

SHORT COMMUNICATION

Autosomal dominant cutis laxa with progeroid features due to a novel, *de novo* mutation in *ALDH18A1*

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De novo dominant mutations in the aldehyde dehydrogenase 18 family member A1 (*ALDH18A1*) gene have recently been shown to cause autosomal dominant cutis laxa with progeroid features (MIM 616603). To date, all *de novo* dominant mutations have been found in a single highly conserved amino acid residue at position p.Arg138. We report an 8-year-old male with a clinical diagnosis of autosomal dominant cutis laxa (ADCL) with progeroid features and a novel *de novo* missense mutation in *ALDH18A1* (NM_002860.3: c.377G>A (p.Arg126His)). This is the first report of an individual with *ALDH18A1*-ADCL due to a substitution at a residue other than p.Arg138. Knowledge of the complete spectrum of dominant-acting mutations that cause this rare syndrome will have implications for molecular diagnosis and genetic counselling of these families.

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INTRODUCTION

De Bary syndrome is a rare genetic disease characterized by cutis laxa, a progeroid appearance, ophthalmological abnormalities and intellectual disability.^{1–3} Biallelic mutations in either *PYCR1*⁴ or *ALDH18A1*^{5,6} have been identified as responsible for De Bary syndrome (MIM 219150 and 614438). These genes encode mitochondrial enzymes (*PYCR1* and *P5CS*, respectively) that are involved in the biosynthesis of proline, ornithine and arginine.

A dominant form of De Bary syndrome (MIM 616603) that is caused by *de novo* mutations in *ALDH18A1* was recently recognized and is referred to as *ALDH18A1*-autosomal dominant cutis laxa with progeroid features (*ALDH18A1*-ADCL).^{7,8} The individuals described to date share many of the features characteristic of the recessive form of the disease. All reported *de novo* mutations have involved a recurrent substitution of arginine at position 138 for glutamine, leucine or tryptophan. Here we report a novel *de novo* heterozygous substitution in *ALDH18A1*, p.Arg126His in an individual affected with *ALDH18A1*-ADCL.

CASE REPORT

The child was born at term to healthy consanguineous parents (fourth cousins) of Somali descent. He had short long bones antenatally and presented at birth with small stature, cutis laxa, truncal hypotonia, inguinal hernias, bilateral congenital hip dislocations and congenital cataracts. He was later diagnosed with nystagmus and central corneal opacities.

At age 8 years, his height was 96 cm ($Z = -5.8$) and weight was 11.6 kg ($Z = -7.26$). His head circumference was 45.4 cm, ($Z = -5.0$) which is the 50th centile for a 10-month-old boy. The

trajectories of his growth parameters were consistent over time. He had global developmental delay and truncal hypotonia; he walked with support and used 3–5 word sentences. Dysmorphic features included a broad forehead with a triangular face, down-slanted palpebral fissures, a small mouth, soft lax skin and bilaterally adducted thumbs (Figures 1a and c–e).

A brain MRI performed at 15 months of age and at 3 years of age revealed prominent ventricles and marked tortuosity of the intracranial arteries (Figure 1b). He had an older sister and younger brother who were developmentally appropriate and well grown.

A clinical diagnosis of De Bary syndrome was given at 2 years of age. Sanger sequencing of *ALDH18A1* and *PYCR1* revealed a single variant at *ALDH18A1*: c.377G>A. Chromosomal SNP microarray showed no regions of homozygosity encompassing *PYCR1* and *ALDH18A1*, or other chromosomal deletions or duplications. Given the lack of homozygosity at these loci, and the known consanguinity in the parents, a novel form of autosomal recessive cutis laxa was suspected. The family was enrolled in the Care4Rare Canada research project. Research ethics board approval was obtained as was free and informed consent from the family. Whole-exome sequencing (WES) of genomic DNA from the proband was performed and analyzed as previously described.⁹ The single heterozygous missense variant in *ALDH18A1* was observed: NM_002860.3: c.377G>A, (p.Arg126His).

In order to identify rare copy-number variants, two tools were used: FishingCNV,¹⁰ which compared the read depth of the variants on the WES data against the distribution of reads in more than 48 control individuals with unrelated genetic disorders, and eXome-Hidden Markov Model,¹¹ which used principal component analysis to normalize read depth, filtering out extremely variable targets not derived from

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Figure 1 (a) The patient at 8 months with cutis laxa, a broad forehead, triangular facies and adducted thumbs. (b) T2-weighted coronal brain MRI at age 3 years showing no structural malformations, with tortuosity of the vertebral and carotid system, and their proximal branches. (c) The patient's feet and (d) right hand at age 8 demonstrating cutis laxa. (e) The patient at age 8, with broad forehead and cutis laxa again noted. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

copy-number changes. These analyses did not identify any significant copy-number variation in the WES data, including the genes *ALDH18A1* and *PYCR1*.

At the time of interpretation, only the recessive form of *ALDH18A1*-ADCL had been described and the p.Arg126His variant was not pursued further. No other compelling candidates were identified. Upon publication of Fischer-Zirnsak *et al.*'s⁷ report of *de novo* mutations in *ALDH18A1* causing *ALDH18A1*-ADCL, the p.Arg126His variant was reviewed. Subsequent sequencing in unaffected parents demonstrated that it was a *de novo* variant (Figure 2), which had not been reported in presumed healthy control databases, including EVS,¹² 1000 Genomes¹³ and the ExAC browser.¹⁴

The arginine at codon 126 is a moderately conserved residue (to *Tetraodon nigroviridis*) in the gamma-glutamyl kinase domain of P5CS. Its conversion to a histidine is predicted to be deleterious by several *in silico* programs, including SIFT¹⁵ and Mutation Taster.¹⁶ PolyPhen-2¹⁷ predicts the variant to be possibly damaging.

DISCUSSION

We report a novel dominant mutation in a patient with *ALDH18A1*-ADCL. Evidence that the c.377G>A variant is responsible for the disease includes: (1) its *de novo* status, (2) the absence of the variant in control databases, (3) the *in silico* predicted deleterious effect, (4) the clinical similarity between our patient and the others reported, (5) p.Arg126His is in proximity to the known p.Arg138 substitution and located in the same domain of P5CS, suggesting a similar functional effect and (6) that no other candidates were

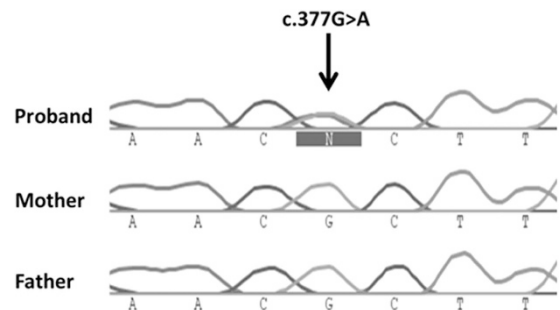


Figure 2 Sanger sequencing traces showing the identified mutation in *ALDH18A1* (c.377G>A(p.Arg126His)) in the affected patient and its absence in the patient's parents. A full color version of this figure is available at the *Journal of Human Genetics* journal online.

identified by WES. Our patient's features are similar to those previously described, including growth restriction, microcephaly, cranial vessel tortuosity, cataracts, dysmorphic features and cutis laxa (Figure 1).

The identification of a *de novo* dominant mutation responsible for *ALDH18A1*-ADCL had implications for genetic counselling. A sibling recurrence risk was considered low (<1%), although the possibility of gonadal mosaicism could potentially increase this risk. This was markedly different than the recessive form hypothesized to be present in this family prior to recognition of the dominant form.

The mechanism by which dominant mutations in *ALDH18A1* cause a similar phenotype to that of recessive mutations is still unclear.

Studies on p.Arg138 patient cell lines have demonstrated altered mitochondrial localization.⁷ These cell lines also have decreased proline levels, which has also been seen in cell lines with biallelic mutations.⁷ Fischer-Zirnsak *et al.*⁷ speculated that the mutant P5CS protein may have a dominant-negative effect on the wild-type P5CS protein.

In conclusion, we report the first individual with *ALDH18A1*-ADCL due to a substitution other than p.Arg138. Further study of *ALDH18A1*-ADCL and associated mutations in *ALDH18A1* will enhance our understanding of this disease and its pathogenesis, and will have implications for diagnosis and genetic counselling.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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