

**TABLE I.** Results of allergy workup in our leucovorin-reactive patients

Patients	ST to oxaliplatin/irinotecan	ST to both leucovorin and L-isomer calcium folinate	DPT with leucovorin	Tryptase levels during DPT with leucovorin (60 min after reaction) (ng/mL)	DPT with L-isomer calcium folinate	DPT with oxaliplatin/irinotecan
Case 1	Negative	Negative	Positive: urticaria	1.87	Positive: urticaria	Negative
Case 2	Negative	Negative	Positive: general urticaria, rhinoconjunctivitis	3.04	Positive: general urticaria, rhinoconjunctivitis, shortness of breath	Negative
Case 3	Negative	Negative	Positive: chills, back pain, elevated blood pressures, fever	2.46	Not performed	Negative
Case 4	Negative	Negative	Positive: general urticaria, eyelid angioedema	4.85	Not performed	Negative
Case 5	Negative	Negative	Positive: chills, chest pain, facial erythema	1.23	Positive: chills, facial erythema	Negative

ST concentrations used for oxaliplatin were 5 mg/mL and 0.5 mg/mL.<sup>1</sup> For irinotecan (20 mg/mL; 2 mg/mL), leucovorin (10 mg/mL; 1 mg/mL), and calcium levofolate (10 mg/mL; 1 mg/mL) were empirically obtained: full-strength solution according to manufacturer instructions and diluted further in normal saline to 1:10, and these concentrations were tested in 10 control patients to prove them nonirritant.  
ST, Skin test.

Our patients could continue their therapy either by avoiding leucovorin or by rapid desensitization (with adequate installations, standardized protocols, and expert personnel).

Up to 3 patients suffered overlooked milder symptoms during previous administrations. Helping patients identify and communicate these symptoms may prevent unnecessary risks.

In conclusion, we describe an important number of confirmed HSRs to leucovorin during a 1-year period. We show how patients reacting to leucovorin may also react to L-isomer calcium folinate. We believe that protocols studying FOLFOX/FOLFIRI HSRs should be undergone by drug allergy experts, and include systematic skin testing and DPT with folinic acid, to avoid infra-diagnosis and its resulting risks. Moreover, we report the first intravenous rapid desensitization to leucovorin in a reactive patient (confirmed by DPT).

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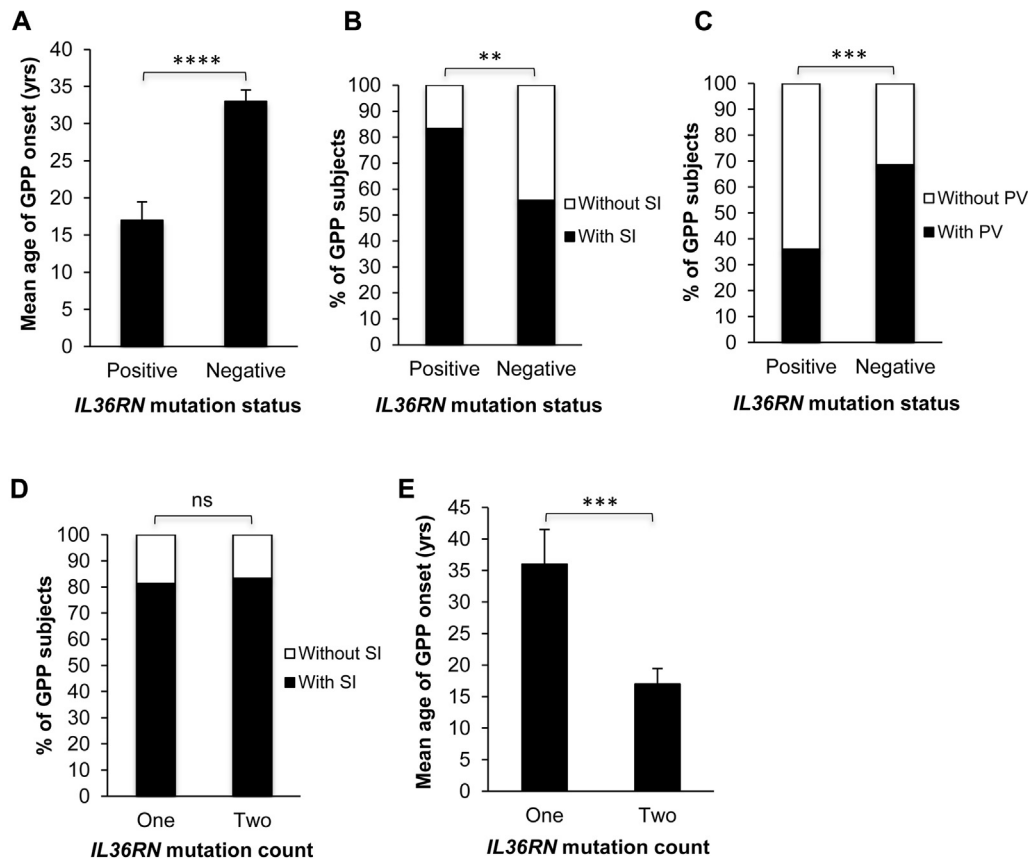
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### **IL36RN mutations define a severe autoinflammatory phenotype of generalized pustular psoriasis**

To the Editor:

Autoinflammatory diseases are a heterogeneous group of disorders mediated by abnormal activation of the innate immune system, resulting in recurrent episodes of systemic and organ-specific inflammation.<sup>1</sup> In recent years, the pace of autoinflammatory disease gene discovery has undergone a dramatic acceleration with the emergence of novel autoinflammatory phenotypes, highlighting the need to establish reliable diagnostic criteria through the analysis of extended case series.<sup>1</sup>

Generalized pustular psoriasis (GPP) is a rare autoinflammatory condition presenting with recurrent episodes of skin pustulation that are often accompanied by systemic inflammation (acute-phase response with neutrophilia) and concurrent psoriasis vulgaris (PV).<sup>2</sup> We and others demonstrated that a proportion of GPP cases carry recessive mutations of *IL36RN*, the gene encoding the IL-36 receptor antagonist.<sup>3,4</sup> This anti-inflammatory protein modulates the activity of IL-36  $\alpha$ ,  $\beta$ , and  $\gamma$ , a group of IL-1 family cytokines that have repeatedly been shown to be overexpressed in psoriatic lesions. Importantly, studies of animal models and human primary



**FIG 1.** A-C, Subjects with recessive *IL36RN* alleles have earlier disease onset (Fig 1, A), more frequently have systemic inflammation (Fig 1, B), and less frequently have PV (Fig 1, C) compared with *IL36RN*-negative subjects. D and E, Although the prevalence of systemic inflammation remains high among cases with a single mutation (Fig 1, D), these subjects present with significantly delayed disease onset compared with those with recessive alleles (Fig 1, E). ns, Not significant; SI, systemic inflammation, which was defined according to the American College of Chest Physicians criteria (leukocyte count  $>12 \times 10^9/L$  and fever  $>38^\circ C$ ).  $**P < .01$ ,  $***P < .001$ , and  $****P < 10^{-6}$ .

**TABLE I.** Frequency distribution of heterozygous *IL36RN* alleles

Origin	Allele counts (%)		P value	OR
	Cases	Control subjects		
British	2/22 (9.1%)	2/568 (0.3%)	.008	28.3
Chinese	4/72 (5.6%)	8/394 (2.0%)	.10	2.8
Japanese	3/66 (4.5%)	0/178 (0%)	.019	19.7
Malay	5/110 (4.5%)	0/192 (0%)	.006	20.1

OR, Odds ratio.

cell cultures indicate that IL-36 molecules induce the activation of keratinocytes and antigen-presenting cells, thus propagating skin inflammation in patients with psoriasis.<sup>5</sup>

Although these discoveries have shed new light on the pathogenesis of GPP, the rarity of the disease has thus far hindered a robust definition of the symptoms associated with deficiency of IL-36 receptor antagonist (DITRA), so that reliable indications for *IL36RN* screening are still lacking. Here we sought to address this issue by ascertaining an extended patient resource. We examined 233 cases (see Tables E1-E3 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)) recruited in accordance with the principles of the Declaration of Helsinki and with ethical approval from the relevant committees of participating institutions. This data

set originated from 3 sources: (1) 177 cases were ascertained through a systematic literature search based on the terms "*IL36RN*" and "generalized pustular psoriasis" (see Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)); (2) 45 patients received diagnoses from the coauthors of this study, according to established criteria<sup>2</sup>; and (3) 11 cases were initially ascertained by the International Registry of Severe Cutaneous Adverse Reaction Consortium. After an in-depth case review, the consortium expert committee proposed the presentation to be consistent with GPP. Thus the key inclusion criterion underlying the 3 ascertainment streams was a clinical diagnosis of GPP. The subsequent identification of patients with systemic flares was based on the criteria established by the American College of Chest Physicians (leukocytosis and fever  $>38^\circ C$ ).<sup>6</sup>

To delineate the phenotypic spectrum associated with DITRA, we first determined the frequency of *IL36RN* mutations in our cohort. We found that 49 (21.0%) of 233 cases carried recessive *IL36RN* alleles (see Table E1). Because information on age of onset, systemic involvement, and PV concurrence was available for 99.6%, 72.1%, and 86.7% of cases, we compared these features in patients bearing recessive *IL36RN* mutations ( $n = 49$ ) and in those without pathogenic alleles at this locus ( $n = 166$ , see Table E1 and the Methods section in this article's Online

Repository at [www.jacionline.org](http://www.jacionline.org)). We found that *IL36RN*-positive subjects manifested a strikingly more severe clinical phenotype characterized by an earlier age of onset ( $17 \pm 2.4$  vs  $33 \pm 1.5$  years,  $P = 5.9 \times 10^{-7}$ ) and a markedly increased risk of systemic inflammation (83.3% vs 55.6%,  $P = 1.5 \times 10^{-3}$ ; Fig 1, A and B). We also observed a very significant reduction in the prevalence of PV in the *IL36RN*-positive cohort (36.1% vs 68.7%,  $P = 5.0 \times 10^{-4}$ ; Fig 1, C), validating the results of a small Japanese study.<sup>7</sup>

We previously reported 6 patients with GPP bearing single heterozygous *IL36RN* mutations.<sup>8</sup> In keeping with this observation, we observed 18 cases (including the subjects we had originally described) with a single disease allele. To validate the significance of these findings, we compared the frequency of monoallelic *IL36RN* mutations in cases versus population-matched control subjects. We found that heterozygous disease alleles were consistently enriched among cases, with statistically significant  $P$  values ( $P < .02$ ; false discovery rate  $< 0.05$ ) observed in most ethnic groups (Table I). We also performed a meta-analysis of our case-control resources, which demonstrated that monoallelic *IL36RN* mutations confer a very substantial increase in disease risk (weighted pooled odds ratio, 7.32; 95% CI, 3.02-17.7;  $P = 1.1 \times 10^{-5}$ ).

We next compared disease severity in subjects carrying 1 or 2 mutations. We focused our analysis on age of onset and systemic inflammation because PV concurrence is not considered a reliable indicator of GPP severity.<sup>2</sup> We observed a high prevalence of systemic inflammation (>80%) in both patient groups (Fig 1, D), but we noted that the mean age of onset in *IL36RN* heterozygotes exceeded by 2-fold that of patients with biallelic mutations ( $36 \pm 5.5$  vs  $17 \pm 2.4$ ;  $P = 6.0 \times 10^{-4}$ ; Fig 1, E).

The aim of our study was to investigate the correlation between *IL36RN* mutation status and the clinical presentation of GPP to aid the definition of diagnostic criteria for the stratification of patient cohorts. We found that *IL36RN* alleles define a GPP phenotype characterized by early onset, high risk of systemic inflammation, and low prevalence of PV. Of note, these conclusions were drawn by comparing the *IL36RN*-positive data set with a heterogeneous cohort that was solely defined by the lack of *IL36RN* mutations. As further disease genes are identified and systematically genotyped, the designation of more homogeneous patient subgroups will become possible, allowing the development of formal diagnostic algorithms.

We recognize that our study design, which combined the analysis of newly recruited cases with a literature review, might have been vulnerable to ascertainment bias. However, we note there was no significant variability in the frequency of *IL36RN* mutations across data sets (see Table E4 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)), indicating that our inclusion criteria were sufficiently robust to allow the ascertainment of a reasonably homogeneous resource.

Our analysis demonstrated a gene dosage effect whereby GPP onset is significantly delayed in subjects with monoallelic mutations. Intriguingly, we found that these subjects were still at high risk of systemic inflammation. Thus heterozygous patients might require a longer or more intense exposure to environmental triggers to manifest overt disease. Once an abnormal immune response is initiated, however, the presence of a wild-type *IL36RN* allele does not appear sufficient to prevent the onset of systemic inflammation. This suggests that abnormal cytokine signaling might be propagated by molecules acting downstream of *IL36RN*. Further *ex vivo* analyses will be required to validate this model and define the cytokines that sustain abnormal inflammatory responses in patients with GPP.

In conclusion, we have defined a clinical triad (early onset, systemic inflammation, and absence of concurrent PV) that could be used to prioritize patients with GPP for *IL36RN* screening. Importantly, pilot studies indicate that a proportion of patients with *IL36RN* mutations could be treated with the IL-1 antagonist anakinra.<sup>9,10</sup> Therapeutic agents that specifically target the IL-36 receptor are also being developed.<sup>11</sup> Thus our work is expected to facilitate the identification of patients who might benefit from personalized treatment with IL-1 or IL-36 blockers.

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## Is there a risk using hypoallergenic cosmetic pediatric products in the United States?

### To the Editor:

Health care providers wisely advise the parents of children with atopic dermatitis (AD) to apply emollients to treat xerotic and inflamed skin. So-called hypoallergenic products are typically recommended because patients with AD have an elevated risk of contact allergy to fragrances, surfactants, and preservatives.<sup>1-3</sup> This is likely explained by more frequent allergen exposure via topical products in combination with an impaired skin barrier facilitating allergen penetration.<sup>4</sup>

Chronic exposure to contact allergens in cosmetics increases the risk of not only allergic contact dermatitis (ACD) but also AD.<sup>5</sup> Repeated cutaneous exposure to skin sensitizers initially leads to ACD characterized by T<sub>H</sub>1 inflammation, but then a gradual shift toward T<sub>H</sub>2 inflammation, resulting in AD.<sup>4</sup> In addition, AD skin has a specific initial propensity to T<sub>H</sub>2 programming following exposure to contact allergens in contrast to the normal T<sub>H</sub>1 programming in non-AD skin.<sup>6</sup>

Anecdotally, we have observed a lack of correlation between marketing terms highlighting hypoallergenicity or dermatologist/pediatrician-recommended status and the actual content of contact allergens in topical products. We therefore evaluated the allergen content of 187 unique pediatric cosmetics marketed in the United States as hypoallergenic. Inclusion criteria were products marketed as pediatric and "hypoallergenic," "dermatologist recommended/tested," "fragrance free," or "paraben free."

Products from 6 different retailers in and around Redlands, California, were purchased or photographed in September 2013. The ingredients, name, brand, type, and advertising term for each product were recorded. To identify contact allergens, the ingredients were compared with allergens in the North American Contact Dermatitis Group standard screening tray using a customized search algorithm programmed into Matlab 7.4 (Mathworks, Natick, Mass).

We found that 167 (89%) of the 187 products contained at least 1 contact allergen, 117 (63%) 2 or more, and 21 (11%) 5 or more (Table I). The average number of allergens in each product was 2.4 (95% CI, 2.05-2.51). The most prevalent single allergen was cocamidopropyl betaine, found in 45 (24%) followed by propolis/beeswax in 35 (19%), phenoxyethanol in 33 (18%), tocopherol in 25 (13%), and DMDM hydantoin in 24 (13%) (Table II). Of note, 11.2% of the products contained methylisothiazolinone. By allergen category, the most prevalent sensitizers were preservatives 108 (58%) and fragrances 55 (29%).

**TABLE I.** Number of allergens in products according to the advertising term used

	Total n	Percent with ≥1 allergen (n)	Percent with ≥2 allergens (n)	Percent with ≥3 allergens (n)	Percent with ≥4 allergens (n)	Percent with ≥5 allergens (n)	95% CI*
All products	187	88.8 (166)	62.6 (117)	38.5 (72)	22.5 (42)	11.2 (21)	NA
By advertising term:							
Dermatologist recommended	66	78.8 (52)	50.0 (33)	21.2 (14)	9.1 (6)	3.0 (2)	73.8-83.8
Fragrance free	52	80.8 (42)	55.8 (29)	30.8 (16)	17.3 (9)	11.5 (6)	75.3-86.2
Hypoallergenic	135	88.2 (119)	65.2 (88)	42.2 (57)	23.7 (32)	11.1 (15)	85.2-90.9
Paraben free	72	88.9 (64)	56.9 (41)	29.2 (21)	18.1 (13)	5.6 (4)	85.2-92.6

NA, Not applicable/available.

\*95% CI reflects the CI for % with 1 or more allergen.

## METHODS

### Mutation screening

The *IL36RN* coding region was screened by using primers and conditions reported elsewhere.<sup>E1</sup> In those instances in which Sanger sequencing uncovered a single disease allele, the possibility that the second mutation might be accounted for by the insertion/deletion of an entire exon was excluded by amplifying the entire *IL36RN* gene region, as previously described.<sup>E2</sup> Nucleotide changes were considered deleterious if (1) experimentally derived evidence was available in the literature or (2) a high-confidence pathogenicity prediction was returned by using at least 4 of the following programs: SIFT,<sup>E3</sup> PolyPhen-2,<sup>E4</sup> Provean,<sup>E5</sup> MutPred,<sup>E6</sup> and MutationTaster.<sup>E7</sup> The sequence of the *IL36RN* transcript ENST00000393200 was used as a reference in all bioinformatics analyses.

### Statistical tests

Differences in the frequency distribution of dichotomous clinical findings (presence/absence of PV or systemic inflammation) and mean ages of disease onset were assessed with the Fisher exact test and Student unpaired *t* test, respectively. Both were implemented with the online tools available at <http://graphpad.com/quickcalcs/>.

The combined frequency of heterozygous *IL36RN* alleles was compared in cases versus control subjects by using the Fisher exact test. Control allele frequencies were determined in the following resources: 284 British subjects sequenced by the 1000 Genomes Project (*n* = 89) and TwinsUK (*n* = 195), 89 Japanese and 197 Han Chinese subjects sequenced by the 1000 Genomes Project, and 96 subjects sequenced by the Singapore Sequencing Malay Project.<sup>E8-E10</sup> The meta-analysis of multiple case-control data sets was implemented with Review Manager 5.2.<sup>E11</sup> *P* values of less than .05 were deemed statistically significant.

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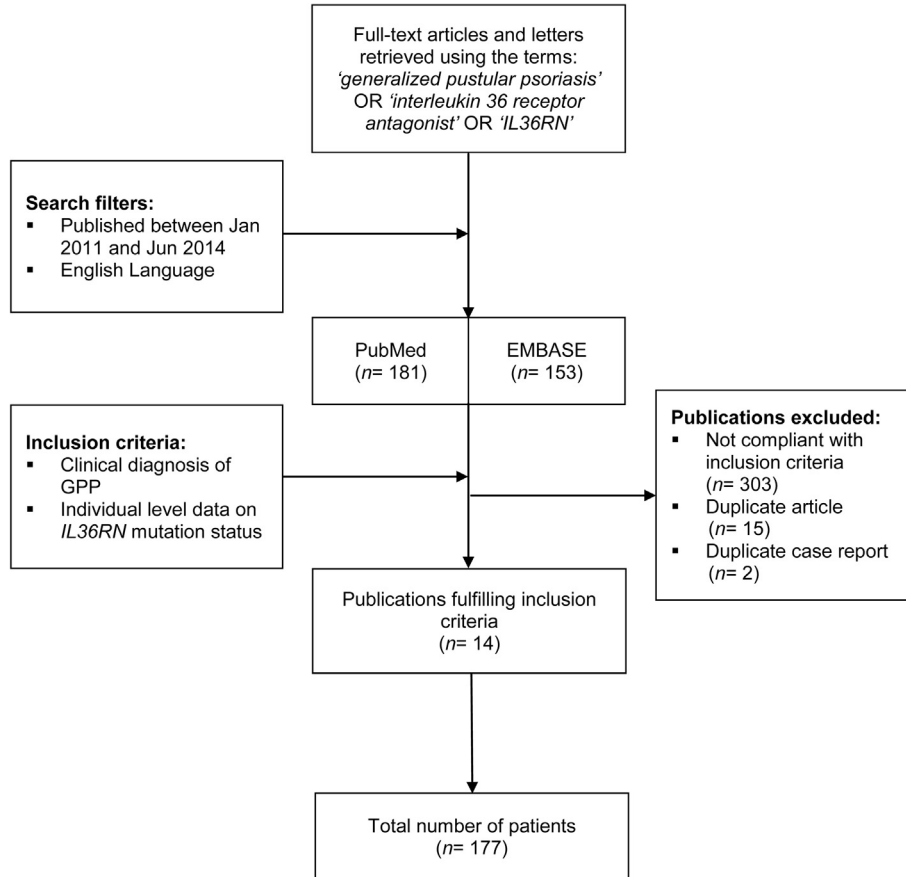


FIG E1. Flow diagram illustrating the criteria underlying the literature search.

**TABLE E1.** Study cohort summary statistics

	Sex		Ethnicity			<i>IL36RN</i> mutation count		
	Male	Female	European	Asian	African	0	1	2
Patients, no. (%)	92/233 (39.5%)	141/233 (60.5%)	49/233 (21.0%)	172/233 (73.8%)	12/233 (5.2%)	166/233 (71.3%)	18/233 (7.7%)	49/233 (21.0%)

TABLE E2. Clinical presentation of GPP in cases bearing *IL36RN* mutations

Study	Study no.	Origin	Sex	Age of onset (y)	<i>IL36RN</i> mutations*		PV	Fever (>38°C)	Leukocytosis	Systemic inflammation
Marrakchi et al, 2011 <sup>E12</sup>	V.4	Tunisian	M	2	p.Leu27Pro	p.Leu27Pro	Unknown	Y	Y	Y
	IV.2	Tunisian	F	0 (1 wk)	p.Leu27Pro	p.Leu27Pro	Y	Y	Y	Y
	V.2	Tunisian	M	4	p.Leu27Pro	p.Leu27Pro	Unknown	Y	Y	Y
	V.3	Tunisian	M	0 (2 mo)	p.Leu27Pro	p.Leu27Pro	Unknown	Y	Y	Y
	II.1	Tunisian	M	5	p.Leu27Pro	p.Leu27Pro	Unknown	Y	Y	Y
	V.1	Tunisian	F	0 (2 wk)	p.Leu27Pro	p.Leu27Pro	Y	Y	Y	Y
	IV.1	Tunisian	F	25	p.Leu27Pro	p.Leu27Pro	Unknown	Y	Y	Y
	V.4	Tunisian	F	20	p.Leu27Pro	p.Leu27Pro	Unknown	Y	Y	Y
	V.1	Tunisian	F	22	p.Leu27Pro	p.Leu27Pro	Unknown	Y	Y	Y
Onoufriadis et al, 2011 <sup>E1</sup>	GPP-01 II:5	British	F	51	p.Ser113Leu	p.Ser113Leu	N	Y	Y	Y
	GPP-02 II:1	British	M	5	p.Ser113Leu	p.Ser113Leu	N	Y	Y	Y
	GPP-03 II:2	British	F	7	p.Ser113Leu	p.Arg48Trp	N	Y	Y	Y
Farooq et al, 2013 <sup>E13</sup>	JPP12	Japanese	F	51	p.Arg10Argfs*1	p.Thr123Arg	N	Y	Y	Y
	JPP14	Japanese	M	16	p.Arg10Argfs*1	p.Arg10X	Y	Y	Y	Y
Li et al, 2013 <sup>E14</sup>	<b>Patient 3</b>	<b>Chinese</b>	<b>F</b>	<b>8</b>	<b>p.Pro76Leu</b>	—	<b>N</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
Setta-Kaffetzi et al, 2013 <sup>E2</sup>	<b>GLA-I</b>	<b>British</b>	<b>M</b>	<b>29</b>	<b>p.Ser113Leu</b>	—	<b>N</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	GLA-II	British	M	26	p.Ser113Leu	p.Ser113Leu	N	Y	Y	Y
	<b>GLA-III</b>	<b>British</b>	<b>M</b>	<b>39</b>	<b>p.Ser113Leu</b>	—	<b>N</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	MAL-I	Malay	F	37	p.Arg10Argfs*1	p.Arg10Argfs*1	Y	N	N	N
	MAL-II	Chinese	F	21	p.Arg10Argfs*1	p.Arg10Argfs*1	Y	Y	Y	Y
	<b>MAL-III</b>	<b>Malay</b>	<b>F</b>	<b>9</b>	<b>p.Arg10Argfs*1</b>	—	<b>N</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	<b>MAL-IV</b>	<b>Malay</b>	<b>M</b>	<b>42</b>	<b>p.Arg10Argfs*1</b>	—	<b>Y</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	<b>MAL-V</b>	<b>Malay</b>	<b>F</b>	<b>12</b>	<b>p.Arg10Argfs*1</b>	—	<b>Y</b>	<b>Y</b>	<b>N</b>	<b>N</b>
	MAL-VI	Chinese	M	12	p.Arg10Argfs*1	p.Arg10Argfs*1	N	Y	Unknown	Unknown
	MAL-VII	Malay	M	8	p.Arg10Argfs*1	p.Ser113Leu	Y	Y	Y	Y
	MAL-VIII	Malay	F	2	p.Arg10Argfs*1	p.Arg10Argfs*1	Y	Y	Y	Y
	<b>MAL-IX</b>	<b>Chinese</b>	<b>F</b>	<b>40</b>	<b>p.Arg10Argfs*1</b>	—	<b>Y</b>	<b>N</b>	<b>Y</b>	<b>N</b>
	<b>MAL-X</b>	<b>Chinese</b>	<b>M</b>	<b>12</b>	<b>p.Arg10Argfs*1</b>	—	<b>Y</b>	<b>N</b>	<b>N</b>	<b>N</b>
P01	Turkish	M	0 (4 mo)	p.Pro76Leu	p.Pro76Leu	N	Unknown	Unknown	Unknown	
P02	German/Iraqi	F	1	p.Ser113Leu	p.Ser113Leu	N	Unknown	Unknown	Unknown	
Körber et al, 2013 <sup>E15</sup>	P04	German	F	16	p.Glu94X	p.Ser113Leu	N	Unknown	Unknown	Unknown
	P05	German/Polish	F	17	p.Ser113Leu	p.Ser113Leu	N	N	Unknown	N
	P06	German	F	40	p.Arg48Trp	p.Ser113Leu	Y	Y	Y	Y
	P07	German/Czech	F	0 (4 mo)	p.Pro76Leu	p.Ser113Leu	N	Unknown	Unknown	Unknown
	<b>P08</b>	<b>German</b>	<b>M</b>	<b>55</b>	<b>p.Ser113Leu</b>	—	<b>Y</b>	<b>Unknown</b>	<b>Unknown</b>	<b>Unknown</b>
Sugiura et al, 2013 <sup>E16</sup>	Patient 1	Japanese	M	34	p.Arg10X	p.Arg10X	N	Y	Y	Y
	Patient 2	Japanese	M	2	p.Arg10X	p.Arg10Argfs*1	N	Y	Y	Y
	Patient 4	Japanese	F	5	p.Arg10X	p.Arg10Argfs*1	N	Y	Y	Y
	Patient 5	Japanese	F	65	p.Arg10X	p.Arg10X	N	Y	Y	Y
	Patient 6	Japanese	F	40	p.Arg10X	p.Arg10X	N	Y	Y	Y
	Patient 7	Japanese	F	21	p.Arg10X	p.Arg10X	N	Y	Y	Y
	Patient 8	Japanese	M	6	p.Arg10X	p.Arg10Argfs*1	N	Y	Y	Y
	Patient 9	Japanese	M	8	p.Arg10X	p.Arg10X	N	Y	Y	Y
	Patient 25	Japanese	F	20	p.Arg10X	p.Arg10Argfs*1	Y	Y	Y	Y
Kanazawa et al, 2013 <sup>E17</sup>	—	Japanese	M	3	p.Arg10X	p.Thr123Met	Y	Y	Unknown	Unknown

(Continued)



TABLE E2. (Continued)

Study	Study no.	Origin	Sex	Age of onset (y)	<i>IL36RN</i> mutations*		PV	Fever (>38°C)	Leukocytosis	Systemic inflammation
Rossi-Semerano et al, 2013 <sup>E18</sup>	—	Tunisian	M	0 (2 wk)	p.Leu27Pro	p.Leu27Pro	Unknown	N	Y	N
Abbas et al, 2013 <sup>E19</sup>	—	Lebanese	F	21	p.Ser113Leu	p.Ser113Leu	Unknown	Y	Y	Y
Sugiura et al, 2014 <sup>E20</sup>	Case 1	Japanese	F	23	p.Arg10Argfs*1	p.Arg10Argfs*1	Unknown	Y	N	N
	Case 2	<b>Japanese</b>	<b>F</b>	<b>8</b>	<b>p.Arg10X</b>	—	<b>Unknown</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
Renert-Yuval et al, 2014 <sup>E21</sup>	—	Palestinian	M	0 (1 mo)	p.Arg10X	p.Arg10X	N	Y	Y	Y
Sugiura et al, 2014 <sup>E22</sup>	Patient 3	Japanese	M	6	p.Arg10Argfs*1	p.Arg10Argfs*1	N	Y	Y	Y
	Patient 4	<b>Japanese</b>	<b>F</b>	<b>53</b>	<b>p.Arg10Argfs*1</b>	—	<b>Y</b>	<b>Unknown</b>	<b>Unknown</b>	<b>Unknown</b>
Song et al, 2014 <sup>E23</sup>	—	<b>Korean</b>	<b>F</b>	<b>4</b>	<b>p.Arg10Argfs*1</b>	—	<b>Unknown</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
This study	—	Swiss	M	40	p.Ser113Leu	p.Ser113Leu	N	Y	Y	Y
	<b>78GPP1</b>	<b>Malay</b>	<b>F</b>	<b>57</b>	<b>p.Arg10Argfs*1</b>	—	<b>Y</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	82GPP1	Malay	F	19	p.Arg10Argfs*1	p.Arg10Argfs*1	Y	Y	N	N
	<b>89GPP1</b>	<b>Malay</b>	<b>F</b>	<b>40</b>	<b>p.Arg10Argfs*1</b>	—	<b>Y</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	96GPP1	Chinese	F	7	p.Arg10Argfs*1	p.Arg10Argfs*1	Y	Y	Unknown	Unknown
	<b>101GPP1</b>	<b>Chinese</b>	<b>F</b>	<b>30</b>	<b>p.Arg10Argfs*1</b>	—	<b>N</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	103GPP1	Chinese	M	5	p.Arg10Argfs*1	p.Arg10Argfs*1	N	N	N	N
	SCAR1646	German	F	43	p.Ser113Leu	p.Ser113Leu	Unknown	Y	Y	Y
	<b>SCAR1690</b>	<b>German</b>	<b>F</b>	<b>68</b>	<b>p.Ser113Leu</b>	—	<b>Unknown</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	SCAR2074	German	F	53	p.Ser113Leu	p.Ser113Leu	Unknown	N	Y	N
	<b>SCAR2548</b>	<b>Polish</b>	<b>M</b>	<b>84</b>	<b>p.Ser113Leu</b>	—	<b>N</b>	<b>Y</b>	<b>Y</b>	<b>Y</b>
	—	Algerian	M	0 (5 mo)	p.Leu27Pro	p.Leu27Pro	Y	Y	Y	Y
	—	Spanish	F	0 (6 mo)	p.Gly141Metfs*29	p.Gly141Metfs*29	Unknown	Y	Y	Y

F, Female; M, male.

\*The details of subjects bearing a single disease allele are shown in boldface.

**TABLE E3.** Clinical presentation of GPP in patients who do not harbor *IL36RN* mutations

Study	Study no.	Origin	Sex	Age of onset (y)	Psoriasis vulgaris	Fever (>38°C)	Leukocytosis	Systemic inflammation
Onoufriadis et al, 2011 <sup>E1</sup>	GPP-04 I:1	British	F	10	N	Y	Y	Y
	GPP-05 I:1	British	F	45	N	N	N	N
Farooq et al, 2013 <sup>E13</sup>	JPP1	Japanese	M	74	N	Y	N	N
	JPP2	Japanese	M	72	Y	Y	N	N
	JPP3	Japanese	M	72	Y	Y	Y	Y
	JPP4	Japanese	M	20	Y	N	N	N
	JPP5	Japanese	M	45	N	Y	Y	Y
	JPP6	Japanese	F	43	N	Y	Y	Y
	JPP7	Japanese	F	73	N	Y	Y	Y
	JPP8	Japanese	M	42	N	Y	Y	Y
	JPP9	Japanese	F	58	N	Y	Y	Y
	JPP10	Japanese	M	36	Y	Y	Y	Y
	JPP11	Japanese	M	48	N	Y	Y	Y
	JPP13	Japanese	F	17	N	N	N	N
	Li et al, 2013 <sup>E14</sup>	Patient 1	Chinese	M	16	N	N	Unknown
Patient 2		Chinese	M	1.5	N	Y	N	N
Patient 4		Chinese	M	2.5	N	Y	N	N
Patient 5		Chinese	F	8	N	Y	N	N
Patient 6		Chinese	M	3	N	Y	N	N
Patient 7		Chinese	M	0 (4 mo)	N	Y	N	N
Patient 8		Chinese	M	6	Y	Y	N	N
Patient 9		Chinese	F	5	N	Y	N	N
Patient 10		Chinese	F	9	N	Y	N	N
Setta-Kaffetzi et al, 2013 <sup>E2</sup>		T009361	British	F	45	N	Unknown	Unknown
	10167	Dutch-Romani	F	9	Y	Y	Y	Y
	20368	Dutch-North African	Unknown	6	Y	N	Y	N
	20299	Dutch-Hispanic	M	2	Y	N	Unknown	N
	2GPP1	Indian	M	28	Y	Y	Y	Y
	3GPP1	Indian	F	24	Y	Y	Y	Y
	4GPP1	Malay	F	44	Y	Unknown	Y	Unknown
	5GPP1	Malay	M	26	Y	Y	Y	Y
	6GPP1	Malay	F	24	Y	Unknown	Y	Unknown
	7GPP1	Chinese	F	29	Y	Y	Y	Y
	8GPP1	Chinese	F	30	Y	Unknown	Y	Unknown
	9GPP1	Malay	F	45	Y	Y	Y	Y
	10GPP1	Malay	M	36	Y	Unknown	Y	Unknown
	11GPP1	Malay	M	21	Y	Y	Y	Y
	12GPP1	Indian	F	28	Y	Unknown	Y	Unknown
	13GPP1	Chinese	F	30	Y	N	Y	N
	14GPP1	Chinese	F	25	Y	Y	Y	Y
	16GPP1	Chinese	F	25	Y	Y	Y	Y
	17GPP1	Indian	F	2	Y	Y	Y	Y
	18GPP1	Malay	M	28	Y	N	N	N
	19GPP1	Malay	M	30	N	N	N	N
	20GPP1	Chinese	F	46	Y	N	Y	N
	21GPP1	Malay	F	46	Y	Y	Y	Y
	22GPP1	Chinese	M	38	Y	Y	N	N
	23GPP1	Malay	F	31	Y	Y	Y	Y
	24GPP1	Malay	F	38	Y	Y	Y	Y
	25GPP1	Malay	F	42	Y	Y	Unknown	Unknown
	26GPP1	Malay	F	31	Y	Y	Y	Y
	28GPP1	Malay	F	5	Y	Y	N	N
	29GPP1	Chinese/Indian	F	24	Y	N	N	N
30GPP1	Malay	F	37	N	Y	Y	Y	
31GPP1	Malay	M	4	Y	N	Y	N	
32GPP1	Malay	F	55	N	Y	Y	Y	
33GPP1	Indian	F	59	N	Unknown	Y	Unknown	
36GPP1	Chinese	F	30	N	Unknown	Y	Unknown	
37GPP1	Malay	F	56	Y	Y	Y	Y	

(Continued)

TABLE E3. (Continued)

Study	Study no.	Origin	Sex	Age of onset (y)	Psoriasis vulgaris	Fever (>38°C)	Leukocytosis	Systemic inflammation
	38GPP1	Malay	M	27	Y	Y	Y	Y
	39GPP1	Indian	F	15	Y	N	N	N
	41GPP1	Malay	F	52	Y	N	N	N
	42GPP1	Malay	M	15	Y	N	N	N
	43GPP1	Malay	M	42	Y	Y	Y	Y
	45GPP1	Chinese	M	41	Y	Y	Y	Y
	46GPP1	Malay	M	34	Y	Y	Unknown	Unknown
	47GPP1	Chinese	F	17	Y	Y	Y	Y
	48GPP1	Indian	F	37	Y	Unknown	Y	Unknown
	49GPP1	Malay	F	26	Y	Unknown	Y	Unknown
	51GPP1	Malay	F	14	Y	N	N	N
	52GPP1	Malay	M	25	Y	Y	Y	Y
	53GPP1	Chinese	F	30	Y	N	N	N
	54GPP1	Malay	F	29	Y	Y	N	N
	56GPP1	Malay	F	12	N	Y	N	N
	57GPP1	Malay	M	30	N	Y	Y	Y
	58GPP1	Malay	F	23	Y	Y	Y	Y
	59GPP1	Malay	F	17	Y	Y	Y	Y
	60GPP1	Chinese	M	63	N	Y	Y	Y
	61GPP1	Malay	F	48	Y	Y	Y	Y
	62GPP1	Malay	M	43	Y	Y	Y	Y
	63GPP1	Malay	F	43	N	Unknown	Y	Unknown
	65GPP1	Malay	M	6	Y	Unknown	Y	Unknown
	66GPP1	Chinese	F	28	Y	Y	Y	Y
	67GPP1	Indian	M	29	Y	Y	Y	Y
	68GPP1	Malay	F	31	Y	N	N	N
	69GPP1	Malay	F	12	Y	Y	Y	Y
	70GPP1	Chinese	M	23	Y	N	N	N
	71GPP1	Malay	F	54	Y	Unknown	Y	Unknown
	72GPP1	Malay	F	30	N	Y	Y	Y
	73GPP1	Malay	F	20	Y	Y	Y	Y
	75GPP1	Indian	F	42	N	N	N	N
	76GPP1	Indian	F	26	N	N	N	N
	77GPP1	Malay	F	38	Y	Y	Y	Y
Körber et al, 2013 <sup>E15</sup>	P03	Iraqi	M	14	N	Unknown	Unknown	Unknown
	P09	German	F	3	N	Unknown	Unknown	Unknown
	P10	Turkish	F	5	N	Unknown	Unknown	Unknown
	P11	German	F	9	Y	Unknown	Unknown	Unknown
	P12	German/Polish	F	16	Y	Unknown	Unknown	Unknown
	P13	German	M	17	N	Unknown	Unknown	Unknown
	P14	German	F	27	N	Unknown	Unknown	Unknown
	P15	German	F	41	Y	N	Unknown	N
	P16	German	M	45	N	Unknown	Unknown	Unknown
	P17	German/Finnish	F	49	N	Unknown	Unknown	Unknown
	P18	German	F	69	N	Unknown	Unknown	Unknown
	P19	German	M	72	Y	Unknown	Unknown	Unknown
Sugiura et al, 2013 <sup>E16</sup>	Patient 11	Japanese	M	2	N	Y	Y	Y
	Patient 12	Japanese	F	9	Y	Y	Y	Y
	Patient 13	Japanese	F	15	Y	Y	Y	Y
	Patient 14	Japanese	F	75	Y	Y	Y	Y
	Patient 15	Japanese	F	58	Y	Y	Y	Y
	Patient 16	Japanese	M	45	Y	Y	Y	Y
	Patient 17	Japanese	F	32	Y	Y	Y	Y
	Patient 18	Japanese	F	27	Y	Y	Y	Y
	Patient 19	Japanese	M	22	Y	Y	Y	Y
	Patient 20	Japanese	M	59	Y	Y	Y	Y
	Patient 21	Japanese	F	72	Y	Y	Y	Y
	Patient 22	Japanese	M	28	Y	Y	Y	Y
	Patient 23	Japanese	M	20	Y	Y	Y	Y
	Patient 26	Japanese	F	42	Y	Y	Y	Y
	Patient 27	Japanese	M	59	Y	Y	Y	Y
	Patient 28	Japanese	M	78	Y	Y	Y	Y

(Continued)

TABLE E3. (Continued)

Study	Study no.	Origin	Sex	Age of onset (y)	Psoriasis vulgaris	Fever (>38°C)	Leukocytosis	Systemic inflammation
This study	Patient 30	Japanese	M	24	Y	Y	Y	Y
	Patient 31	Japanese	M	38	Y	Y	Y	Y
	T002229	British	F	19	Y	Unknown	Y	Unknown
	T003673	British	F	29	Y	Unknown	Y	Unknown
	T009359	British	F	49	N	N	N	N
	T009360	British	F	40	N	Unknown	Unknown	Unknown
	81GPP1	Chinese	F	13	Y	N	N	N
	83GPP1	Indian	M	23	Y	N	N	N
	84GPP1	Malay	M	41	Y	Y	Y	Y
	85GPP1	Malay	F	54	N	Y	N	N
	86GPP1	Malay	M	34	Y	Y	Y	Y
	87GPP1	Malay	F	15	Y	N	N	N
	88GPP1	Indian	M	27	Y	Y	Unknown	Unknown
	90GPP1	Indian	F	36	Y	Unknown	Y	Unknown
	91GPP1	Malay	M	10	N	Unknown	Y	Unknown
	92GPP1	Chinese	M	30	Y	N	N	N
	93GPP1	Chinese	F	61	Y	Y	N	N
	94GPP1	Malay	F	49	Y	N	N	N
	95GPP1	Chinese	M	20	Y	N	N	N
	97GPP1	Malay	M	7	Y	Y	Unknown	Unknown
	98GPP1	Malay	F	5	Y	Y	N	N
	99GPP1	Indian	F	26	Y	Unknown	Y	Unknown
	100GPP1	Chinese	F	25	Y	N	N	N
	102GPP1	Indian	F	51	Y	Unknown	N	N
	104GPP1	Malay	F	21	Y	Y	Y	Y
	105GPP1	Chinese	F	57	N	Unknown	Y	Unknown
	106GPP1	Indian	F	62	Y	N	N	N
	107GPP1	Chinese	M	67	N	Y	Y	Y
	108GPP1	Chinese	M	38	Y	Unknown	Y	Unknown
	109GPP1	Chinese	M	68	Y	N	N	N
	110GPP1	Indian	F	16	Y	Unknown	Y	Unknown
111GPP1	Malay	F	23	N	N	N	N	
T018712	Ethiopian	F	22	N	Unknown	Y	Unknown	
T011497	Indian	F	31	Y	Unknown	Unknown	Unknown	
T002189	British	F	Unknown	Y	Unknown	Unknown	Unknown	
T023653	British/Irish	M	15	Y	Y	Y	Y	
T025165	Polish	F	0 (4 mo)	Y	N	N	N	
T024653	Bangladeshi	M	9	Y	Y	Y	Y	
SCAR659	Italian	F	75	Y	Y	Y	Y	
SCAR673	Italian	F	69	N	N	Y	N	
SCAR1789	German	F	58	N	N	Y	N	
SCAR1798	German	F	47	Y	N	Y	N	
SCAR2082	German	M	46	Y	Y	Y	Y	
SCAR2479	German	F	70	N	Y	Y	Y	
SCAR2540	Sri Lankan	F	41	N	N	Y	N	

F, Female; M, male.

**TABLE E4.** *IL36RN* mutation frequencies across patient cohorts\*

<b>Study</b>	<b>Cases with <math>\geq 1</math> <i>IL36RN</i> mutation (%)</b>
Farooq et al, 2012 <sup>E13</sup>	2/14 (14.3%)
Sugiura et al, 2013 <sup>E16</sup>	10/28 (35.7%)
Setta-Kaffetzi et al, 2013 <sup>E2</sup>	13/84 (15.5%)
Körber et al, 2013 <sup>E15</sup>	7/19 (36.8%)
This study	13/56 (23.2%)
Significance of frequency variation	$P = .22$

\*Frequencies were only calculated in data sets that included more than 10 patients.