Contributions of Accelerated Skin Aging in Recessive Dystrophic Epidermolysis Bullosa to Squamous Cell Carcinoma Development

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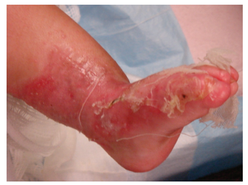
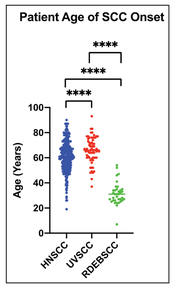
BACKGROUND

- Recessive dystrophic epidermolysis bullosa (RDEB) is a debilitating genetic disorder caused by mutations in the COL7A1 gene.



Fleming et al., 2009



Tartaglia et al., 2021

- RDEB patients are at high risk of developing squamous cell carcinomas (SCC), which result in high mortality
- Skin changes associated with aging shares many similarities with RDEB:
  - ultrastructural changes
  - defects in wound healing
  - increased inflammation
- Patients with RDEB show early onset of SCC

HYPOTHESIS

We hypothesize that accelerated skin aging contributes to early onset of SCC in RDEB.

METHODS

Patient
- Blood, skin and SCC tumor were obtained from a female RDEB patient who developed SCC in her second decade of life.

Sequencing
- Whole genome sequencing (WGS) performed on blood, skin, SCC tumor
- RNA sequencing (RNAseq) performed on skin and SCC tumor

Variant Calling & Annotation
- DeepVariant (Poplin et al., 2018)
- MuTect (Cibulskis et al., 2013)

Mutational Signature Analysis
- deconstructSig R package (Rosenthal et al., 2016)

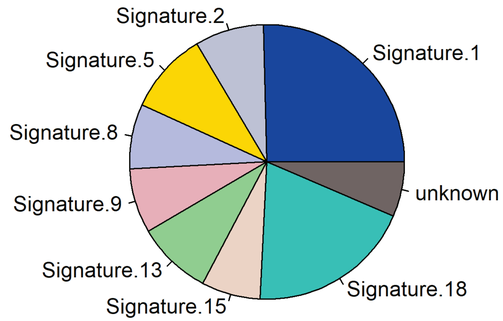
Gene Ontology Analysis
- enrichGO in clusterProfiler R package (Yu et al., 2012)

RESULTS

Table 1. Germline COL7A1 pathogenic variants

HGVS	Gene region	Germline mutation	Effect	Prediction	Source
NM_000094.4:c.1564C>T	Exon 12	Yes	Stop codon	Pathogenic	ClinVar
NM_000094.3:c.3551-3T>G	Intron 26	Yes	Abnormal splicing	Likely pathogenic	Kern et al., 2006

Figure 1. Mutational signatures in SCC compared to skin



Annotation:
- Signature 1 & 5: clock-like signatures, associated with age in various cancers
- Signature 2 &13: APOBEC signatures, major mutational mechanism in human cancers
- Signature 9: associated with somatic hypermutation in lymphoid cells
- Signature 15: associated with defective DNA mismatch repair & microsatellite instability
- Signature 18: associated with damage from reactive oxygen species

cancer.sanger.ac.uk, Tate et al., 2018, Nik-Zainal et al., 2012, Alexandrov et al., 2013

Figure 2. SCC vs. skin comparative analysis of genomic variants and differentially expressed (DE) genes.

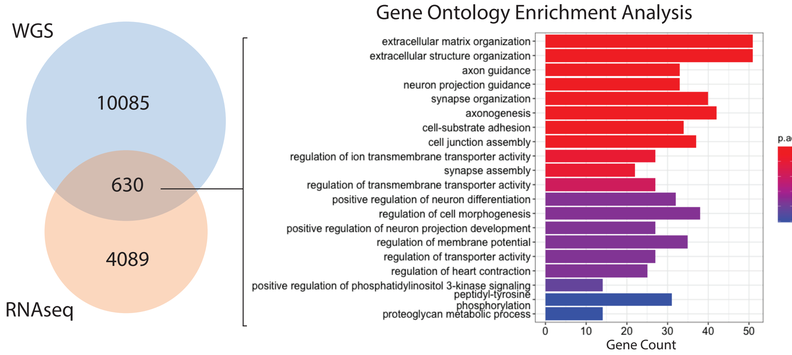
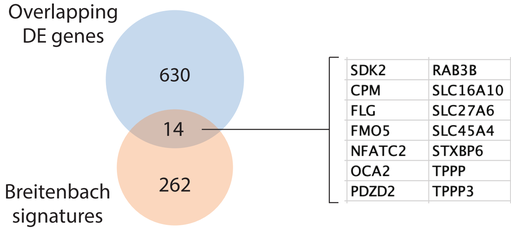


Figure 3. Comparison of 630 DE genes in SCC vs. skin to RDEB- and normal skin aging-specific transcriptome signatures (Breitenbach et al 2015)



SDK2	RAB3B
CPM	SLC16A10
FLG	SLC27A6
FMO5	SLC45A4
NFATC2	STXBP6
OCA2	TPPP
PDZD2	TPPP3

CONCLUSIONS

Our pilot study points to a possibility that skin aging-associated transcriptional changes might contribute to RDEB-associated SCC development.

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