The IL31 Locus Shows Phenotype-Specific Genetic Association Across Chronic Pruritic Diseases

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A genome-wide significant variant at the IL31 locus (rs4319543) was recently associated with prurigo nodularis (PN), a chronic prurigo phenotype characterized by prominent neuroimmune itch (Patrick et al., 2025). IL-31 signaling has also been implicated in a broader range of inflammatory skin diseases[2], but whether this PN-associated variant reflects a phenotype-specific mechanism or a general predisposition to itch has not been directly evaluated.

Using FinnGen R13 summary statistics, we tested rs4319543 for association with seven phenotypes spanning chronic prurigo (lichen simplex chronicus and prurigo, n = 2,489; PN, n = 894), general pruritus (n = 4,708), inflammatory skin diseases (atopic dermatitis, n = 34,368; psoriasis, n = 13,309), histaminergic itch (urticaria, n = 14,649), and neuropathic itch (small fiber neuropathy, n = 1,022). Effect estimates were harmonized to the C allele. We evaluated shared genetic signals between PN and each comparator phenotype using approximate Bayes factor colocalization within 250-kb and 500-kb windows.

rs4319543-C showed its strongest associations with chronic prurigo phenotypes (lichen simplex chronicus and prurigo: OR = 1.240, $P = 4.5 \times 10^{-14}$; PN: OR = 1.204, $P = 8.8 \times 10^{-5}$), with progressively weaker associations in general pruritus (OR = 1.090, $P = 5.1 \times 10^{-5}$), atopic

dermatitis (OR = 1.028, P = 1.1×10^{-3}), and psoriasis (OR = 1.034, P = 8.9×10^{-3}), and no association with urticaria (P = 0.41) or small fiber neuropathy (P = 0.60). Colocalization supported shared signals between PN and lichen simplex chronicus and prurigo, general pruritus, and atopic dermatitis (PP4 = 0.89–0.98), but not psoriasis, urticaria, or small fiber neuropathy (PP4 < 0.07; Figure 1).

The IL31 locus demonstrates a phenotype-dependent association across pruritic disorders, with the strongest signal in chronic prurigo, weaker associations in general pruritus and inflammatory dermatoses, and no detectable association in histaminergic or neuropathic itch. IL31-associated genetic susceptibility may preferentially characterize prurigo-related neuroimmune biology rather than a nonspecific predisposition to itch. This specificity distinguishes chronic prurigo from other pruritic disorders and underscores the value of clinical phenotype, rather than itch severity alone, when investigating IL-31–mediated disease. These results provide a rationale for examining whether IL31 genetic variation predicts differential response to IL-31–targeted therapies[3,4].

References:

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Figure 1: Association of rs4319543-C at the IL31 locus with pruritic disease phenotypes in FinnGen R13, ordered by effect size. Filled circles indicate phenotypes that colocalize with prurigo nodularis (PP4 ≥ 0.8), open circles indicate phenotypes that do not colocalize (PP4 < 0.1), and the diamond indicates prurigo nodularis (the index phenotype).

