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Splicing of the cake can affect the severity of epidermolysis bullosa

D Murrell
University of NSW

Jouni Uitto
Thomas Jefferson University

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COMMENTARY

Splicing of the cake can affect the severity of epidermolysis bullosa

A detailed understanding of genetics is important for dermatologists to appreciate the variability in severity of their patients' diseases, not only in complex polygenic disorders such as skin cancers, but also in rare single-gene syndromes. In general, how much normal functional protein is remaining as a result of the mutations can be related to the severity of the patient's clinical appearance. In most cases of single-gene disorders, the types of mutation(s) determine the amount of functional protein. In a broad sense, there are three types of mutations: the good, the bad and the ugly. Relatively speaking, the 'good' ones lead to milder disease, often as a result of single base-pair substitutions, where an amino acid is substituted by another, resulting in a dominant-negative effect in autosomal dominant conditions, such as epidermolysis bullosa (EB) simplex or dominant dystrophic EB. The 'ugly' mutations include those in which no functional protein is being made – examples include premature termination codons, or 'PTC's', which cause a stop of translation and no full-length protein being made, such as in many cases with severe recessive forms of EB. The 'bad' mutations cause a disease of intermediate severity and are often 'splicing' mutations – *i.e.* nucleotide substitutions at the exon/intron borders affecting DNA sequences critical for canonical splicing, *i.e.* removal of introns and linking adjacent exons. In the case of splicing mutations, sometimes one or more exons can be skipped, and the affected exon can join up again 'in-frame' with another exon further down the length of the gene, thus *splicing out* variable exons in-between. These events of aberrant splicing result in synthesis of proteins that are shorter than the original protein, thus resulting in structure, or 'cake', that has had some slices removed. The clinical features, or the 'phenotype', of these splice variants can vary a lot, as for example, between localized milder and generalized severe recessive forms of EB.

In addition to these mechanisms, in some families with recessive forms of EB, the children who all have the same two mutations, or the 'genotype', can on occasion have vastly different phenotypes. Sometimes, one of them improves with age whilst the other does not, as reported in this issue by Mittwollen *et al.*¹ of two siblings, a male and a female, with junctional EB (JEB) caused by *LAMB3* gene mutations. JEB may be caused by mutations in up to six different genes, but more than 50% of them are caused by 'hotspot' mutations in the *LAMB3* gene,² which

encodes one of the three subunit polypeptides of Laminin 332. This protein makes up anchoring filaments, important attachment structures which are like velcro, sticking the basal cells of the epidermis into the underlying dermo-epidermal basement membrane.

In the family reported by Mittwollen *et al.*, both siblings had one 'ugly' hotspot PTC mutation in *LAMB3*, p.Arg635X, whilst the second mutation was supposed to be a relatively 'good' one, c.628G>A, predicting an amino acid substitution, p.Glu210Lys, and a generalized intermediate JEB phenotype.^{1,3} However, this mutation resides at the end of exon 7 at the exon 7/intron 7 border, and can therefore affect splicing, being in fact a 'bad' mutation. The brother in this family improved dramatically after the age of 6 years, whilst his younger sister continued to deteriorate. Biopsies of their skin in their mid-20s to study the splicing of *LAMB3* found that each of them had many different splicing variants, but the brother, who was mildly affected and able to live independently and hold down a job, had many more full-length splice variants than his much more severely affected sister. Why this difference in the splicing pattern happened remains unclear, but spliceosomes are dynamic macromolecular complexes composed of small nuclear RNAs and proteins whose proper interactions are critical for physiological splicing.^{4,5}

Intriguingly, the brother with the milder phenotype was treated at age 21 with oral ivermectin after contracting scabies and his EB becoming worse. Following treatment with ivermectin, his EB returned to baseline. We previously reported a patient with dominant dystrophic EB whose blistering became much worse after endemic scabies epidemics, but following eradication with repeated courses of ivermectin, his blistering drastically improved.⁶ We assumed that this was related to improved hygiene after this patient was incarcerated or possibly to reduced itching after eradication of the scabies infection.

Interestingly, it turns out that ivermectin interferes with various pathways which affect RNA synthesis, including interacting with various epigenetic regulators such as RNA helicase 1, SIN3A and SIN3B, chloride channel receptors, purigenic receptors and signalling pathways, and even stem cell populations, such that ivermectin is being potentially repurposed as an anti-tumour therapy.⁷ As the reason for phenotypic severity differences was found in differential splicing patterns between these two siblings, it would be interesting to study the effects of ivermectin on splicing in patients with EB.

Why is this important? Firstly, the genetic mutation information will help to predict the phenotype to some extent, but is not always predictive, as in this family, and determination of the

levels of functional protein in the skin from biopsies should be helpful. Secondly, while treatments under development for genetic conditions, such as EB, include drugs which facilitate read-through of PTC mutations or allow skipping of exons containing the pathogenic mutations, better understanding of how to induce full-length protein variants from splice mutations, instead of deletion of large splices, could benefit patients with these types of mutations in the future.

Conflicts of interest

None to declare.

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D.F. Murrell,^{1,2,*} J. Uitto³

¹Department of Dermatology, St George Hospital, Sydney, NSW, Australia, ²Faculty of Medicine, University of NSW, Sydney, NSW, Australia, ³Department of Dermatology and Cutaneous Biology, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

*Correspondence: D. Murrell. E-mail: d.murrell@unsw.edu.au

This is a commentary on the article in this issue by Mittwollen *et al.* To view this article, visit <http://doi:10.1111/jdv.16332>

Linked article: R. Mittwollen *et al.* *J Eur Acad Dermatol Venereol* 2020; **34**: 2127–2134. <https://doi.org/10.1111/jdv.16332>.

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