Letter to the Editor

Autosomal recessive LMNA mutation causing Restrictive Dermopathy

To the Editor:

Restrictive dermopathy (OMIM 275210) is a rare lethal genetic disorder that is characterized by congenital tautness of the skin causing fetal akinesia or hypokinesia deformation sequence, characteristic facial features (small mouth, small pinched nose, and micrognathia), bone mineralization defects including thin, dysplastic clavicles, and pulmonary hypoplasia. Patients usually die immediately after birth or may struggle to survive for several weeks (1). Navarro et al. (2) recently reported that restrictive dermopathy is either a primary or a secondary laminopathy, caused by dominant de novo mutations in the lamin A gene (LMNA) or, more frequently, recessive null mutations in the gene coding the endoprotease ZMPSTE24. The lamina, which lies just inside the inner nuclear membrane, is a complex structure with variable functional and structural proteins including lamin A. The lamina is thought to have a role in maintaining nuclear structure, regulating transcription, controlling differentiation and organizing chromatin. ZMPSTE24 is required for post-translational processing of prelamin A, encoded by LMNA, allowing mature lamin A to be inserted into the nuclear lamina.

In addition to restrictive dermopathy, laminopathies that result from defects in LMNA include premature ageing syndromes (Hutchinson-Gilford progeria syndrome and Werner syndrome), myopathies and neuropathies (Emery–Dreifuss muscular dystrophy, Limb-Girdle muscular dystrophy type 1B, dilated cardiomyopathy type 1A, and Charcot-Marie-Tooth type 2B1), and lipodystrophies (Dunnigan-type familial partial lipodystrophy and Mandibuloacral dysplasia) (3).

The majority of the laminopathies have an autosomal dominant mode of inheritance with rare exceptional cases. Emery–Dreifuss muscular dystrophy type 3, Charcot-Marie-Tooth disease type 2B1, and Mandibuloacral dysplasia have been reported to have an autosomal recessive mode of inheritance (3). To date, no reports of patients with lamin A-associated restrictive dermopathy inherited as an autosomal recessive manner have been reported.

We recently encountered a Guatemalan male infant with atypical, mild restrictive dermopathy. He was born to a 17-year-old healthy mother and a non-consanguineous healthy 27-year-old father, at 43 weeks and weighed 3090 g. He was noted to have severe peeling of the skin and decreased subcutaneous tissue at birth. He was hospitalized at age 5 months for failure to thrive, developmental delay and the characteristic skin findings. He had alopecia, sparse eyebrows and eyelashes, and micrognathia. Range of motion was limited at all joints due to tautness of the skin (Fig. 1). Radiographs showed characteristic changes with bilateral clavicular hypoplasia, and radial and ulnar hypoplasia. Cardiac ultrasound studies were normal. His respiratory status continued to decline. High resolution computed tomography of the chest showed an overall constricted thorax, areas of atelectasis and consolidation in the multiple lobes. He died of respiratory failure at age of 7 months.

LMNA sequencing was performed on the proband, his unaffected 2-year-old sister and his parents. A homozygous c.1303C>T mutation predicting a p.Arg435Cys amino acid substitution in the lamin A protein was identified in the proband. The parents and sibling were heterozygous for the mutation. No mutation was identified in ZMPSTE24 in the proband. The LMNA mutation affects a highly conserved amino acid residue (4), and the same p.Arg435Cys substitution has been found in the heterozygous state in a patient with severe dilated cardiomyopathy (4). Patients

Fig. 1. Multiple views of the patient demonstrating sparse eyebrows and eyelashes, micrognathia, diffusely tight shiny skin, and joint contractures.
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with this mutation have not been reported to date except for the case with severe dilated cardiomyopathy (4).

All of the carriers in his family showed unremarkable cardiac ultrasound studies. This mutation is reported only in one case that developed adult onset dilated cardiomyopathy at age 24 years. The range of findings and long-term prognosis of the cardiac manifestations in carriers of this mutation is unclear at this time.

In conclusion, a homozygous c.1303C>T (p.Arg435Cys) LMNA mutation, previously identified in the heterozygous state in one case of adult onset dilated cardiomyopathy, has been found in an infant with atypically mild restrictive dermopathy. Restrictive dermopathy should be added to the clinical phenotypes of autosomal recessive laminopathies due to LMNA mutations.

References


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