Journal of the Formosan Medical Association (2015) 114, 1017–1019

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

CORRESPONDENCE

A shared founder mutation underlies lethal restrictive dermopathy in the Austronesian aboriginal Atayal tribe of Taiwan

Jia-Woei Hou [a,b,*]

[a] Department of Pediatrics, Cathay General Hospital, Taipei, Taiwan
[b] College of Medicine, Fu-Jen Catholic University, New Taipei City, Taiwan

Received 21 February 2014; received in revised form 28 July 2014; accepted 22 August 2014

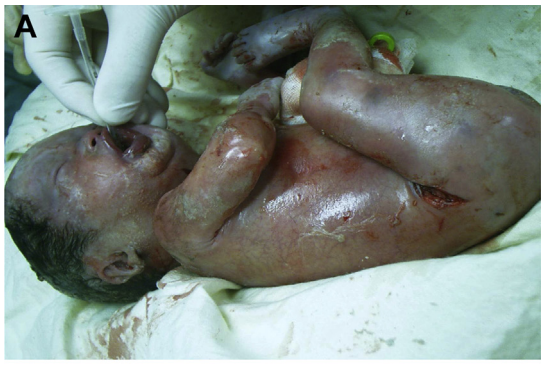
Lethal restrictive dermopathy (RD, OMIM#275210) belongs to the laminopathies. It is characterized by abnormal skin growth and differentiation and is a very rare, lethal genodermatosis. Since the cases of two newborn girls with RD in Taiwan were published in 2003,[1] a total of nine Taiwanese patients with RD have been described, including six previously-reported cases[1–4] and three novel patients. The diagnosis of RD made was based on the facial features including hypertelorism, short, downslanting palpebral fissures, small, pinched nose, posteriorly rotated and low-set ears, micrognathia, and mouth fixed in the "o" position, as well as thin, rigid and tense skin with erosions and scaling, prominent skin vessels, multiple joint contractures, absent or small nails, rocker-bottom feet, and a narrow chest (Fig. 1A). Other perinatal signs can include intrauterine growth retardation, polyhydramnios, premature rupture of the membranes with subsequent delivery at about 30–32 weeks of gestation, large placentas, neonatal teeth, and pulmonary hypoplasia leading to respiratory insufficiency.[1–4] RD should be differentiated from other diseases and syndromes, including Hutchinson-Gilford progeria, generalized scleroderma, collodion or harlequin baby, Pena-Shokeir, and Neu-Laxova syndromes. The characteristic facies (after extreme tautness of the skin *in utero*), absence of neurological abnormalities, differences in clinical course (lethal outcome), and unique histopathological findings (near-absence of the dermal elastic fibers) could distinguish RD from the other diseases mentioned.

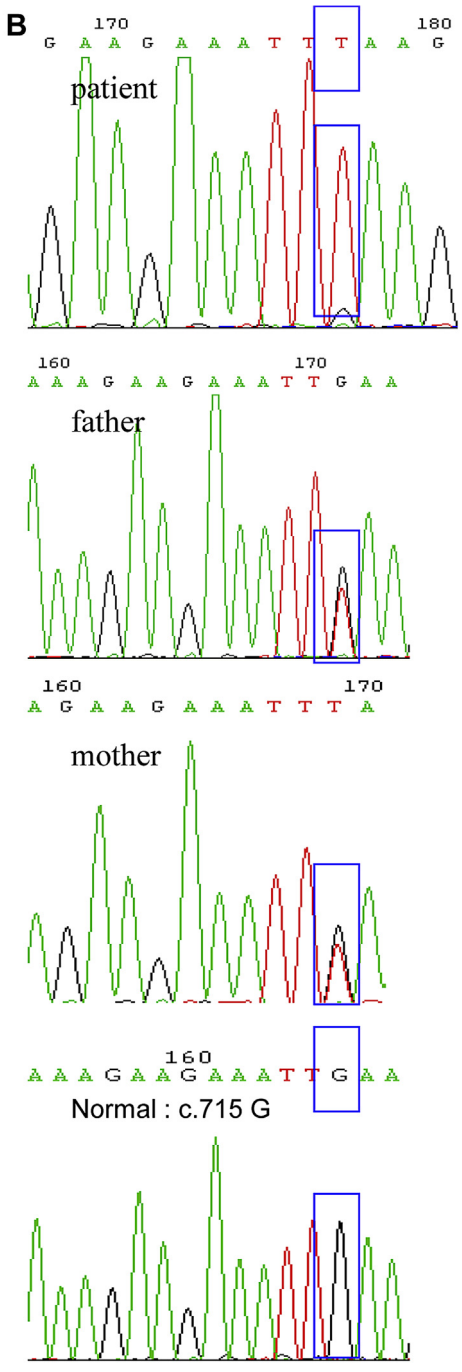
These RD patients are all from seven different Atayal families, with a male-to-female ratio of 5:4, and the babies died between birth and 75 days post-partum. Recurrent abortions were found in five pairs of parents. Clinical information was collected from their medical records (Patients 1–8) and the reported papers (patients 1–5, 9).[1–4] Decreased levels of serum albumin (5–7 g/dL, 2.3–3.4 g/dL; reference range of 3.9–5.0 g/dL), and cholestasis (Patient 6 and Patient 7, peak total/direct bilirubin at 1 month: 7.8/3.5 mg/dL and 5.2/3.1 mg/dL, respectively) were noted. Urine gas chromatography/mass spectrometry studies showed N-acetyl tyrosinuria and generalized organic aciduria with lactic ketoaciduria (Patient 5); and generalized organic aciduria (Patient 6). Tandem mass spectrometry showed diffusely low levels of amino acids, free carnitine and fatty acids in patients 5–8 (except for high isovaleryl (C5) carnitine in patient 6). These metabolic findings might be secondary either to systemic disease or liver function impairment, and moreover originate primarily from RD itself.

Conflicts of interest: The author has no conflicts of interest relevant to this article.

* Corresponding author. Department of Pediatrics, Cathay General Hospital, 280 Sec 4 Jen-Ai Road, Taipei 106, Taiwan.
E-mail address: hou76@cgh.org.tw.

http://dx.doi.org/10.1016/j.jfma.2014.08.007





Chromosome studies from amniocytes or peripheral blood showed normal findings in Patients 1—8. Breakage tests with mitomycin C (40 ng/mL) showed increased breakage rates in Patients 1—8 (control 0.6—6.0%): Patient 7 (157%), Patient 8 (144%), Patient 1, Patient 2, Patient 5, and Patient 6 (100—121%), and Patient 3 and Patient 4 (90—97%). Markedly increased breakage rates were noted in all patients undergoing examination. The features of premature aging in RD or other laminopathies are linked to the accumulation of DNA double-strand breaks, which may result in genome and chromosomal instability. Molecular studies were performed on the genes encoding for lamins A and C (*LMNA*, 12 exons), and all 10 exons and splice sites of the *ZMPSTE24* gene (encoding a zinc metalloproteinase). No disease-causing mutations were observed in *LMNA*, while a disease-causing homozygous stop codon TAA on exon 6 (c.715 G> T, p.E239X, Fig. 1B) was noted in all patients. All the parents were found to be heterozygous carriers from the Atayal tribe.

RD can be caused by dominant mutations of the *LMNA* (primary laminopathy) or, more frequently, recessive mutations of the *ZMPSTE24* (secondary laminopathy) genes. Defects in the *ZMPSTE24* gene may impair the processing of prelamin A into mature lamin A, leading to the development of RD. These patients presented different intra- and interfamilial expressivity or severity, but no good genotype—phenotype correlation exists. Some patients (Patients 5—7) lived up to 1—2.5 months, suggesting some residual function of the mutant protein. Recent studies have shown that the frequency of misshapen nuclei can be reduced by treating cells with a farnesyltransferase inhibitor. Removal of unprocessed prelamin A (progerin) or rescue of defective DNA repair could be potential therapeutic strategies for the treatment of Hutchinson—Gilford progeria syndrome or RD in the future.

The shared, common mutation c.715 G> T in *ZMPSTE24* may reveal a founder mutation in the Austronesian aboriginal Atayal population residing in the northern part of Taiwan's Central Mountain areas. As an autosomal recessive disorder, RD with *ZMPSTE24* mutation may be more prevalent in selected inbred populations with a high frequency of consanguinity. Certain ethnicities have demonstrated a higher incidence with common mutations (c.1085dupT) due to endogamous practices, such as Ashkenazi Jews and Mennonites, possibly attributable to a founder effect.[5] Although the Taiwanese aboriginal tribes are considered to share a common origin, the founder mutation noted in this study suggests that diversities among the different tribes in Taiwan may be due to geographic isolation over a long period of time.

Figure 1 (A) Patient 6 shows very tight and rigid skin with erosions, prominent superficial vasculature, joint contractures, and facial features including fixed facial expression, absent eyelashes and eyebrows, small mouth in O position, and micrognathia. (B) Direct sequencing over the *ZPMSTE24* gene in Patient 8 showing a homozygous stop codon TAA over the exon 6 [c.715 G> T leading to GAA (glutamic acid)→ TAA(stop), p.E239X]. Both parents are heterozygous carriers.

References

1. Hou JW, Mai CF. Restrictive dermopathy in two sisters. *Chang Gung Med J* 2003;**26**:510—4.
2. Chiang MC, Huang SF, Hsueh C, Lai MW, Hou JW. Restrictive dermopathy: report of one case and the metabolic and post-mortem findings. *Turk J Pediatr* 2008;**50**:492—4.
3. Chen M, Kuo HH, Huang YC, Ke YY, Chang SP, Chen CP, et al. A case of restrictive dermopathy with complete chorioamniotic membrane separation caused by a novel homozygous nonsense mutation in the *ZMPSTE24* gene. *Am J Med Genet* 2009;**149A**:1550—4.
4. Lu CS, Wu SC, Hou JW, Chu CP, Tseng LL, Lue HC. Restrictive dermopathy: report of two siblings. *Pediatr Neonatol* 2013;**54**:198—201.
5. Loucks C, Parboosingh JS, Chong JX, Ober C, Siu VM, Hegele RA, et al. A shared founder mutation underlies restrictive dermopathy in Old Colony (Dutch-German) Mennonite and Hutterite patients in North America. *Am J Med Genet* 2012;**158A**:1229—32.