Letter to the Editor

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.[1] 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.[1]

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).[2] We and others demonstrated that a proportion of GPP cases carry recessive mutations of *IL36RN*, the gene encoding the IL-36 receptor antagonist.[3,4] This anti-inflammatory protein modulates the activity of IL-36 α, β, and γ, 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 cell cultures indicate that IL-36 molecules induce the activation of keratinocytes and antigen-presenting cells, thus propagating skin inflammation in patients with psoriasis.[5]

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) 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); (2) 45 patients received diagnoses from the coauthors of this study,

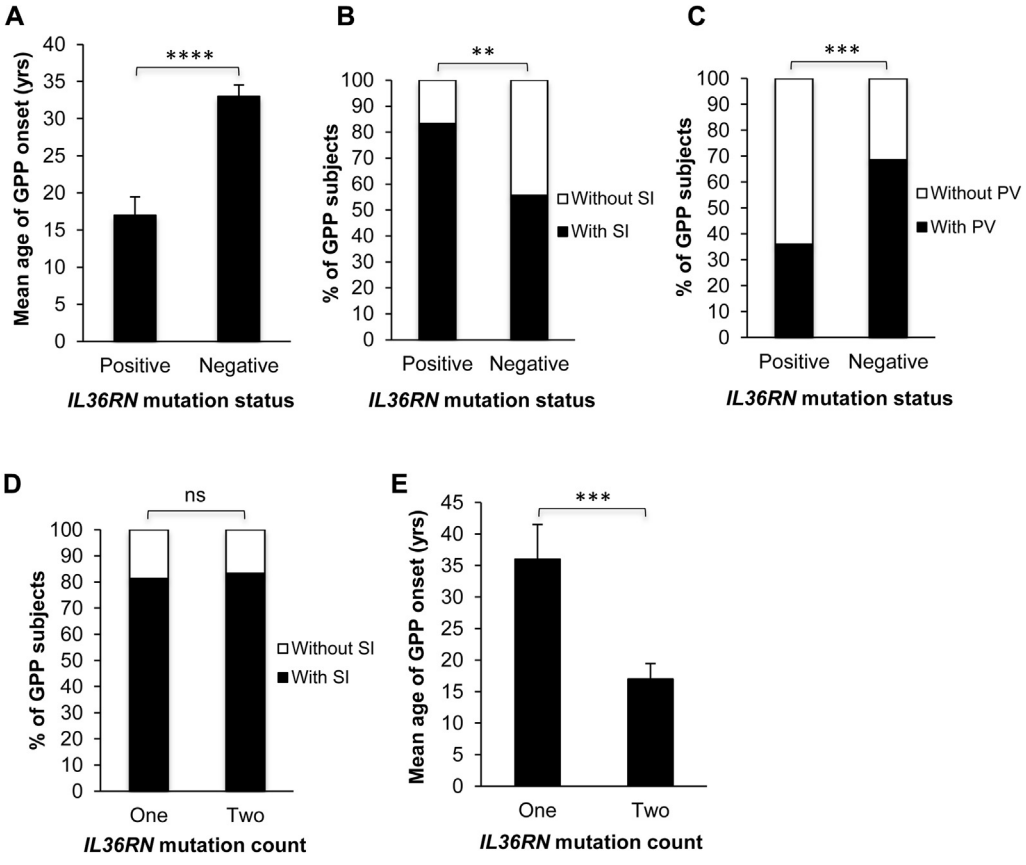

FIG 1. A-C, Subjects with recessive *IL36RN* alleles have earlier disease onset (Fig 1, *A*), more frequently have systemic inflammation (Fig 1, *B*), and less frequently have PV (Fig 1, *C*) compared with *IL36RN*-negative subjects. **D** and **E,** Although the prevalence of systemic inflammation remains 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 × 10^9/L and fever >38°C)[6]. $^{**}P < .01$, $^{***}P < .001$, 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.

according to established criteria[2]; 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°C).[6]

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). We found that *IL36RN*-positive subjects manifested a strikingly more severe clinical phenotype characterized by an earlier age of onset (17 ± 2.4 vs 33 ± 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.[7]

We previously reported 6 patients with GPP bearing single heterozygous *IL36RN* mutations.[8] 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.[2] 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 ± 5.5 vs 17 ± 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), 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.[9,10] Therapeutic agents that specifically target the IL-36 receptor are also being developed.[11] Thus our work is expected to facilitate the identification of patients who might benefit from personalized treatment with IL-1 or IL-36 blockers.

Safia Hussain, BSc[a]
Dorottya M. Berki, BSc[a]
Siew-Eng Choon, MRCP[b]
A. David Burden, MD, FRCP[c]
Michael H. Allen, PhD[a]
Juan I. Arostegui, MD, PhD[d]
Antonio Chaves, MD[e]
Michael Duckworth[a]
Alan D. Irvine, MD[f,g]
Maja Mockenhaupt, MD, PhD[h]
Alexander A. Navarini, MD, PhD[a,i]
Marieke M. B. Seyger, MD, PhD[j]
Pere Soler-Palacin, MD, PhD[k]
Christa Prins, MD[l]
Laurence Valeyrie-Allanore, MD[m]
M. Asuncion Vicente, MD[n]
Richard C. Trembath, FMedSci[o]
Catherine H. Smith, MD, FRCP[a]
Jonathan N. Barker, MD, FRCP[a]*
Francesca Capon, PhD[a]*

From [a]the Division of Genetics and Molecular Medicine, King's College London, London, United Kingdom; [b]the Department of Dermatology, Hospital Sultanah Aminah, Johor Bahru, Malaysia; [c]the Department of Dermatology, University of Glasgow, Glasgow, United Kingdom; [d]the Department of Immunology-CDB, Hospital Clinic,

Barcelona, Spain; [e]the Department of Dermatology, Hospital Infanta Cristina, Badajoz, Spain; [f]Paediatric Dermatology, Our Lady's Children's Hospital, Dublin, Ireland; [g]Clinical Medicine, Trinity College Dublin, Dublin, Ireland; [h]the Department of Dermatology, Dokumentationszentrum Schwerer Hautreaktionen (dZh), Universitäts-Hautklinik, Freiburg, Germany; [i]the Department of Dermatology, Zurich University Hospital, Zurich, Switzerland; [j]the Department of Dermatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; [k]the Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [l]the Dermatology Service, Geneva University Hospital, Geneva, Switzerland; [m]the Department of Dermatology, Henri Mondor Hospital, Paris, France; [n]the Department of Dermatology, Hospital Sant Joan de Deu, Esplugues, Spain; and [o]Queen Mary University of London, Barts and The London School of Medicine and Dentistry, London, United Kingdom. E-mail: francesca.capon@kcl.ac.uk. Or: jonathan.barker@kcl.ac.uk.

*These authors contributed equally to this work.

Supported by the Department of Health via the NIHR BioResource Clinical Research Facility and comprehensive Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. This work was funded by a Medical Research Council Stratified Medicine award (MR/L011808/1; to F.C., C.H.S., and J.N.B.). The exome sequencing of the TwinsUK cohort was funded by Wellcome Trust and European Community's Seventh Framework Programme (FP7/2007-2013) grants. The International Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) Consortium was funded by unrestricted grants from the European Commission (QLRT-2002-01738), GIS-Institut des Maladies Rares and INSERM (4CH09G) in France, and a consortium of pharmaceutical companies (Bayer Vital, Boehringer Ingelheim, Cephalon, GlaxoSmithKline, MSD Sharp and Dohme, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, and Servier). S.H. is supported by the Genetics Society and D.M.B.'s studentship is funded by the Psoriasis Association.

Disclosure of potential conflict of interest: S. Hussain is supported by the Genetics Society. D. Berki has received funding from the Psoriasis Association. J. I. Arostegui's institution has received or has grants pending from Novartis and he has received payment for delivering lectures from Novartis, and Swedish Orphan Biovitrum. L. Valeyrie-Allanore has received compensation for board membership from Jansen, MedImmune, and Boehringer Ingelheim. P. Soler-Palacin has received consultancy fees, fees for supplying expert testimony, payment for the development of educational presentations, and payment for delivering lectures from CSL Behring, and Baxter and has received or has grants pending from CSL Behring and has received compensation for travel and other meeting-related expenses from CSL Behring and Baxter. M. M. B. Seyger's institution receives compensation for board membership from Pfizer, has received or has grants pending from Pfizer, and has received payment for delivering lectures from Pfizer, as well as consultancy fees from Boehringer Ingelheim, Allmiral, and Pfizer and compensation for travel and other meeting-related expenses from Pfizer. M. Mockenhaupt receives royalties from UpToDate. J. N. Barker's institution has received funding from the National Institute for Health Research. F. Capon has grants pending from the British Skin Foundation. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Aksentijevich I, Kastner DL. Genetics of monogenic autoinflammatory diseases: past successes, future challenges. Nat Rev Rheumatol 2011;7:469-78.
2. Griffiths CEM, Barker JN. Psoriasis. In: Burns T, Breathnach S, Cox N, Griffiths CEM, editors. Rook's textbook of dermatology. Chichester: Wiley-Blackwell; 2010. pp. 20.1-20.60.
3. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med 2011;365:620-8.
4. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet 2011;89:432-7.
5. Dietrich D, Gabay C. Inflammation: IL-36 has proinflammatory effects in skin but not in joints. Nat Rev Rheumatol 2014 [Epub ahead of print].
6. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-55.
7. Sugiura K, Takemoto A, Yamaguchi M, Takahashi H, Shoda Y, Mitsuma T, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. J Invest Dermatol 2013;133:2514-21.
8. Setta-Kaffetzi N, Navarini AA, Patel VM, Pullabhatla V, Pink AE, Choon SE, et al. Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phenotypes. J Invest Dermatol 2013;133:1366-9.
9. Rossi-Semerano L, Piram M, Chiaverini C, De Ricaud D, Smahi A, Koné-Paut I. First clinical description of an infant with interleukin-36-receptor antagonist deficiency (DITRA) successfully treated with interleukin-1-receptor antagonist anakinra. Pediatrics 2013;132:e1043-7.
10. Tauber M, Viguier M, Le Gall C, Smahi A, Bachelez H. Is it relevant to use an interleukin-1-inhibiting strategy for the treatment of patients with deficiency of interleukin-36 receptor antagonist? Br J Dermatol 2014;170:1198-9.
11. Wolf J, Ferris LK. Anti-IL-36R antibodies, potentially useful for the treatment of psoriasis: a patent evaluation of WO2013074569. Expert Opin Ther Pat 2014;24:477-9.

http://dx.doi.org/10.1016/j.jaci.2014.09.043

METHODS

Mutation screening

The *IL36RN* coding region was screened by using primers and conditions reported elsewhere.[E1] 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.[E2] 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,[E3] PolyPhen-2,[E4] Provean,[E5] MutPred,[E6] and MutationTaster.[E7] 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.[E8-E10] The meta-analysis of multiple case-control data sets was implemented with Review Manager 5.2.[E11] *P* values of less than .05 were deemed statistically significant.

REFERENCES

E1. Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet 2011;89:432-7.

E2. Setta-Kaffetzi N, Navarini AA, Patel VM, Pullabhatla V, Pink AE, Choon SE, et al. Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phenotypes. J Invest Dermatol 2013;133:1366-9.

E3. Kumar P, Henikoff S, Ng PC. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat Protoc 2009;4:1073-81.

E4. Adzhubei I, Jordan DM, Sunyaev SR. Predicting functional effect of human missense mutations using PolyPhen-2. Curr Protoc Hum Genet 2013;Chapter 7:Unit 7.20.

E5. Choi Y, Sims GE, Murphy S, Miller JR, Chan AP. Predicting the functional effect of amino acid substitutions and indels. PLoS One 2012;7:e46688.

E6. Li B, Krishnan VG, Mort ME, Xin F, Kamati KK, Cooper DN, et al. Automated inference of molecular mechanisms of disease from amino acid substitutions. Bioinformatics 2009;25:2744-50.

E7. Schwarz JM, Rodelsperger C, Schuelke M, Seelow D. MutationTaster evaluates disease-causing potential of sequence alterations. Nat Methods 2010;7:575-6.

E8. Abecasis GR, Auton A, Brooks LD, DePristo MA, Durbin RM, Handsaker RE, et al. An integrated map of genetic variation from 1,092 human genomes. Nature 2012;491:56-65.

E9. Williams FM, Scollen S, Cao D, Memari Y, Hyde CL, Zhang B, et al. Genes contributing to pain sensitivity in the normal population: an exome sequencing study. PLoS Genet 2012;8:e1003095.

E10. Wong LP, Ong RT, Poh WT, Liu X, Chen P, Li R, et al. Deep whole-genome sequencing of 100 southeast Asian Malays. Am J Hum Genet 2013;92:52-66.

E11. Review Manager (RevMan). Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration; 2012.

E12. Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med 2011;365:620-8.

E13. Farooq M, Nakai H, Fujimoto A, Fujikawa H, Matsuyama A, Kariya N, et al. Mutation analysis of the IL36RN gene in 14 Japanese patients with generalized pustular psoriasis. Hum Mutat 2013;34:176-83.

E14. Li M, Lu Z, Cheng R, Li H, Guo Y, Yao Z. IL36RN gene mutations are not associated with sporadic generalized pustular psoriasis in Chinese patients. Br J Dermatol 2013;168:426-60.

E15. Körber A, Mössner R, Renner R, Sticht H, Wilsmann-Theis D, Schulz P, et al. Mutations in IL36RN in patients with generalized pustular psoriasis. J Invest Dermatol 2013;133:2634-7.

E16. Sugiura K, Takemoto A, Yamaguchi M, Takahashi H, Shoda Y, Mitsuma T, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. J Invest Dermatol 2013;133:2514-21.

E17. Kanazawa N, Nakamura T, Mikita N, Furukawa F. Novel IL36RN mutation in a Japanese case of early onset generalized pustular psoriasis. J Dermatol 2013;40:749-51.

E18. Rossi-Semerano L, Piram M, Chiaverini C, De Ricaud D, Smahi A, Koné-Paut I. First clinical description of an infant with interleukin-36-receptor antagonist deficiency successfully treated with anakinra. Pediatrics 2013;132:e1043-7.

E19. Abbas O, Itani S, Ghosn S, Kibbi AG, Fidawi G, Farooq M, et al. Acrodermatitis continua of Hallopeau is a clinical phenotype of DITRA: evidence that it is a variant of pustular psoriasis. Dermatology 2013;226:28-31.

E20. Sugiura K, Oiso N, Iinuma S, Matsuda H, Minami-Hori M, Ishida-Yamamoto A, et al. il36rn mutations underlie impetigo herpetiformis. J Invest Dermatol 2014;9:1-12.

E21. Renert-Yuval Y, Horev L, Babay S, Tams S, Ramot Y, Zlotogorski A, et al. IL36RN mutation causing generalized pustular psoriasis in a Palestinian patient. Int J Dermatol 2014;53:866-8.

E22. Sugiura K, Endo K, Akasaka T, Akiyama M. Successful treatment with infliximab of sibling cases with generalized pustular psoriasis caused by deficiency of interleukin-36 receptor antagonist. J Eur Acad Dermatol Venereol 2014;9:1-2.

E23. Song HS, Yun SJ, Park S, Lee ES. Gene mutation analysis in a Korean patient with early-onset and recalcitrant generalized pustular psoriasis. Ann Dermatol 2014;26:424-5.

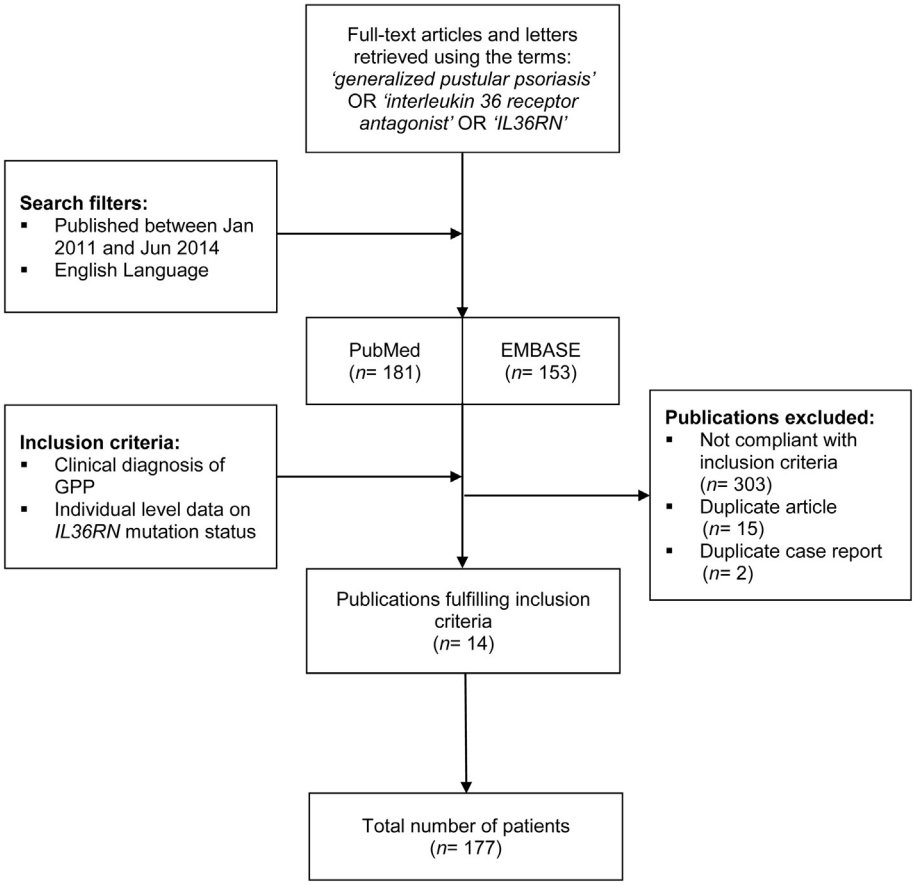

FIG E1. Flow diagram illustrating the criteria underlying the literature search.

TABLE E1. Study cohort summary statistics

	Sex		Ethnicity			*IL36RN* 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)	*IL36RN* mutations*		PV	Fever (>38°C)	Leukocytosis	Systemic inflammation
Marrakchi et al, 2011[E12]	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[E1]	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[E13]	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[E14]	**Patient 3**	**Chinese**	**F**	**8**	**p.Pro76Leu**	**—**	**N**	**Y**	**Y**	**Y**
Setta-Kaffetzi et al, 2013[E2]	**GLA-I**	**British**	**M**	**29**	**p.Ser113Leu**	**—**	**N**	**Y**	**Y**	**Y**
	GLA-II	British	M	26	p.Ser113Leu	p.Ser113Leu	N	Y	Y	Y
	GLA-III	**British**	**M**	**39**	**p.Ser113Leu**	**—**	**N**	**Y**	**Y**	**Y**
	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
	MAL-III	**Malay**	**F**	**9**	**p.Arg10Argfs*1**	**—**	**N**	**Y**	**Y**	**Y**
	MAL-IV	**Malay**	**M**	**42**	**p.Arg10Argfs*1**	**—**	**Y**	**Y**	**Y**	**Y**
	MAL-V	**Malay**	**F**	**12**	**p.Arg10Argfs*1**	**—**	**Y**	**Y**	**N**	**N**
	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
	MAL-IX	**Chinese**	**F**	**40**	**p.Arg10Argfs*1**	**—**	**Y**	**N**	**Y**	**N**
	MAL-X	**Chinese**	**M**	**12**	**p.Arg10Argfs*1**	**—**	**Y**	**N**	**N**	**N**
	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[E15]	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
	P08	**German**	**M**	**55**	**p.Ser113Leu**	**—**	**Y**	**Unknown**	**Unknown**	**Unknown**
Sugiura et al, 2013[E16]	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
	Patient 29	**Japanese**	**M**	**50**	**p.Arg10X**	**—**	**Y**	**Y**	**Y**	**Y**
Kanazawa et al, 2013[E17]	—	Japanese	M	3	p.Arg10X	p.Thr123Met	Y	Y	Unknown	Unknown

(Continued)

TABLE E2. (*Continued*)

Study	Study no.	Origin	Sex	Age of onset (y)	*IL36RN* mutations*		PV	Fever (>38°C)	Leukocytosis	Systemic inflammation
Rossi-Semerano et al, 2013[E18]	—	Tunisian	M	0 (2 wk)	p.Leu27Pro	p.Leu27Pro	Unknown	N	Y	N
Abbas et al, 2013[E19]	—	Lebanese	F	21	p.Ser113Leu	p.Ser113Leu	Unknown	Y	Y	Y
Sugiura et al, 2014[E20]	Case 1	Japanese	F	23	p.Arg10Argfs*1	p.Arg10Argfs*1	Unknown	Y	N	N
	Case 2	**Japanese**	**F**	**8**	**p.Arg10X**	**—**	**Unknown**	**Y**	**Y**	**Y**
Renert-Yuval et al, 2014[E21]	—	Palestinian	M	0 (1 mo)	p.Arg10X	p.Arg10X	N	Y	Y	Y
Sugiura et al, 2014[E22]	Patient 3	Japanese	M	6	p.Arg10Argfs*1	p.Arg10Argfs*1	N	Y	Y	Y
	Patient 4	**Japanese**	**F**	**53**	**p.Arg10Argfs*1**	**—**	**Y**	**Unknown**	**Unknown**	**Unknown**
Song et al, 2014[E23]	**—**	**Korean**	**F**	**4**	**p.Arg10Argfs*1**	**—**	**Unknown**	**Y**	**Y**	**Y**
This study	—	Swiss	M	40	p.Ser113Leu	p.Ser113Leu	N	Y	Y	Y
	78GPP1	**Malay**	**F**	**57**	**p.Arg10Argfs*1**	**—**	**Y**	**Y**	**Y**	**Y**
	82GPP1	Malay	F	19	p.Arg10Argfs*1	p.Arg10Argfs*1	Y	Y	N	N
	89GPP1	**Malay**	**F**	**40**	**p.Arg10Argfs*1**	**—**	**Y**	**Y**	**Y**	**Y**
	96GPP1	Chinese	F	7	p.Arg10Argfs*1	p.Arg10Argfs*1	Y	Y	Unknown	Unknown
	101GPP1	**Chinese**	**F**	**30**	**p.Arg10Argfs*1**	**—**	**N**	**Y**	**Y**	**Y**
	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
	SCAR1690	**German**	**F**	**68**	**p.Ser113Leu**	**—**	**Unknown**	**Y**	**Y**	**Y**
	SCAR2074	German	F	53	p.Ser113Leu	p.Ser113Leu	Unknown	N	Y	N
	SCAR2548	**Polish**	**M**	**84**	**p.Ser113Leu**	**—**	**N**	**Y**	**Y**	**Y**
	—	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 mo.	Origin	Sex	Age of onset (y)	Psoriasis vulgaris	Fever (>38°C)	Leukocytosis	Systemic inflammation
Onoufriadis et al, 2011[E1]	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[E13]	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[E14]	Patient 1	Chinese	M	16	N	N	Unknown	N
	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[E2]	T009361	British	F	45	N	Unknown	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
	38GPP1	Malay	M	27	Y	Y	Y	Y
	39GPP1	Indian	F	15	Y	N	N	N

(Continued)

TABLE E3. (*Continued*)

Study	Study mo.	Origin	Sex	Age of onset (y)	Psoriasis vulgaris	Fever (>38°C)	Leukocytosis	Systemic inflammation
	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[E15]	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[E16]	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
	Patient 30	Japanese	M	24	Y	Y	Y	Y
	Patient 31	Japanese	M	38	Y	Y	Y	Y

(Continued)

TABLE E3. (*Continued*)

Study	Study mo.	Origin	Sex	Age of onset (y)	Psoriasis vulgaris	Fever (>38°C)	Leukocytosis	Systemic inflammation
This study	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*

Study	Cases with ≥1 *IL36RN* mutation (%)
Farooq et al, 2012[E13]	2/14 (14.3%)
Sugiura et al, 2013[E16]	10/28 (35.7%)
Setta-Kaffetzi et al, 2013[E2]	13/84 (15.5%)
Körber et al, 2013[E15]	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.