Comorbid acne inversa and Dowling-Degos disease due to a single NCSTN mutation - is there enough evidence?: reply from the authors

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Dear Editor, we thank Hermasch et al. for their comments on our paper describing the novel NCSTN R583* mutation associated to familial acne inversa (FAI) in an Italian family, where the proband was also clinically diagnosed with Dowling-Degos disease (DDD). In our report, we raised the attention on this particular patient subset with comorbid FAI-DDD, emphasizing the connection between autoinflammatory-keratinization disorders and genetic reticulated pigmentary disorders. Based on our findings, we think that there ais enough evidence to claim that R583* NCSTN mutation is associated with DDD and FAI. No pathogenic mutations were found in the coding exons and intron-exon junctions of genes associated with DDD in the proband (see Table 1). The two missense variants in *KRT5,* detected in heterozygosis, were located in the C-terminal region of the protein and unlikely able to cause KRT5 haploinsufficiency associated with DDD[1]. They were also classified as benign following AMCG guidelines[2], mainly because their minor allele frequency in the healthy population was too high for a rare disease. To rule out a role for these variants in FAI and DDD, we sequenced *KRT5* in the two children (one healthy and the other with AI), and both were heterozygous.

The nonsense *NCSTN* R583* mutation caused a reduced quantity of NCSTN in hair follicles outer root sheath cells, and NCSTN deficiency affected the stability of other γ-secretase subunits such as PEN-2, a mechanism that was already reported in NCSTN-null fibroblasts and probably shared by all mutations causing NCSTN haploinsufficiency[3]. We hypothesized that PEN-2 deficiency triggered by NCSTN haploinsufficiency could cause DDD that becomes clinically observable when inflammation is kept in check, as shown in DDD patients with *PSENEN* mutations[4].

We think that in the future, the co-occurrence of AI and DDD in patients with *NCSTN* mutations should be better investigated, especially in FAI individuals with a milder disease. We acknowledge that in the setting of both familial or sporadic AI, DDD diagnosis may prove difficult, as it can be overlooked or confused with other conditions, such as acanthosis nigricans or post-inflammatory hyperpigmentation, even by experienced dermatologists. Furthermore, the diagnosis of DDD should be confirmed by histology, which is routinely not performed in the diagnostic workup of AI. In our case, DDD was a first diagnosis in a patient with long-standing AI. The 30-years-old daughter of the patient did not present flexural pigmentation, probably due to younger age, and the patient's AI-affected father is deceased without an in-depth clinical evaluation. We are further dissecting the molecular mechanism underlying the disruption of the γ-secretase complex activity in this unique FAI-DDD phenotype, with the use of novel cellular-based in-vitro studies and we hope to report soon new experimental evidence.

References

1 Betz RC, Planko L, Eigelshoven S *et al.* Loss-of-function mutations in the keratin 5 gene lead to Dowling-Degos disease. *American journal of human genetics* 2006; **78**: 510-9.

2 Richards S, Aziz N, Bale S *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in medicine : official journal of the American College of Medical Genetics* 2015; **17**: 405-24.

3 Zhang YW, Luo WJ, Wang H *et al.* Nicastrin is critical for stability and trafficking but not association of other presenilin/gamma-secretase components. *The Journal of biological chemistry* 2005; **280**: 17020-6.

4 Ralser DJ, Basmanav FB, Tafazzoli A *et al.* Mutations in gamma-secretase subunit-encoding PSENEN underlie Dowling-Degos disease associated with acne inversa. *The Journal of clinical investigation* 2017; **127**: 1485-90.

Table 1. Genetic variants found in genes associated with DDD in the FAI-DDD patient

RefSeqGene	Gene	Patient 1 Genotype	Ref Genotype	Pos (GRCh38.p12)	rs	Variant type
NG_027934.1	**PSENEN** intron 2	C/G	G/G	19:35746008	rs10402601	Intron Variant
NG_034115.1	**POGLUT1** intron 4	T/T	C/C	3:119477487	rs3732419	Intron Variant
NG_034115.1	**POGLUT1** intron 5	A/A	G/G	3:119480026	rs4688007	Intron Variant
NG_033906.1	**POFUT1** exon 1	A/G	G/G	20:32208016	rs1923095	Synonymous Variant
NG_008297.1	**KRT5**	A/G	G/G	12:52519946	rs11549951	Synonymous

	exon 1					Variant
NG_008297.1	**KRT5** intron 1	A/G	G/G	12:52519907	rs638907	Intron Variant
NG_008297.1	**KRT5** exon 2	A/G	G/G	12:52519086	rs17852231	Synonymous Variant
NG_008297.1	**KRT5** exon 5	A/G	G/G	12:52518984	rs1132948	Synonymous Variant
NG_008297.1	**KRT5** exon 5	G/T	T/T	12:52517617	rs4761924	Synonymous Variant
NG_008297.1	**KRT5** intron 6	G/A	A/A	12:52517067	rs60815939	Intron Variant
NG_008297.1	**KRT5** exon 9	C/T	T/T	12:52515133	rs11549950	Missense Variant
NG_008297.1	**KRT5** exon 9	A/G	G/G	12:52515088	rs11549949	Missense Variant