

# Mosaic variant in *ATP2C1* presenting as relapsing linear acantholytic dermatosis

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## Summary

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Relapsing linear acantholytic dermatosis (RLAD) is a rare disease that manifests as recurring episodes of crusted and vesicular lesions distributed in a Blaschkoid pattern with histology resembling Hailey–Hailey disease. RLAD, in the presence of generalized disease, has been shown to be a type 2 mosaic form of Hailey–Hailey disease. RLAD, without systemic disease, has been hypothesized to be type 1 mosaic Hailey–Hailey disease, but this assertion has lacked genetic confirmation. To determine the genetic abnormalities causing RLAD, we performed exome sequencing of affected tissue and blood in one patient. Exome sequencing of a punch biopsy revealed a c.238A>T, p.(Lys80\*) variant in *ATP2C1* found in 26% of the reads from lesional skin but absent in germline DNA. This somatic variant causes a truncated protein that would likely result in loss of function. Our findings indicate that, in this patient, RLAD is a clinical presentation of type 1 segmental Hailey–Hailey disease.

### What's already known about this topic?

- Relapsing linear acantholytic dermatosis (RLAD) is postulated to be a mosaic form of Hailey–Hailey disease.
- This hypothesis has remained unproven for type 1 disease and the putative gene and driving genetic variants have remained unknown.

### What does this study add?

- Exome sequencing, performed on lesional skin and matched blood, found RLAD lesions to be mosaic for variants causing a premature stop codon in *ATP2C1*.
- Our findings support the hypothesis that RLAD is a type 1 segmental form of Hailey–Hailey disease caused by postzygotic variants in *ATP2C1*.

Autosomal dominant skin diseases that typically present diffusely can also occasionally occur in segmental patterns. In type 1 segmental disease, a postzygotic variant occurs during embryogenesis, resulting in both allelic heterozygosity and clinical disease restricted to a segment of skin that reflects the migration pattern of the original mutated cell and its progeny. Type 2 segmental disease develops in heterozygous embryos that will later manifest diffuse disease. A loss of heterozygosity, which occurs during embryogenesis, causes segmental homozygosity of the variant allele, thereby resulting in more severe disease in a segmental pattern superimposed on the diffuse disease.

Relapsing linear acantholytic dermatosis (RLAD) is a rare disease, first described in 1985.<sup>1</sup> It is characterized by unilateral vesicular, bullous or crusted lesions that present in a Blaschkoid or zosteriform pattern. Histology of these lesions resembles Hailey–Hailey disease.<sup>2</sup> In 1995, Duschet *et al.* speculated that RLAD may be a mosaic disorder.<sup>2</sup> However, to our knowledge, this hypothesis has never been verified experimentally for type 1 disease. Poblete-Gutierrez *et al.* described a patient with known Hailey–Hailey disease that developed earlier and more severe lesions in a segmental pattern.<sup>3</sup> The segmental lesions were superimposed on the typical diffuse disease. They further demonstrated that the segmental lesions were specifically caused by loss of heterozygosity of *ATP2C1*, resulting in homozygosity

of the germline *ATP2C1* variant. Although these authors demonstrated an elegant mechanism for type 2 mosaicism in segmental Hailey–Hailey disease, they did not address the causative gene in RLAD without generalized disease, which is hypothesized to be an example of type 1 mosaicism. We tested the hypothesis that RLAD is a mosaic form of either Hailey–Hailey or Darier disease, which result from variants in *ATP2C1* and *ATP2A2*, respectively.<sup>4–6</sup>

## Materials and methods

### Samples

Blood samples and an intact punch biopsy containing both dermis and epidermis were taken with informed consent under an approved protocol from the Carilion Clinic (Roanoke, VA, U.S.A.) Institutional Review Board.

### Sequencing

Exome capture was performed using a SureSelect Human All Exon UTR (v5) kit (Agilent, Santa Clara, CA, U.S.A.) according to manufacturer's protocol. Exome sequencing was performed with the Illumina HiSeq 125 cycle paired end sequencing v4 Protocol (Illumina, San Diego, CA, U.S.A.).

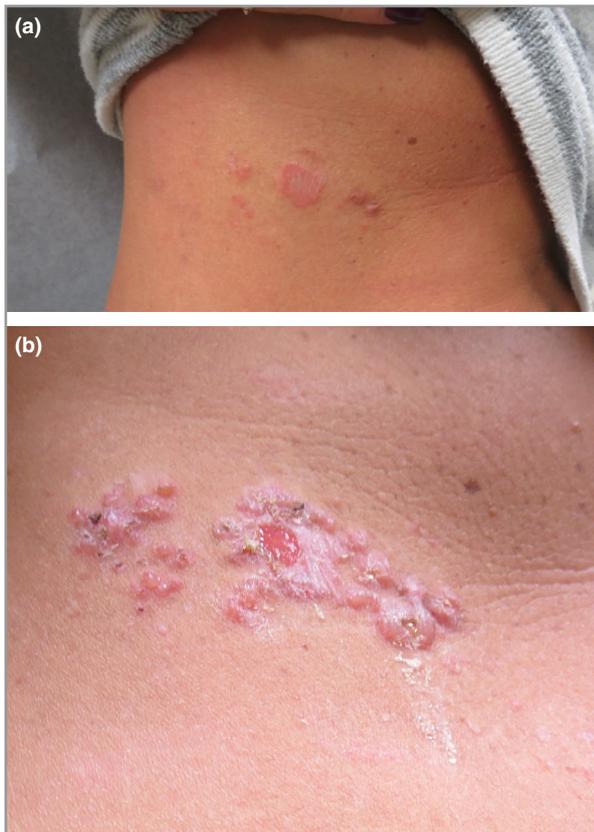


Fig 1. Relapsing linear acantholytic disease. (a, b) Vesicles, crusted papules and plaques in a zosteriform distribution on the right chest wall. These photographs were taken 1 year apart.

## Bioinformatics

Variants were identified and screened by the Sention TNseq Algorithm on the DNAnexus platform (Mountainview, CA, U.S.A.). Further visualization was performed on the Integrative Genomics Viewer (Broad Institute, Cambridge, MA, U.S.A.).

## Results

A 47-year-old woman presented with a several-year history of an intermittent pruritic rash distributed in a Blaschkoid segment over the right chest wall. The eruption always recurred in the same area and was refractory to previous treatments, which included high-potency topical steroids, oral prednisone and tacrolimus ointment. The patient denied any family history of similar lesions. Physical examination revealed crusted papules and plaques in a segmental distribution on the right chest wall (Fig. 1). A biopsy showed downward elongation of the rete with acantholysis, dyskeratosis and suprabasal clefting (Fig. 2). The patient was diagnosed with RLAD and was

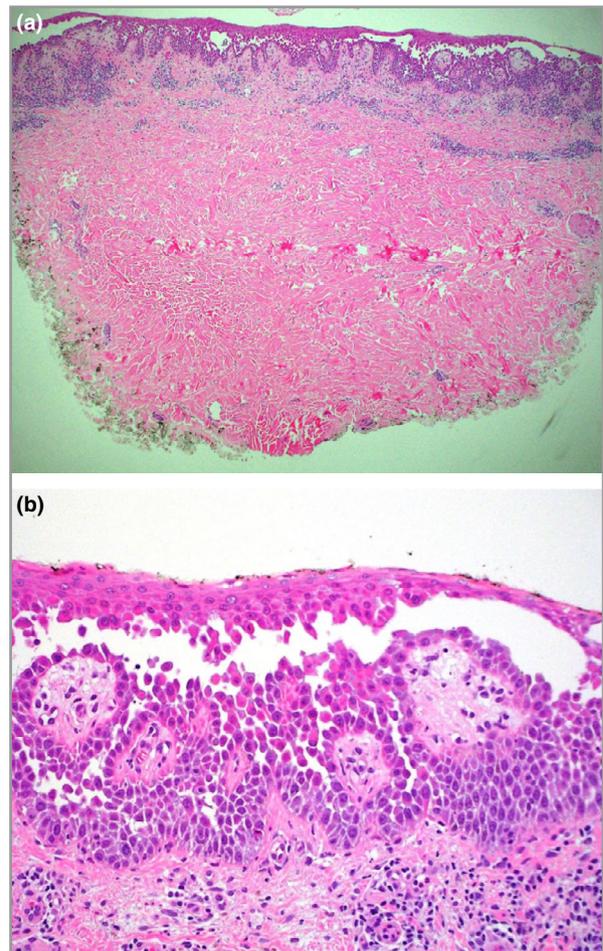


Fig 2. Relapsing linear acantholytic disease biopsy reveals downward elongation of the rete with acantholysis, dyskeratosis and suprabasal clefting. (a) Magnification:  $\times 4$ ; (b) magnification:  $\times 20$ .

started on dapsone, with minimal improvement. The patient was then started on oral retinoids but was lost to follow-up.

We screened the entire exome for coding variants present in > 10% of the reads in lesional skin but not significantly present in blood (> 1% of the reads). Only two variants passed our screen, c.238A>T in *ATP2C1* and c.469G>A in *ZNRF2*. The c.238A>T in *ATP2C1* was present in 26% of the reads. This *ATP2C1* variant, p.(Lys80\*), creates a premature stop codon in exon 4 (reference sequences: NM\_001199179 and NP\_001186108). This variant was confirmed by Sanger sequencing of a polymerase chain reaction amplicon from the paraffin block that was originally used to diagnose RLAD. We also performed Sanger sequencing on exon 4 from an archived skin punch biopsy taken distant from the RLAD that showed a cutaneous tinea infection. The c.238A>T variant was not seen in this specimen of normal skin. We also found a second variant c.457C>T, p.(153Arg\*) predicted to cause a premature stop codon in exon 7 of *ATP2C1*. This c.457C>T variant was present in only 10 of 297 (3.4%) of the reads, could not be verified by Sanger sequencing and is of uncertain significance. Finally, we performed a manual screen in the genome browser of exonic and intronic regions of *ATP2A2*, the gene whose identified variants may cause Darier disease, but failed to identify any somatic coding or noncoding variants.

## Discussion

Our findings support the hypothesis that postzygotic variants in *ATP2C1* cause type 1 RLAD. Variants in this gene cause Hailey–Hailey disease by decreasing levels of its protein product, secretory pathway  $\text{Ca}^{2+}/\text{Mn}^{2+}$ -ATPase pump type 1.<sup>7,8</sup> Hailey–Hailey occurs in patients hemizygous for germline variants in *ATP2C1*.<sup>5,8</sup> Known Hailey–Hailey variants occur throughout the gene without apparent hotspots.<sup>8</sup> However, the majority of Hailey–Hailey variants cause premature protein termination,<sup>4</sup> as do the mosaic variants in our patient. In the case presented, the premature stop codons, generated by the variants, occur early on in the mRNA and likely lead to loss of function of the resulting protein. Our genetic findings, coupled with the observation that the skin histology in our patient resembles that of Hailey–Hailey disease,<sup>6</sup> suggests that the same underlying disease process occurs in RLAD. We suspect that the variant identified in *ZNRF2* is a silent mosaic change unrelated to the development of RLAD in this patient as there are currently no known *ZNRF2* variants associated with any form of acantholytic skin disease.

In the mosaic model, a somatic variant acquired early on in development is passed on to daughter cells, resulting in a cell

lineage genetically distinct from the rest of the organism. The unilateral Blaschkoid pattern of RLAD reflects the migration of the mutated cell lineage. We identified a c.238A>T, p.(Lys80\*) *ATP2C1* variant in the affected segment likely to cause loss of protein function. The observed allele frequency of < 50% was likely due to the presence of inflammatory and mesenchymal cells in the sample.

While we have successfully identified the underlying pathology of RLAD in this case, we cannot say if all cases of type 1 RLAD are due to variations in *ATP2C1*. However, our patient does validate the hypothesis that postzygotic variants in acantholytic disease genes can cause RLAD, suggesting that systemic retinoids, which are effective for generalized Hailey–Hailey disease,<sup>9</sup> may also be successful for RLAD. Future research is needed to identify the factors that cause periodic increases in disease activity that drive the relapsing nature of RLAD.

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## References

- Vakilzadeh F, Kolde G. Relapsing linear acantholytic dermatosis. *Br J Dermatol* 1985; **112**:349–55.
- Duschet P, Happle R, Schwarz T, Gschnait F. Relapsing linear acantholytic dermatosis. *J Am Acad Dermatol* 1995; **33**:920–2.
- Poblete-Gutierrez P, Happle R, Frank J. Allelic loss underlies type 2 segmental Hailey–Hailey disease, providing molecular confirmation of a novel genetic concept. *J Clin Invest* 2004; **114**:1467–74.
- Sakunabhai A, Ruiz-Perez V, Carter S *et al.* Variants in *ATP2A2*, encoding a  $\text{Ca}^{2+}$  pump, cause Darier disease. *Nat Genet* 1999; **21**:271–7.
- Hu Z, Bonifas JM, Beech J *et al.* Mutations in *ATP2C1*, encoding a calcium pump, cause Hailey–Hailey disease. *Nat Genet* 2000; **24**:61–5.
- Sudbrak R, Brown J, Dobson-Stone C *et al.* Hailey–Hailey disease is caused by mutations in *ATP2C1* encoding a novel  $\text{Ca}^{2+}$  pump. *Hum Mol Genet* 2000; **9**:1131–40.
- Micaroni M, Mironov A. Roles of  $\text{Ca}^{2+}$  and secretory pathway  $\text{Ca}^{2+}$ -ATPase pump type 1 (SPCA1) in intra-Golgi transport. *Commun Integr Biol* 2010; **3**:504–7.
- Micaroni M, Giacchetti G, Plebani R *et al.* *ATP2C1* gene mutations in Hailey–Hailey disease and possible roles of SPCA1 isoforms in membrane trafficking. *Cell Death Dis* 2016; **7**:e2259.
- Hunt M, Salisbury E, Painter D, Lee S. Vesiculobullous Hailey–Hailey disease: successful treatment with oral retinoids. *Australas J Dermatol* 1996; **37**:196–8.