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SHORT REPORT

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CATSHL syndrome, a new family and phenotypic expansion

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Abstract

We report the case of a 12-year-old girl and her father who both had marked postnatal tall stature, camptodactyly and clinodactyly, scoliosis and juvenile-onset hearing loss. The CATSHL (CAmptodactyly – Tall stature – Scoliosis – Hearing Loss syndrome) syndrome was suspected, and molecular analysis revealed a hitherto unreported, monoallelic variant c.1861C>T (p.Arg621Cys) in *FGFR3*. This variant affects the same residue, but is different than, the variant p.Arg621His reported in the two families with dominant CATSHL described so far. Interestingly, peg-shaped incisors were observed in the proband, a feature never reported in CATSHL but typical of another *FGFR3*-related condition, LADD (Lacrimo – Auricolo – Dento – Digital) syndrome. The *FGFR3* p.Arg621Cys variant seems to be a newly identified cause of CATSHL syndrome with some phenotypic overlap with the LADD syndrome.

KEYWORDS
camptodactyly, CATSHL syndrome, deafness, *FGFR3*, LADD syndrome, overgrowth, scoliosis

1 | INTRODUCTION

CATSHL syndrome [MIM: #610474] is an ultrarare condition first described by Toydemir et al in 2006.[1] They found a novel missense monoallelic variant in *FGFR3* gene in 27 affected individuals from seven generations of the same family with an autosomal dominant transmission, and named the condition CATSHL syndrome, an acronym for CAmptodactyly – Tall stature – Scoliosis – Hearing Loss syndrome. Less frequent clinical features are microcephaly, pectus excavatum and intellectual disability.

FGFR3 is a membrane-spanning receptor tyrosine kinase that plays as high affinity receptor for multiple fibroblast growth factors. Activating *FGFR3* mutations resulted in impaired endochondral bone growth through defective proliferation and differentiation of growth plate chondrocytes, thus leading to short-limbs skeletal dysplasias and craniosynostosis syndromes (Achondroplasia, Hypochondroplasia, Thanatophoric dysplasia I/II, Muenke syndrome, Crouzon syndrome with acanthosis nigricans, and SADDAN—severe achondroplasia with developmental delay and acanthosis nigricans—syndrome). On the contrary, loss of function *FGFR3* mutations cause overgrowth of long bones in mice and in individuals with CATSHL syndrome, highlighting the important role of *FGFR3* as a negative regulator of bone growth.[1–5] In 2016 a second report of two members from another family, described by Escobar et al., confirms the unique phenotype of this condition and the specificity of the pathogenic variant in *FGFR3*.[3] Here we report a new family with CATSHL syndrome with some shared features with LADD (Lacrimo – Auricolo – Dento – Digital) syndrome.

2 | CASE REPORT

The proband (P1) is a 12-year-old girl born to non-consanguineous Italian couple, which was addressed to our Center in the suspicion of an overgrowth syndrome.

Pregnancy was uneventful, except for dysplastic multicystic right kidney and femur length at the upper limits at morphology scan. She was born at 40 weeks of gestation; birth weight was 3.250 kg (50–75th centile) and length 52 cm (50th centile). Length became >97th centile since the first months of life, and the right dysplastic kidney atrophied over time.

Thyroid and pelvic US scan were normal, whereas carpal x-ray revealed a bone age 4 years older than chronological age. In addition, spine x-ray revealed left-convex lumbar rotoscoliosis with moderate right-convex compensatory curvature. She also had valgus knees and flat feet. At the age of 10 years, bilateral pantonal sensorineural hearing loss was diagnosed. Dental examination revealed peg-shaped incisors.

At 12 years of age, she weighed 74.8 kg (+2.04 SD), height was 185.5 cm (+4.35 SD), and she had relative microcephaly, since occipitofrontal circumference (OFC) was 52.2 cm (−0.95 SD); body mass index (BMI) was 21.7 (+0.44 SD), arm-span was 182 cm with normal arm span/height ratio (0.98). Her intellectual and social development was normal. Mild dysmorphic features include high frontal hairline, slight asymmetric face, deeply set eyes, slight prognathism, small ears, bifid uvula and peg-shaped incisors. She had long and thin fingers, prominent phalanx epiphyses, camptodactyly of fingers and toes, first and second fingers clinodactyly on the left hand and of second and third fingers on the right hand. She also had clinodactyly and proximal placement of the fifth toes bilaterally (Figure 1). She showed mild joint hyperextensibility with Beighton score of 5/9 (Positive Beighton score ≥5). Skin examination revealed no striae distensae, bruising, atrophic scars or pigmentation disorders.

The proband's father (P2) was tall 201 cm (+3.96 SD), he had camptodactyly and hypoplasia of the left second finger, and bilateral clinodactyly of second and third right fingers, with prominent interphalangeal epiphyses (Figure 1). He had thoracic scoliosis that required spinal surgery at the age of 23. During childhood he also showed progressive bilateral pantonal sensorineural hearing loss, and he did not have dental anomalies. The other members of the family were reported with normal stature and in good health (Figure 2).

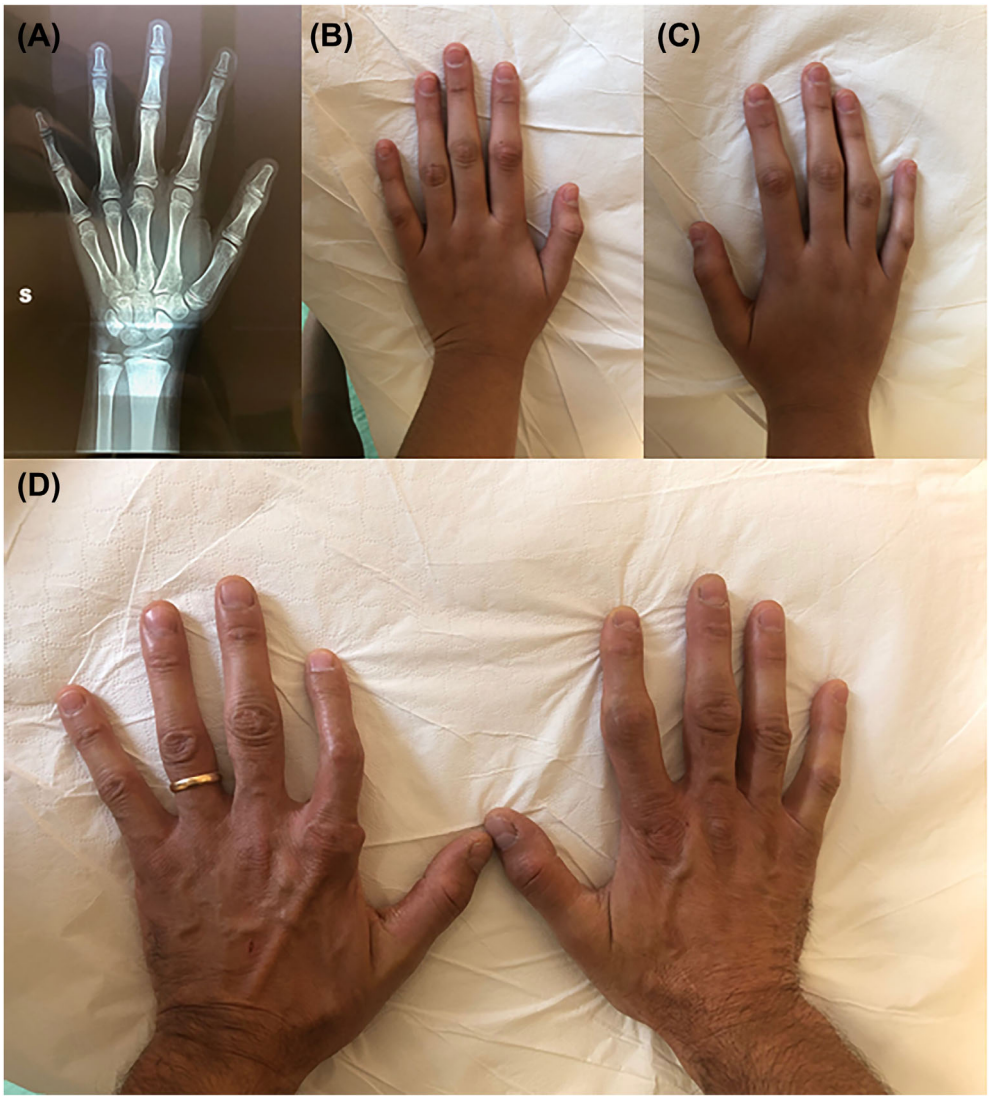

FIGURE 1 P1 (A–C) and P2 (D) hands compared. [Colour figure can be viewed at wileyonlinelibrary.com]

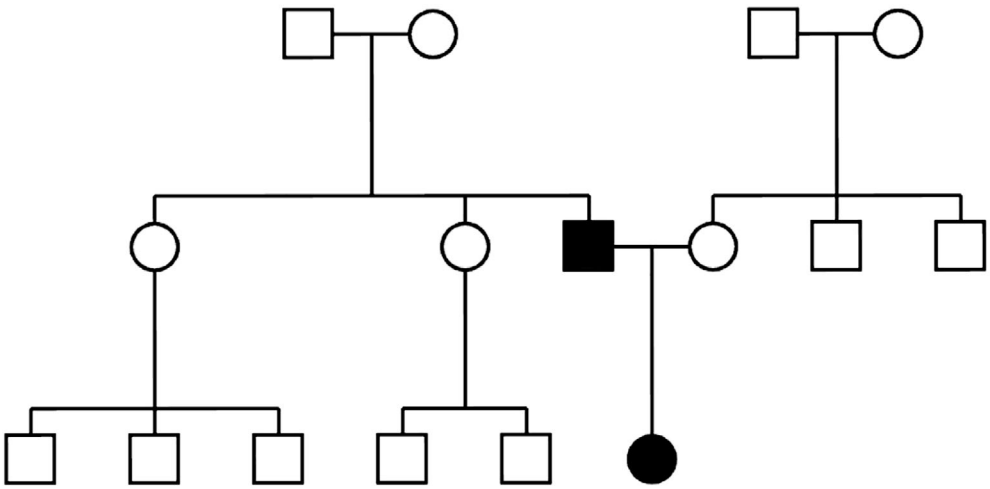

FIGURE 2 Pedigree of the family.

Based on the clinical features shared by the two patients CATSHL syndrome was suspected, then exon 14 and flanking exons of *FGFR3* gene sequencing was performed.

3 | MATERIALS AND METHODS AND RESULTS

This study was approved by the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Ethical Committee and Scientific Board (N°734-2018). Written informed consent has been obtained from the patients.

DNA was extracted from peripheral blood leukocytes by an automated DNA extractor (iPrep Blood Invitrogen) followed by PCR amplification of *FGFR3* (NM_000142.5) gene using the standard method. Utilizing forward and reverse primers separately were amplified by PCR using BigDye Terminator Cycle Sequencing kit (Thermo Fisher Scientific). Following the amplification, purification was conducted to prepare the samples for sequencing, which was performed using the series Genetic Analyzer 3500 (Thermo Fisher Scientific). Variants were described according to the HGVS nomenclature.

The analysis allowed the detection of the heterozygous likely pathogenic variant c.1861C>T, p.(Arg621Cys) in *FGFR3* in the two probands P1 and P2.

4 | DISCUSSION

Here we report the case of a 12-year-old girl that came to our observation for statural overgrowth, sensorineural hearing loss, scoliosis, and monolateral kidney dysplasia. At clinical examination she also had relative microcephaly and camptodactyly of fingers. We hypothesized a CATSHL syndrome, an exceedingly rare condition characterized by camptodactyly, tall stature, scoliosis, hearing loss and variably associated with intellectual disability. To date, only two families with autosomal dominant transmission, and a more severe presentation caused by homozygous missense mutation in in exon 12 of *FGFR3* (c.1637C>A, p.(Thr546Lys)) have been reported in the literature.[6] All the patients harbored the missense variant p.Arg621His in the catalytic loop of the tyrosine kinase domain of *FGFR3* gene,[1,3] that seems to lead to loss of function of the encoded protein. Our patients have a hitherto unreported, likely pathogenic monoallelic variant [(c.1861C>T; p.(Arg621Cys)] in the same catalytic loop of the tyrosine kinase domain already described in the literature. This result supported our clinical diagnosis, revealing a new causative variant of CATSHL syndrome. Moreover, we observed novel clinical features (peg-shaped incisors and renal anomalies; Table 1). These features are quite distinct from those reported in CATSHL syndrome to date but are classically described in LADD syndrome.[7–10] LADD syndrome is a rare disorder, with less than 70 cases reported in the literature, caused by monoallelic pathogenic variants in encoding fibroblast growth factor receptors 2 (*FGFR2*), 3 (*FGFR3*), or 10 (*FGF10*) genes. LADD syndrome is characterized by aplasia, hypoplasia or atresia of the lacrimal and salivary ducts, hearing loss, dental anomalies such as peg-shaped incisors, long thin-rooted teeth, malformed molars, microdontia or

TABLE 1 Comparison between our patient's clinical findings and clinical features reported in literature considering both CATSHL and LADD syndrome.

Features	CATSHL Syndrome	LADD Syndrome	Current report
Tall stature	X		X
Hearing loss	X	X	X
Camptodactyly of hands and/or feet	X		X
Intellectual disability and/or development delay	X		
Scoliosis	X		X
Relative microcephaly	X		X
Lacrimal and salivary ducts abnormalities		X	
Dental anomalies		X	X
Pectus excavatum	X		
Renal anomalies		X	X

partial anodontia, small and cup-shaped ears, and variable anomalies of the hands and feet such as duplicated terminal phalanx of the thumbs, preaxial polydactyly, and clinodactyly. Additional features may include renal abnormalities, such as agenesis or nephrosclerosis, and hiatus hernia. Conversely, to the best of our knowledge no patients with LADD syndrome had tall stature, relative microcephaly or scoliosis, which represent typical findings of CATSHL syndrome.

Of note, in 2006 Rohmann pointed out that all *FGFR* mutations identified so far in LADD syndrome are located in the tyrosine kinase domains, in loops that have a regulatory function in the control of tyrosine kinase activity, and concluded that a reduced functional activity of *FGFR2* and *FGFR3* seems to be a plausible mechanism underlying the molecular basis ofLADD.[11] Then, both LADD and CATSHL syndromes seems to be related to *FGFR* (3) tyrosine kinase domains loss-of-function variants. CATSHL and LADD syndromes are traditionally described as two different conditions but with shared common clinical signs such as deafness and fingers anomalies; intriguingly, our CATSHL cases showed further overlapping features. Whilst renal dysplasia (P1) and clinodactyly (P1 and P2) are quite common and non-specific findings, peg-shaped incisors (P1) represent an overlapping feature with LADD syndrome. In addition, we highlight the impressive similarity of hypoplastic left second finger of P2 with that of the LADD patient *LADD-Nij, II-3* reported by Rohmann.[11]

For all these reasons, we could hypothesize that our cases might represent a phenotypic expansion of CATSHL syndrome or a partial phenotypic overlap with LADD syndrome.

As already described for activating *FGFR3* mutations that lead to multiple different Mendelian diseases, LADD and CATSHL syndromes could be further evidences of high pleiotropy of the gene. Since pleiotropy is generally caused by a single molecular function involved in multiple biological processes, it should not surprise that different *FGFR3*-related diseases show some shared and overlapping features. Nevertheless, further reports of affected families together with additional functional studies are needed to deepen the real interconnections between CATSHL and LADD phenotypes, and definitely clarify whether they are individual conditions or a phenotypic continuum.

AUTHOR CONTRIBUTIONS

Conceptualization: Lidia Pezzani, Donatella Milani and Silvia Cannova; *Methodology*: Francesca Crosti, Claudia Cesaretti; *Investigation*: Silvia Cannova, Federica Alberti, Camilla Meossi, Federico Grilli and Lidia Pezzani, *Writing-original draft*: Silvia Cannova, Camilla Meossi; *Writing–review and editing*: Lidia Pezzani; *Supervision*: Donatella Milani, Paola Giovanna Marchisio and Lidia Pezzani.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14455.

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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