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Investigating established and non-established susceptibility genes in generalized pustular psoriasis

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Background & Aim

Generalized pustular psoriasis (GPP) is a rare severe form of psoriasis that can be life-threatening. Main disease genes are *IL36RN* (1) and *MPO* (2). Other genes such as *AP1S3* (3) and recently *BTN3A3* (4) have also been implicated in European or Asian study groups, respectively. Here we aim to combine different studies of European individuals to perform a meta-analysis of known disease genes and to perform an association study of truncating *BTN3A3* variants in European GPP patients.

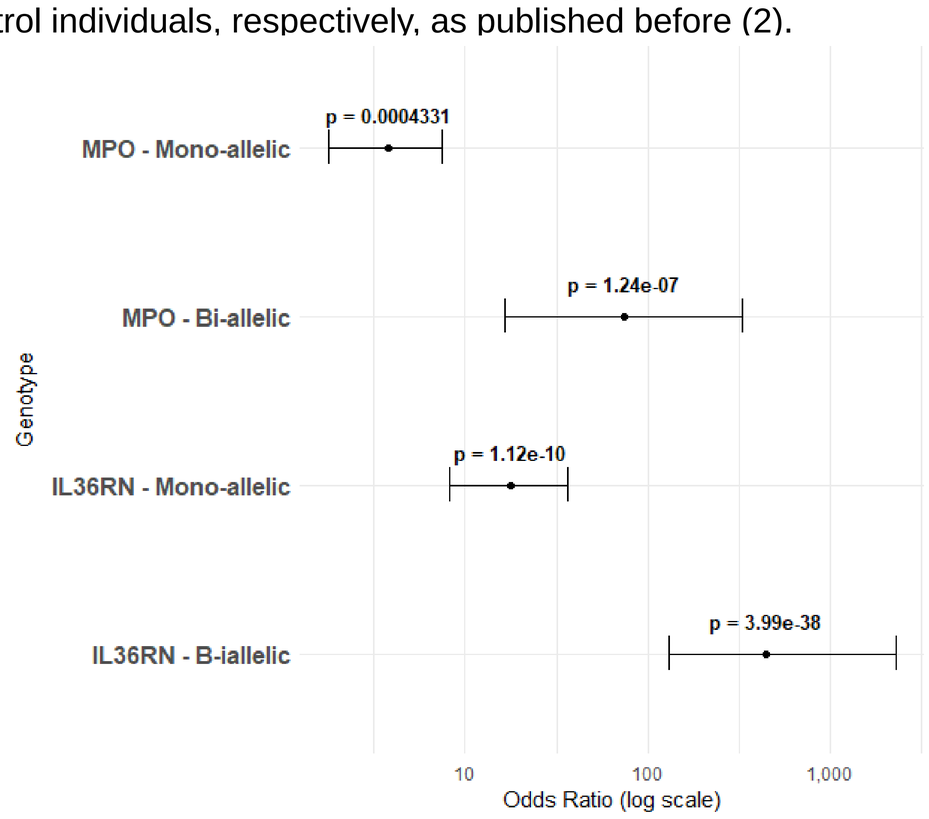
Methods and patients

We analyzed 79 exomes of European GPP patients for truncating *BTN3A3* variants and assessed the cumulative effect of disease-relevant variants per gene in *IL36RN, MPO*, and *AP1S3* in our and published patient groups (5). We also included 4896-4934 internal controls and/or Non-Finnish European (NFE) individuals of gnomAD v2.1.1 (6). We used Fisher's exact test to perform comparisons between genotypes or allele frequencies.

Table 1. Comparison of allele frequencies of *BTN3A3* variants between 79 patients and 64586 controls (NFE from gnomAD (6)).

	% of trunc. alleles (absolute no.)	% of wildtype alleles (absolute no.)
GPP patients	0 (0)	100 (158)
Control individuals	0.8 (977)	99.2 (127.234)

Figure 1. Forest plot showing elevated effect sizes (OR) and significance levels of association of different genotypes in *MPO* and *IL36RN*. Effect sizes shown in logarithmic scale on the X axis in 123/ 79 European affected individuals compared to 4934 and 4896 control individuals, respectively, as published before (2).



Results and conclusions

This meta-analysis confirms significant association and effect sizes for mono- and bi-allelic variants in *IL36RN* and *MPO.* We observe an increased effect size of bi-allelic *MPO* (p=1.24E-07; 73.67 [16.52-328.48] variants in GPP compared to heterozygous carriers of *IL36RN* variants (p=1.12E-10,17.7[8.14-36.11]) as expected for a monogenic disease.

We did not find truncating variants in *BTN3A3* (Table 1) and can therefore not confirm this as relevant disease gene in European patients; similarly, this meta-analysis does not support a role for *AP1S3* variants in GPP (Table 2).

Key Findings

- ***IL36RN*** and ***MPO*** are still the main genes in European GPP patients; biallelic ***MPO*** variants show a larger effect size than heterozygous carriers of *IL36RN* variants (Figure 1).
- Variants in ***BTN3A3*** are not associated with GPP in a first European study group; ***AP1S3*** is unlikely to be a key driver of GPP.

Table 2. Allele frequencies (AF) of sum of risk alleles in disease genes in 79-123 GPP patients compared to controls (NFE from gnomAD, 64.090-64.599 (6))**) and effect sizes (given as odds ratios with 95% confidence intervals) and level of association, if applicable.**

Gene	AF_cases	AF_contr.	OR [95 CI]	P_value
IL36RN	24.4	0.8	42.2 [18.4-33.78]	1.19E-69
MPO	11.8	6.1	2.37 [1.42-3.77]	6.84E-4
AP1S3	2.5	2.5	-	-

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