrum carries de novo pathogenic variants in cohesin-complex coding genes like *NIPBL*, *RAD21*, *SMC3*, *BRD4*, *MAU2*, with autosomal dominant inheritance, and *SMC1A* and *HDAC8* which present an X-linked inheritance. Less than 1% of individuals with autosomal dominant CdLS inherit the variant from an affected parent while X-linked variants are usually de novo (Huisman et al., 2017). Besides classic CdLS presentation, other nonclassic and overlapping phenotypes have been outlined. With the widespread application of whole exome sequencing (WES), subjects within the CdLS spectrum have been diagnosed with pathogenic variants in morbid genes already acknowledged for partially overlapping conditions, such as KBG, Kabuki, Rubinstein-Taybi and Coffin-Siris syndromes (Avagliano et al., 2020).

Chung–Jansen Syndrome is a recently identified condition (CHUJANS OMIM #617991), featuring global DD, ID, behavioral problems, obesity and facial dysmorphisms. To date, about 50 cases of CHUJANS have been described, with variable clinical expressivity and severity. ID is reported in most affected individuals and can vary from mild to severe. Behavioral problems may include ADHD (Attention-Deficit/Hyperactivity Disorder), autistic features, mood and/or anxiety disorders (Craddock et al., 2019; Jansen et al., 2018; Webster et al., 2016). Overweight and obesity have been suggested as core clinical features, although their prevalence vary among case series (Craddock et al., 2019). Facial dysmorphisms may include full eyebrows, synophrys, upturned nose, large ears, tapering fingers and bilateral clinodactyly of the fifth finger. CHUJANS has been related to missense or presumably loss-of-function (nonsense, frameshift, splice site, translocation, gene deletion) heterozygous variants in the gene *PHIP* (Craddock et al., 2019; Jansen et al., 2018; Webster et al., 2016), mapping to chromosome 6q14 and encoding a Pleckstrin homology domain-interacting protein (*PHIP*). *PHIP* is involved in insulin signaling pathway (Farhang-Fallah et al., 2002), neuronal differentiation, E3 ubiquitination and histone binding (Han et al., 2013; Lee & Zhou, 2007; Morgan et al., 2017). All the reported variants occurred de novo, with the exception of one single case, in which the pathogenic variant was inherited from an affected parent (Craddock et al., 2019; Jansen et al., 2018).

In addition to some nonspecific features such as DD and ID, CHUJANS shares prominent features of CdLS facial gestalt, which are also enlisted in its clinical score (Table S1). Based on the CHUJANS individuals described so far, the two conditions seem to differentiate mostly on growth parameters (pre-natal and post-natal growth delay being characteristic only for CdLS), and the overall malformative pattern; contrary to CdLS, CHUJANS does not appear to be associated with major malformations. Furthermore, the obesity/overweight that currently seems to characterize the clinical picture of CHUJANS is not a typical feature of CdLS.

In this report, we describe a familial case of a syndromic presentation initially framed within the CdLS spectrum and subsequently diagnosed with CHUJANS.

2 | METHODS

The patients received standard healthcare services. All genetics tests were performed after counseling and written consent. Array-CGH analysis was performed using a 60-mer oligonucleotide probes technology (SurePrint G3 Human CGH 8x60K, Agilent Technologies, Santa Clara, CA, USA) according to manufacturer's protocol. Trio-based WES was performed as previously described (Pezzani et al., 2018). The exonic and flanking splice junctions regions of the genome were captured using the Clinical Research Exome v.2 kit (Agilent Technologies, Santa Clara, CA). Sequencing was performed on a NextSeq500 Illumina system with 150 bp paired-end reads. Reads were aligned to human genome build GRCh37/UCSC hg19 and analyzed for sequence variants using a custom-developed analysis tool. On average, coverage on target was ≥10X for 97.6% with a mean coverage of 250X.

Two pipelines were used to identify the copy number variants (CNVs) based on ExomeDepth and one created in-house, as previously described (Pezzoli et al., 2021). All the CNVs detected by both pipelines were annotated by matching every call with the genes involved and related diseases and classified according to ACMG and ClinGen guidelines (Riggs et al., 2020).

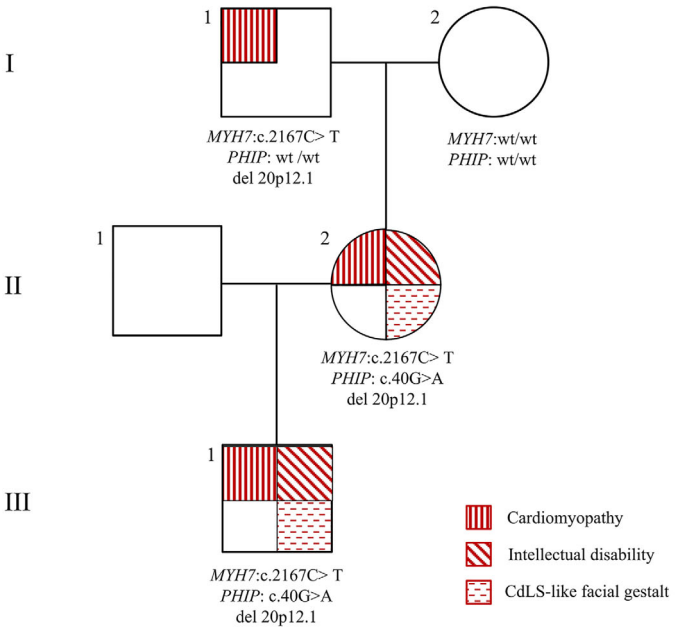
3 | RESULTS

3.1 | Patient 1 (P1)

P1 is a firstborn to nonconsanguineous parents of Italian origin (individual III.1 in Figure 1a). He was born at term from elective C-section, birth weight was 2450 g (SGA 10° percentile). At birth, the child experienced neonatal distress and needed resuscitation with intubation and cardiac massage.

The clinical evaluation showed the presence of minor anomalies of the face such as triangle shaped face, synophrys, long eyelashes, short nose, thin upper lip vermilion. An esophageal atresia with fistula was identified and surgically corrected. Echocardiography showed biventricular nonobstructive cardiac hypertrophy, with asymmetric hypertrophy (left > right) of the ventricular septum. Cerebral MRI revealed the presence of a thinned corpus callosum, malrotation of the hippocampi and a thinning of the olfactory bulbs. The abdomen ultrasound found horseshoe kidneys with differentiated parenchyma. The neurofunctional examination was characterized by axial hypotonia and rigidity of the limbs. During the follow-up his clinical picture was enriched with new features suggestive for the CdLS spectrum, such as small widely spaced teeth, short fifth finger with clinodactyly and hypertrichosis, while some facial anomalies became coarser and a global delay in psychomotor development and a failure to thrive emerged (Figure 1b,c). Using the CdLS Clinical score he scored

(a)



(b)

Cornelia de Lange syndrome clinical score	P1	P2
Cardinal features (2 points each if present)		
Synophrys (HP:0000664) and/or thick eyebrows (HP:0000574)	2	2
Short nose (HP:0003196), concave nasal ridge (HP:0011120) and/or upturned nasal tip (HP:0000463)	2	2
Long (HP:0000343) and/or smooth philtrum (HP:0000319)	2	2
Thin upper lip vermilion (HP:0000219) and/or downturned corners of mouth (HP:0002714)	2	2
Hand oligodactyly (HP:0001180) and/or adactyly (HP:0009776)		
Congenital diaphragmatic hernia (HP:0000776)		
Suggestive features (1 point each if present)		
Global developmental delay (HP:0001263) and/or intellectual disability (HP:0001249)	1	1
Prenatal growth retardation (<2 SD) (HP:0001511)		
Postnatal growth retardation (<2 SD) (HP:0008897)		
Microcephaly (prenatally and/or postnatally) (HP:0000252)		
Small hands (HP:0200055) and/or feet (HP:0001773)		
Short fifth finger (HP:0009237)	1	
Hirsutism (HP:0001007)	1	
Score	11	9

(c)

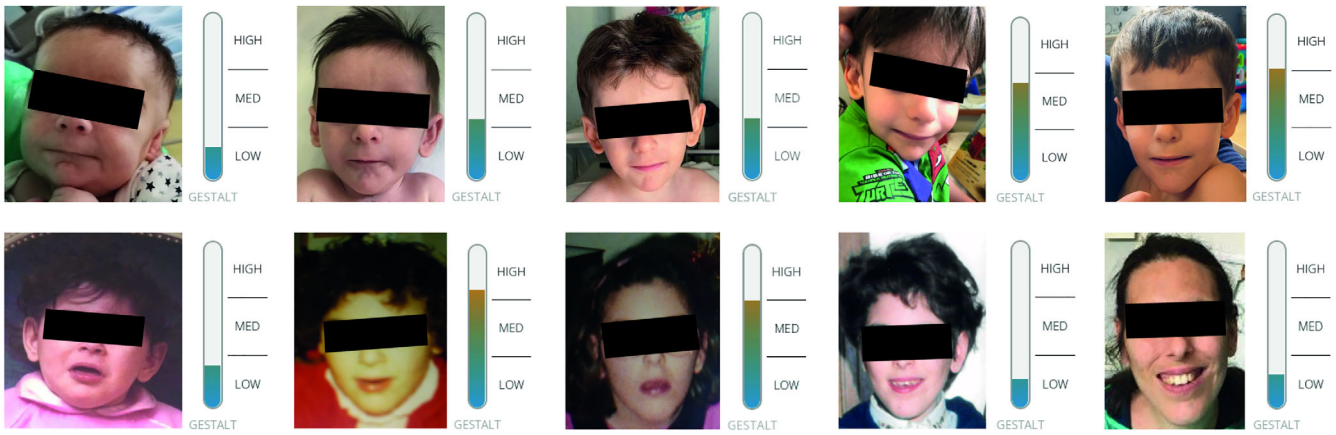


FIGURE 1 Panel a represents the pedigree of P1 and P2; Panel b reports the CdLS clinical score of P1 and P2 according to ref. 2, scoring 11 points (classic CdLS) and 9 points (nonclassic CdLS), respectively; panel c shows the evolution of the facial gestalt of P1 (upper row) and P2 (lower row) together with the gestalt bar graph for CdLS provided by Face2Gene. CdLS, Cornelia de Lange syndrome.

11 points, consistent with a classical CdLS phenotype. At the last evaluation (3 years old), his weight was 11.690 g (<3th percentile), length 89.5 cm (3–5th percentile), CC 47 cm (3–10th percentile). He was able to use some words of complete meaning, even combining them in short sentences, and he has not toilet-trained yet. He started crawling at 30 months of age, walking with support at 34 months. The developmental Griffiths scale was performed at the age of 36 months and revealed a General Quotient (GQ) of 44 (corresponding to 17 months of developmental age), consistent with a moderate psychomotor delay (according to ICD 10). His profile is asymmetric, showing as points of strength the Language/Communication scale, (QS of 86, corresponding to 27 months), and the Personal Social scale, (QS of 67, corresponding to 23 months) and, as weak areas, Gross Motor scale (QS 31 corresponding to 12 months), Eye and Hand Coordination scale (QS 47 corresponding to 19 months), and practical reasoning scale (QS 60 corresponding to 17 months).

3.2 | Patient 2 (P2)

P2 (individual II.2 in Figure 1a) is the mother of P1. She is a firstborn to unrelated parents. She is affected from insulin-dependent diabetes, hypothyroidism and hypertrophic cardiomyopathy (HCM) of the left ventricle. Treated with orthopedic corset during adolescence for dorsal kyphosis. She was diagnosed for the first time at the age of 11 with psychomotor delay and intellectual disability. At the age of 18 she had an IQ evaluation (2001) with Wechsler-Bellevue intelligence scale with FISQ score of 48, with disharmonic profile (QIV = 59, QIP = 48)

consistent with moderate intellectual disability. She also presents synophrys, arched and thick eyebrows, long eyelashes, long philtrum, thin upper lip, high arched palate, proximal thumb implantation, clinodactyly of the II finger, slight shortening of the IV-V metacarpus bilaterally. Her CdLS clinical score is 9 points, consistent with a Cornelia-like phenotype.

The set of clinical features of both patients pointed toward a constitutional basis, subsequently a CGH-array analysis and Whole Exome Sequencing analysis were performed.

3.3 | Genetic analysis

Array-CGH detected in P1 a deletion of about 384 Kb in the region p12.1 of chromosome 20 containing the *FLRT3* gene and part of *MACROD2* gene. The same deletion was inherited from his mother and was also found in the nonsymptomatic maternal grandfather. As array-CGH results were not conclusive, when P1 was 3-month-old, we proceeded with a trio-based WES. This analysis was first focused on the likely syndromic presentation and did not highlight any pathogenic variant. During the follow-up, due to the evolution of the facial gestalt of P1 and the novel diagnosis of HCM also in P2, WES results were reanalyzed, identifying two heterozygous variants of maternal origin: the c.2167C > T (p.Arg723Cys) variant in the *MYH7* gene and the c.40G > A (p.Glu14Lys) variant in the *PHIP* gene. The variant c.2167C > T (GRCh37:g.23895023; NM_000257.3) in exon 20 of the *MYH7* gene (OMIM * 160760) leads to the replacement of the amino acid arginine with a cysteine in position 723 of the protein, is a rare sequence change (gnomAD MAF: 3/251214), bioinformatics prediction tools indicate that the change is deleterious to protein function, is described and classified as pathogenic on ClinVar database (ClinVar Variation ID 14095 accession VCV000014095.28) (Landrum et al., 2018). In consideration of the familiar presentation of the HCM, its echocardiographic features, overlapping what currently known about *MYH7*-related HCM, and the segregation of the variant, we retained the *MYH7* variant as causative of the familiar HCM. P1, P2 and the maternal grandfather (I.1 in Figure 1a) are on cardiological follow-up for monitoring their cardiomyopathy.

The variant c.40G > A (GRCh37:g.79787746; NM_017934.6) in exon 1 of the *PHIP* gene (OMIM * 612870) leads to the substitution of a glutamic acid with a lysine at the residue 14. This variant is not reported in the literature and neither in population database (gnomAD MAF 0). According to current ACMG criteria, since the variant has never been described before and it is of the missense type, considering its presence in both patients and its absence in the maternal grandparents, it was classified as likely pathogenetic. No additional pathogenic variant in chromatinopathy-related genes associated with CdLS-related conditions has been identified.

4 | DISCUSSION

As defined in the International Consensus published in 2018, the CdLS spectrum includes both classic and nonclassic CdLS individuals on the basis of their clinical presentation and the presence of causative variants in genes belonging to chromatin regulators, among which the cohesin family (Kline et al., 2018). Importantly, the clinical diagnosis of CdLS can be equally retained if the CdLS score is equal or higher than 11 points. The availability of genotype-driven analysis has recently broadened the list of genes functionally related to the cohesin machinery and whose haploinsufficiency leads to conditions either belonging to or overlapping with the CdLS spectrum (Avagliano et al., 2020; Cucco et al., 2020).

In our case, the proband (P1) was initially evaluated during his hospitalization in the neonatal intensive care unit. Due to the presence of multiple congenital malformations, a Whole Exome Sequencing (WES) was performed but, at that time, did not reveal any pathogenic variant. During the follow-up the appearance of developmental delay, hirsutism and the evolution of his facial gestalt led to a strong clinical suspicion of CdLS (Figure 1c), corroborated by a clinical CdLS score of 11 points. His clinical picture was partially shared with the mother (P2), who had a CdLS score of 9 points, thus falling within the nonclassic CdLS (Figure 1b). When the proband was 2.5 years old, WES data were reanalyzed and disclosed the maternal c.40G > A variant in the PHIP gene, which in the meantime had been associated to CHUJANS. Reverse phenotyping verified the significant overlap of both subjects with CHUJANS (Table S1), also considering that P2 has shown a significant weight gain from 2018 to 2021 and currently has a BMI of 31, which is consistent with obesity I, expected in CHUJANS. To our knowledge, this is the second report of a CdLS-like phenotype associated with a pathogenic PHIP variant (Aoi et al., 2019).

The strong resemblance of the facial gestalt of P1 to CdLS was also objectified by means of the Face2Gene software (FDNA Inc., Boston, MA, USA; https://www.face2gene.com), already employed to support the facial recognition of cohesinopathies (Basel-Vanagaite et al., 2016; Latorre-Pellicer et al., 2020). Face2Gene showed significant scores in the facial gestalt bar graph, being CdLS the first diagnostic suggestions in all the five pictures of P1 and in 3/5 pictures of P2 shown in Figure 1. Notably, the CdLS score of our proband was sufficient to retain a clinical diagnosis of CdLS in case no causative variant was identified although, retrospectively, the occurrence of esophageal atresia and horseshoe kidney is not strongly associated with CdLS and the presence of hypotonia, usually not described in CdLS, could have made us lean toward a differential diagnosis.

As for other syndromes presenting with a broad clinical spectrum, the boundaries between genic heterogeneity and overlapping differential diagnosis may be thin. Only nontargeted approaches can identify new causative genes and contribute to increase the molecular diagnostic yield in subjects with a clinical diagnosis. Based on our findings, we suggest that *PHIP* should be included among genes routinely analyzed in patients belonging to the CdLS spectrum and underline how gene panels may be inconclusive even following patients' selection based on validated clinical criteria. Further studies will clarify the extent of the overlap between *PHIP* and CdLS, as well as possible genotype–phenotype correlations. The gene *PHIP* encodes a protein, termed PH-interacting protein or *PHIP*, involved in insulin and insulin-like signaling (Farhang-Fallah et al., 2002), cytoskeletal organization (Bai et al., 2011) but also binding to methylated H3K4 in

correspondence of enhancers and promoters, by means of its Crypto-Tudor domain (Morgan et al., 2017). It is not surprising that *PHIP* is not part of the cohesin machinery, as several lines of evidence now support the biological and clinical overlap among cohesinopathies and chromatinopathies/disorders of the epigenetic machinery (García-Gutiérrez & García-Domínguez, 2021; Parenti & Kaiser, 2021): (i) molecular findings demonstrate the increasing and substantial role of the cohesin complex in transcriptional regulation (Dorsett, 2011; Maya-Miles et al., 2019; Schwarzer et al., 2017; Wang et al., 2021); (ii) CdLS cellular models do not show an impaired sister chromatid cohesion but a global transcriptomic perturbance (Castronovo et al., 2009; Liu et al., 2009); (iii) several chromatinopathies represent differential diagnosis of CdLS and pathogenic variants in some of their causative genes (*AFF4*, *ANKRD11*, *EP300*, *KMT2A*, *SETD5*, SWI/SNF complex genes) are found in individuals with suspected CdLS (Avagliano et al., 2020; Cucco et al., 2020); (iv) a genome-wide methylation signature has been described also for CdLS, as for many chromatinopathies (Aref-Eshghi et al., 2020). Finally, regarding the complex clinical presentation of our patients, we want to stress that the presence of HCM has been related to the pathogenic variant c.2167C > T in the gene *MYH7*. With regards to the 20p12.1 deletion, it encompasses the gene *FLRT3* and, partially, the gene *MACROD2*. *FLRT3* is causative of an autosomal dominant form of hypogonadotropic hypogonadism with anosmia (OMIM #615271) (Miraoui et al., 2013) whereas *MACROD2* has been suggested as a susceptibility gene for neurodevelopmental disorders (Kushima et al., 2018) or other malformative phenotypes (Lombardo et al., 2019; Ruaud et al., 2020). Considering the published cases for the *FLRT3*-related hypogonadotropic hypogonadism (Firth et al., 2009), haploinsufficiency does not seem to be the pathogenic mechanism. Regarding *MACROD2*, its two isolated deletions gathered in the DECIPHER database are annotated as likely pathogenic for developmental delay (patients 301,497 and 331,363). In our case, the familial 20p12.1 deletion has been transmitted by the unaffected maternal grandfather. Although it is not possible to exclude that the presence of this deletion might have exerted a contributive role in some traits of the familial phenotype (thinning of the olfactory bulbs in the proband, severity of ID), we do not have clear evidence of its expression in this family. In conclusion, even though CHUJANS has been only recently described, we confirm that this condition may result in CdLS-like/chromatinopathy-related appearance, particularly regarding the facial gestalt. In our opinion CHUJANS should be included among CdLS differential diagnosis and *PHIP* should be likewise added to (virtual) gene panels applied for molecular diagnostics. Further delineation of CHUJANS will improve the definition of this overlap, clarify possible allelic-specific correlations and ascertain the presence of an associated DNA methylation episignatures.

AUTHOR CONTRIBUTIONS

Maria Iascone carried out the experiments and analyzed the data; Berardo Rinaldi and Beatrice Conti drafted the manuscript, designed the figures and wrote the manuscript; Martina Rimoldi and Roberta Villa provided literature review; Maria Francesca Bedeschi, Silvana Gangi, Matteo Porro, Paola Francesca Ajmone, Anna Maria Colli took part in patient follow-up, data management and interpretation; Fabio Mosca provided a critical review of the article; Maria Francesca Bedeschi conceived the study and was in charge of the overall direction and planning; all authors provided critical feedback and helped shape the research, analysis and manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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