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Genotype-phenotype correlation analysis in patients with generalized pustular psoriasis

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Background & Aim

Generalized pustular psoriasis (GPP) is a rare, severe psoriatic subtype (Figure 1) with a strong genetic component characterized by sterile pustules and epidermal neutrophil infiltration. More often it occurs in episodes than continuously, and typical trigger factors are changes in e.g. medication, infections, surgery. Besides GPP, affected individuals can also suffer from concomitant psoriatic subtypes. Bi-allelic variants in *IL36RN* and *MPO* have been identified as the main genetic risk factors and the presence of variants is associated with a younger age of onset. Other genes (*CARD14*, *SERPINA3*, *AP1S3*) are known as rarely affected disease genes. To assess correlation of typical disease features/ concomitant diseases with the presence of disease variants, we performed sub-phenotype analyses in 72 patients.

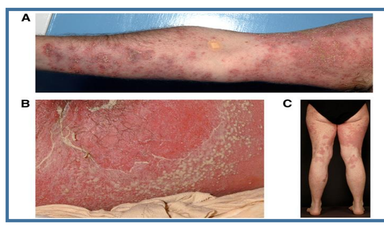

Figure 1: Clinical features of GPP. (A) Extensive plaques of erythema with pustules on the arm (B) erythematous, intensely inflamed skin with active pustulation and desquamation on the buttocks. (C) Widespread, healing, erythematous plaques on the legs (Figure 1 from Onoufradis et al. *Am J Hum Genet* 2011 [4]).

Study group & methods

Whole exomes were analysed for variants in five previously identified disease genes. We selected rare variants in these genes (MAF <2%) that have been previously published and mostly experimentally validated. Differences in patient groups stratified by carrier status of variants in *IL36RN* or *MPO* were determined using Fisher's exact test. Regression analysis was performed to determine the relationship between carrying genetic variants in *IL36RN* or *MPO* or both and age of onset.

Results

The average age of onset was 32.2. ± 22.83 years. *IL36RN* variants were detected in 20 of 72 patients (28%), *MPO* variants in 15 of 72 (21%), while variants in *CARD14*, *SERPINA3* and *AP1S3* were rarer (4%, 3%, 4%, respectively). In 61-68 individuals, we had clinical data for course of disease, palmoplantar pustulosis, plaque psoriasis and joint affection. By performing sub-phenotype analyses for carriers of *IL36RN* or *MPO* variants, we did not find any significant correlation. The largest frequency difference was observed for PsV. PsV was less common in the patient group with *IL36RN* variants: 15.4% vs. 51% (Figure 2A), in agreement with a previous study [1]. Our regression analysis showed a significantly reduced age of onset in carriers of *IL36RN*, variants, while not for carrying *MPO* variants or variants in both genes supporting previous findings [2, 3] (Figure 3).

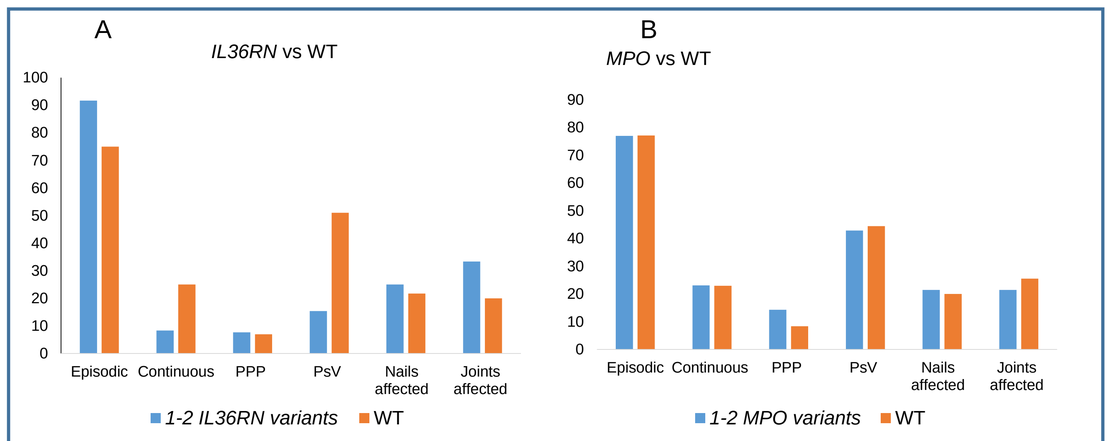

Figure 2: Genotype-phenotype correlation for *IL36RN* and *MPO* and typical disease features or concomitant manifestations, In A and B, the proportion of patients carrying *IL36RN* and *MPO* variants and course of disease, concomitant diseases or extracutaneous manifestations was compared with non-carriers (wildtype = WT). Patients with 1-2 *IL36RN* (A) variants have less concomitant PsV compared to wildtype although not statistically significant (p-value= 0.2). PsV = psoriasis vulgaris, PPP = palmoplantar pustulosis

Conclusions

This study confirms previous correlations of younger age of onset in carriers of *IL36RN* variants (Figure 3A), while the patient group is underpowered to detect further significant correlations, suggesting to increase sample sizes and to collaborate with other groups. Evidence for correlation of genetic factors with concomitant diseases will be important in therapeutic decision-making of this severe entity.

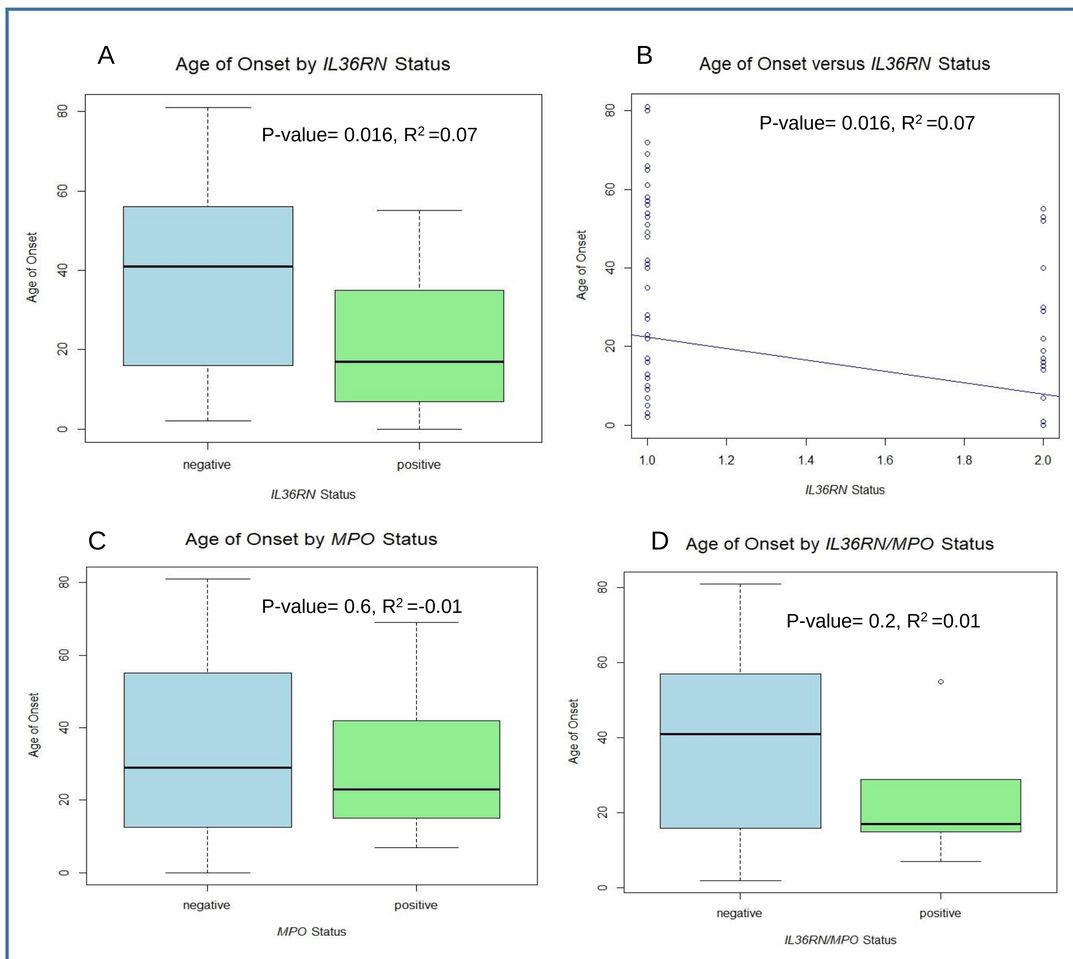

Figure 3: Genotype phenotype correlation of age of onset and genetic variants in *IL36RN* and *MPO*. (A) significant lower age of onset for patients with 1-2 *IL36RN* variants (p-value = 0.016). (B) A strong relationship between age of onset and *IL36RN* variants as depicted by the slope of the plot. (C) and (D) show a reduced age of onset in *MPO* positive patients and *MPO/ IL36RN* positive patients but lack statistical significance.

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