The IFIH1/MDA5 rs1990760 Gene Variant (946Thr) Differentiates Early Versus Late-Onset Skin Disease and Increased the Risk of Arthritis in a Spanish Cohort of Psoriatic Disease

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Article

The *IFIH1/MDA5* rs1990760 Gene Variant (946Thr) Differentiates Early versus Late-Onset Skin Disease and Increased the Risk of Arthritis in a Spanish Cohort of Psoriatic Disease

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Abstract: The melanoma differentiation-associated protein 5 (MDA5; encoded by the *IFIH1* gene) mediates the activation of the interferon pathway in response to viral infection. This protein is also upregulated in autoimmune diseases and psoriasis skin lesions. IFIH1 gene variants that increased the MDA5 activity have been associated with increased risk for immune mediated diseases, including psoriasis. Our aim was to determine the association between three *IFIH1* variants (rs35337543, intron8 +1G>C; rs35744605, Glu627Stop; and rs1990760, Ala946Thr) and the main clinical findings in a cohort of Spanish patients with psoriatic disease (N=572; 77% early-onset). Early-onset psoriasis (EOPs) had a significant higher frequency of severe disease and Cw6+. Carriers of the 946^{Thr} variant were more common in EOPs ($p<0.001$), and the effect was more pronounced among Cw6-negatives. This variant was also associated with an increased risk of psoriatic arthritis (PsA) independently of other factors (OR=1.62, 95%CI=1.11-2.37). The rs3533754 and rs35744605 have been reported as risk factors for viral infection and protective for autoimmune diseases, but we did not find significant differences between the two onset age or PsA groups. However, due to the reduced frequency of the two variants (<0.02) the size of our cohort was too low to conclude a significant effect. In conclusion, the common *IFIH1* rs1990760 T allele that has been linked to increased gene expression was significantly more frequent in EOPs patients. This variant was also an independent risk factor for PsA in our cohort. This risk allele was in linkage disequilibrium with other variants previously associated with the risk of psoriasis and PsA. Our study reinforces the widely reported role of *IFIH1* gene variants on psoriatic disease and other immune mediated diseases.

Keywords: psoriasis; psoriatic arthritis; *IFIH1; MDA5*; polymorphism; genetic association

1. Introduction

Psoriasis is a chronic inflammatory skin disease in which acquired and inherited risk factors contribute to define the individual's risk [1]. Both rare and common gene variants have been associated with the risk of developing psoriasis as well with the onset age, disease severity, or the clinical phenotype, including the risk for psoriatic arthritis (PsA) [2,3]. In addition to the HLA-Cw6*0602 allele, other genes from immunological pathways have been linked to the risk of developing psoriasis [4–9].

The role of innate immunity genes in psoriatic disease is well stablished, including components of the interferon and anti-viral response pathways such as the interferon-induced helicase C domain-containing protein 1 (IFIH1), also known as melanoma differentiation-associated protein 5 (MDA5; encoded by the *IFIH1* gene). IFIH1/MDA5 contains two N-terminal CARD (caspase activation recruitment) domains followed by a helicase ATP-binding domain and a C-terminal RIG-1 like

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domain. Upon recognition of double stranded RNAs (dsRNAs) by the helicase domains, MDA5 undergoes conformational changes that promote assembly into filaments and association of the CARD-domain with anti-viral proteins, leading to the transcription of early innate type-I interferon response genes [10–15]. Type-I interferons and their downstream products are also increased in psoriatic lesions [16–18].

Functional variants in the *IFIH1* that decrease the protein expression and MDA5 activity have been associated with increased risk of viral infections and the extent of viral disease, including COVID-19 (caused by SARS-CoV-2) [19–23]. While low-activity variants would predispose to infection, *IFIH1* variants that result in a MDA5 gain of function might result in the over activation of inflammatory pathways and increased risk of inflammatory and autoimmune diseases [24–26]. Several studies have investigated IFIH1/MDA5 in psoriasis. Among others, cytokines such as TNFα and IFNγ can increase the expression of MDA5 in keratinocytes, and MDA5 is increased in psoriatic skin lesions [27–29]. Moreover, improvement of the skin lesions after treatment with ultraviolet would be correlated with the reduction of MDA5 levels [29]. In agreement with this functional role, *IFIH1* gene variants have been associated with the risk of developing psoriatic disease [30,31].

Several *IFIH1* common variants have been associated with the risk of immune mediated diseases, including the single nucleotide polymorphism (SNPs) rs1990760 C>T. This results in a missense change (p.Ala946Thr) that would affect the ATPase activity due to a conformational protein change and has been associated with type 1 diabetes and other autoimmune diseases [32–40]. This SNP could be also linked to *IFIH1* expression, since the autoimmune risk allele T (946^{Thr}) was associated with increased *IFIH1* transcription in interferon-β stimulated peripheral blood mononuclear cells [39]. Human peripheral blood mononuclear cells with the rs1990760 T allele expressed higher basal type I interferons, while $IFIH1^{946T}$ knock-in mice displayed enhanced basal expression of type I interferons and survived a lethal viral challenge, but also exhibited increased risk for autoimmune traits [34].

In addition to common functional polymorphisms, *IFIH1* has several rare deleterious variants. SNP rs35744605 (c.1879 G>T) results in a premature stop-codon (p.Glu627*) with the loss of the 399 C-terminal amino acids of MDA5. This variant would be in approximately 1% of the Europeans and was associated with increased risk for recurrent viral infection but decreased risk of type 1 diabetes (T1D) [20,39,40]. SNP rs35337543 (c.1641 +1G>C) is a putative splicing change that would skips exon 8 of the mRNA, removing 39 amino acids of the MDA5 helicase domain [20,41]. This variant would be a risk factor for recurrent viral infection while protective for T1D [20,42,43]. These rare T1D-protective alleles were linked to reduced expression of *IFIH1* among heterozygous individuals [40].

The association between *IFIH1* variants and psoriasis has been supported by some authors [44]. Among others, rs1990760 was associated with psoriasis by Genome Wide Association Studies (GWAS) with OR=1.22 [45,46]. Other studies reported significant association with SNP rs17715343 and rs17716942, in strong linkage disequilibrium with rs1990760 [47,48].

Our aim was to investigate the association of the *IFIH1* SNPs rs1990760, rs35744605, and rs35337543 and the risk of developing psoriasis, and whether these variants have a significant effect on onset age, disease severity and the risk of PsA.

2. Methods

2.1. Study population and data collection.

The study was approved by the Ethical Committee of the Principality of Asturias and involved a total of 572 psoriatic disease patients aged ≥18 years. They were of Caucasian ancestry and from the region of Asturias (Northern Spain, total population 1 million). The patient´s cohort was registered as a Biobank Collection by the Spanish Instituto de Salud Carlos III (reference C.0003441).

The patients had been diagnosed with chronic plaque psoriasis and recruited through the Departments of Dermatology and Rheumatology of Hospital Universitario Central de Asturias (HUCA) and Hospital Universitario Alvarez Buylla (HUAB) between January 2007 and August 2017.

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The main demographic and clinical characteristics of the patients are summarized in Table 1. Psoriasis was diagnosed based on clinical findings, and disease severity was defined according to the Psoriasis Area and Severity Index (PASI; severe, PASI ≥10). All the patients were genotyped for the *HLA-Cw6* (PSORS1) [49]. Early-onset psoriasis (EOPs) was defined as a disease beginning at age ≤40 years. The presence of arthritis was assessed by a rheumatologist according to CASPAR criteria. Patients who had not developed arthritis 10 or more years after psoriasis onset were categorized as having pure cutaneous psoriasis (PCP). This is because 10 years is the average time between the onset of skin lesions and the onset of arthritis in most studies, making it unlikely that these patients with PCP would develop arthritis over time. This form of categorization has been shown to be reliable in other studies [50].

Table 1. Main disease characteristics of the early (≤40 years) vs late onset disease. The odds ratio (OR) and confidence intervals (95%CI) corresponded to the multivariate analysis (R-linear generalized model).

	Early onset N=440	**Late onset N=132**	**p-value univariate**	**OR (95%CI) Multivariate**
Male	232 (53%)	77 (58%)	0.26	
Female	208 (47%)	55 (42%)		1.24 (0.81-1.90)
Onset Age range	18-40	41-78		
Median PASI (range)	11 (1-75)	6.1 (4.1-7.2)		
Severe (PASI>10)	248 (56%)	46 (35%)	<0.001	2.35 (1.52-3.66)
Arthritis yes	139 (32%)	32 (24%)	0.11	1.22 (0.76-2.01)
Cw6 positive	211 (48%)	30 (23%)	<0.001	3.25 (2.05-5.29)
rs1990760 C>T * (Ala946Thr)				
TT	179 (41%)	40 (30%)		
CT	220 (50%)	56 (42%)	<0.001	4.07 (2.37-7.04)
CC	41 (9%)	36 (27%)		
ALLELE T (**946Thr**) Eur: T=0.60-0.64	0.66	0.52		
rs35337543 int8 +1G>C				
GG	430 (98%)	128 (97%)	0.62	1.12 (0.29-3.65)
GC	10 (2%)	4 (3%)		
ALLELE C Eur: C=0.02	0.01	0.02		
rs35744605 G>T (Glu627Stop)				
GG	432 (98%)	129 (98%)	0.74	1.11 (0.23.4.10)
GT	8 (2%)	3 (2%)		
ALLELE T Eur: T=0.01	0.01	0.01		

*TT+CT vs CC.

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2.2. IFIH1 variants genotyping.

The DNA was obtained from whole blood leukocytes and all the individuals were genotyped for the *IFIH1* polymorphisms with real time PCR Taqman assays (Fisher scientific): rs35337543, assay id C_25985625_10; rs35744605, assay id C_25982959_10; rs1990760, C_2780299_30. The quality of the genotyping method was determined by sequencing PCR fragments with different genotypes.

2.3. Statistical analysis.

Patient's data were recorded in an Excel file (Microsoft office). The statistical analysis was performed with the R-software (http://www.r-project.org). Allele and genotype frequencies between the groups were compared with the Chi^2 and Fisher's exact tests. A $p< 0.05$ value was considered as statistically significant.

3. Results

A total of 440 patients had an onset age ≤40 years (EOPs) compared to 132 cases >40 years (Table 1). Severe disease (PASI ≥10) and the presence of Cw6 was significantly more frequent in EOPs patients (p<0.001). Arthritis was also more common in this group (32% vs 24%) without significant difference with patients >40 years. In reference to the *IFIH1* variants, rs1990760 T (946^{Thr}) that has been linked to increased gene expression and interferon response was significantly more frequent in the ≤40 years group (0.66 vs 0.52), with higher frequencies for the CC and CT genotypes (Table 1). Thus, this allele was associated with a significantly increased risk for EOPs (CC+TC vs CC, p<0.001) with an OR=3.65 (95%IC=2.21-6.02). Allele frequencies for the rs1990760 SNP were T=0.38 and C=0.62 in the whole cohort, close to the reported frequencies among Europeans (T=0.36-0.40).

The two rare rs35744605 T (627^{Stop}) and rs35337543 C (splicing variant) were found in our patients, all heterozygotes, without significant difference between the two age groups. There were no homozygotes for the two rare alleles, and the reduced sample size did not allow to determine the putative protective effect of the two rare homozygous genotypes (Table 1).

The multiple logistic regression analysis showed that severe psoriasis, Cw6 positivity, and carrying the rs1990760 T allele were independent associated factors for EOPs (Table 1). Psoriasis has been associated with the presence of the Cw6 variant, that would distinguish early versus late-onset disease. In agreement with this, a total of 48% and 23% had an onset age ≤40 and >40 years, respectively (p<0.001). We determined the distribution of the onset-age according to the Cw6 + rs1990760 status. Among Cw6+ there were higher frequencies of rs1990760 TT among EOPs (45% vs 27%, p=0.06), while among Cw6- the TT and TC were increased among EOPs patients (93% vs 72%, p<0.001) (Figure 1). This suggested that the high expression 946^{Thr} might increase disease risk more pronouncedly among Cw6 negative patients than among Cw6+ ones.

We also determined the association between the *IFIH1* variants and PsA (Table 2). The presence of arthritis was significantly associated with a severe psoriasis, with a trend toward increased risk among early-onset patients. We found a significantly increased frequency of rs1990760 TT (946^{Thr} homozygotes) in the arthritis group (47% vs 35%, p=0.006). There were no significant differences between the rs35744605 T and rs35337543 C variants and PsA, although the number of the rare allele carriers was too low to reach a minimum statistical power (Table 2). We performed multiple logistic regression analyses and the presence of PsA was significantly associated with a severe PASI (OR=2.14, 95%CI=1.46-3.16), female sex (OR=1.63, 1.12-2.38), and the rs1990760 TT genotype (OR=1.62, 1.11-2.37), while the Cw6 positivity was protective (OR=0.65, 0.44-0.95) and there was a trend toward increased risk for patients with EOPs (OR=1.29, 0.81-2.09).

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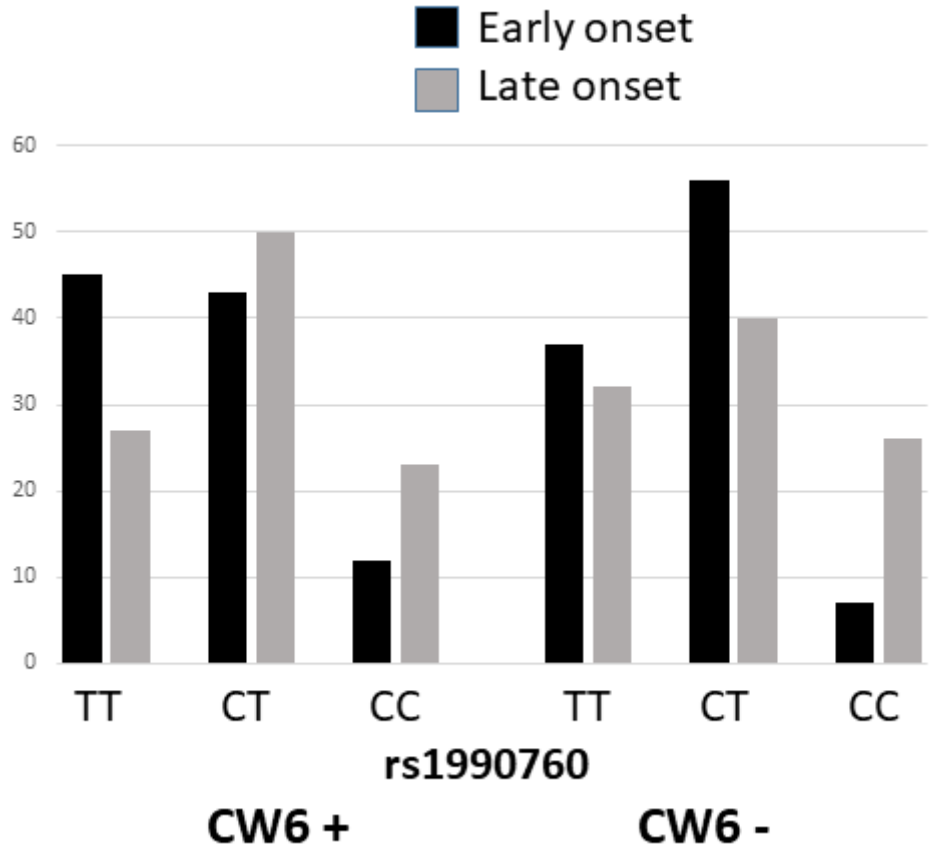

Figure 1. Frequencies of the rs1990760 C/T genotypes in the early and late-onset psoriasis according to the presence of Cw6. Among the Cw6 positive the TT was more frequent in the EOPs (45% vs 27%; p=0.06). Among the Cw6 negative the TT+TC were significantly more common in the EOPs (93% vs 72%; p<0.001).

Table 2. Main characteristics of the patients with/without arthritis. The odds ratio (OR) and confidence intervals (95%CI) corresponded to the multivariate analysis (R-linear generalized model).

	Arthritis yes 171	**Arthritis no 401**	**p-value**	**OR (95%CI) Multivariate**
Male	81	228		
Female	90 (52%)	173 (43%)	0.04	1.63 (1.12-2.38)
Early onset psoriasis	139 (81%)	301 (75%)	0.11	1.29 (0.81-2.09)
Severe (PASI≥10)	110 (64%)	184 (46%)	<0.001	2.14 (1.46-3.16)
Cw6 positive	65 (38%)	176 (44%)	0.19	0.65 (0.44-0.95)
rs1990760 C>T * (Ala946Thr)				
TT	80 (47%)	139 (35%)		
CT	73 (43%)	203 (51%)	0.006	1.62 (1.11-2.37)
CC	18 (11%)	59 (15%)		
Allele C	0.32	0.40		
rs35337543				

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int8 +1G>C				
GG	169 (99%)	389 (97%)	0.20	3.04 (0.77-20.36)
GC	2 (1%)	12 (3%)		
rs35744605 G>T (**Glu627Stop**)				
GG	168 (98%)	393 (98%)	0.85	1.23 (0.32-6.04)
GT	3 (2%)	8 (2%)		

*TT vs CC+CT.

4. Discussion

The population genetics of the functional *IFIH1* variants would be shaped by their effect on the interferon response pathways. Accordingly, variants associated with higher expression/function might be associated with increased protection against viral infection [51–54]. Recently, *IFIH1* variants have been also associated with increased risk for SARS-CoV-2 severe disease (COVID-19) [23,55–57]. In opposition to its antiviral protective effect these higher expression variants might also increase the risk for autoimmune diseases [32–40,58]. *IFIH1* encodes the MDA5 protein, a RIG-I-like receptor dsRNA helicase enzyme which activation induces the transcription of type 1 interferon genes. The type 1 IFN pathway has been implicated in the pathogenesis of psoriatic disease. Thus, type 1 IFN pathway genes were found upregulated in psoriatic skin lesions [17,59]. In mice, the type 1 IFN pathway would play an important role in the T cell-mediated skin inflammation, and mice treated with IFNα or IFNβ neutralizing antibodies showed an attenuated Th17 mediated skin inflammation [60,61].

Our main finding was the significant association of the rs1990760 T (946^{Thr}) and EOPs. Interestingly, in agreement with our results, the alleles associated with increased risk of psoriasis were also associated with younger age of psoriasis onset by other authors [62]. Differences in the genetic association between early and late onset disease have been described for other immune pathway polymorphisms [63]. The association between psoriasis and *IFIH1* variants, either isolated or interacting with other gene variants, has been previously reported [64]. The risk alleles of these variants were in strong linkage disequilibrium (Figure 2). Among others, the rare rs35667974 (p.Ile923Val) was found to be protective for PsA [30,65]. The risk rs35667974 T allele was in strong linkage disequilibrium with the risk rs1990760 T allele. Another *IFIH1* SNP previously associated with psoriasis is rs984971 A/G, with the risk A allele defining haplotype with rs1990760 T [66]. A study in Spanish patients found a significant increased risk for the rs17716942 T allele carriers, with a more pronounced effect for PsA (OR=1.36) [67]. Notably, the T-risk allele is in strong linkage disequilibrium with rs1990760 T.

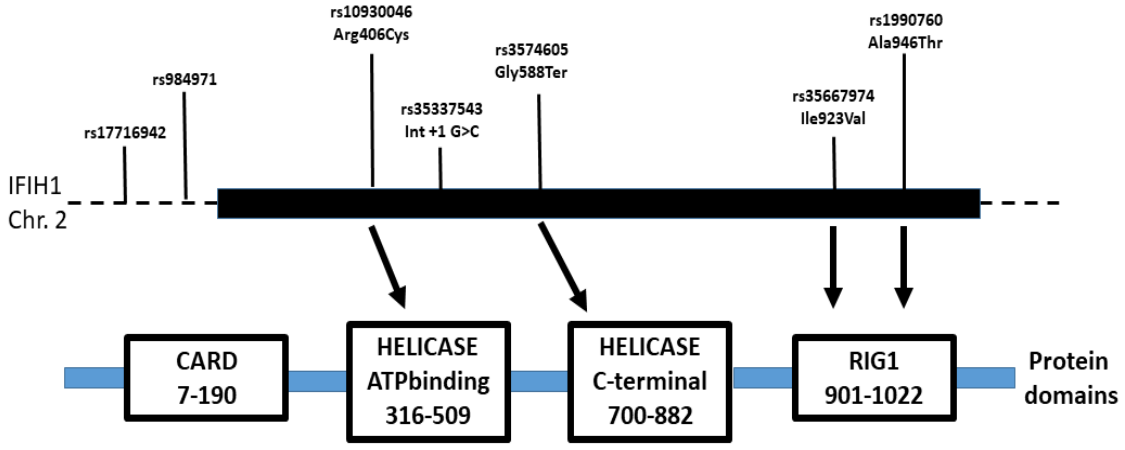

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Figure 2. Map of the *IFIH1* gene indicating the position of the polymorphisms determined in this study and others that were associated with psoriasis and PsA by others. The solid bar indicates the gene, exons plus introns. The location of these variants relative to the MDA5 protein domains is also indicated. The rare rs35337543 C causes skipping of exon 8 (IFIH1-Δ8) removing 39 amino acids of the helicase 1 and the linker part between helicase 1 and helicase 2 domains. The rare 588^{Ter} allele would result in a premature stop codon and a truncated mutant protein lacking the C-terminal RNA-helicase domain.

Although highly conserved among vertebrates the rs1990760 missense change was predicted not to affect the protein function by Shigemoto et al. These authors determined the functional effect of several *IFIH1* variants and found that the Ala946Thr influences neither dsRNA binding nor IFN gene activation [68]. In contrast, the Ile923Val exhibited loss of function without affecting the dsRNA binding activity, a fact that suggested a novel role for this residue in the IFN-signaling. The lack of functional effect for rs1990760 would reinforce the hypothesis that linkage disequilibrium with other *IFIH1* variants might explain the reported association with psoriasis and autoimmune diseases. In contrast, Gorman et al. provided strong evidence of a direct functional effect for the Ala946Thr variant, since peripheral blood mononuclear cells with the risk rs1990760 T allele expressed higher basal IFN-1, and $IFIH1^{946T}$ knock-in mice displayed enhanced basal expression of type I interferons and increased risk for autoimmune traits such as type 1 diabetes and systemic lupus [34].

We did not find significant differences between the two psoriasis age groups for the rare rs35744605 and rs35337543 polymorphisms. The two were likely pathogenic variants causing a truncating protein and an alternative transcript, and were previously associated with increased risk for recurrent viral infections [20]. The rare alleles at the two variants could be also protective against autoimmune diseases [42]. The rare rs35337543 C allele causes skipping of exon 8 (IFIH1-Δ8) without frameshifting, but removes 39 amino acids of the helicase 1 and the linker part between helicase 1 and helicase 2 domains [20]. Cells transfected with IFIH1-Δ8 plasmids showed an attenuated IFN-β induction compared to IFIH1-wt transfected cells, and cotransfection of IFIH1-wt with the mutant isoform showed interference with IFN-β production [20]. Moreover, the ATPase activity after dsRNA stimulation was undetectable in cells transfected with the mutant compared to IFIH1-wt isoform. The deleterious effect of the IFIH1-Δ8 and other mutations might be explained by a reduction in the protein stability and interference with the wild-type protein [20]. The rare rs35744605 allele results in a premature stop codon and a truncated protein lacking the C-terminal RNA-helicase domain. The functional effect of this variant was measured in peripheral blood monocytes transfected with compounds that mimic viral dsRNA, and cells from wild-type individuals showed increased IFN-β secretion compared to cells from mutation carriers [39]. The lack of association between these variants and Psor onset-age might be explained by the reduced size of our study cohort. The rare rs35744605 and rs35337543 alleles showed a frequency of 0.01 in the whole patient cohort, close to the one reported among Caucasians (0.01-0.02). Due to the very low frequencies, to conclude a protective effect on the risk for psoriatic disease would require larger cohort of patients.

We also confirmed the widely reported increased frequency of Cw6 among EOPs compared to late-onset cases. Interestingly, the effect was more pronounced among Cw6 negative patients with rs1990760 TT+TC that was significantly increased among early-onset patients.

The rs1990760 TT genotype was significantly increased also among patients who developed PsA. However, because the arthritis status was stablished taking into account the 10 years period after the initial psoriasis diagnosis, we cannot exclude that this association with PsA might be biased by not including patients who would develop PsA later. Nonetheless, the ten- year period is the average time between the onset of skin lesions and joint complaints, making very unlikely that most of PCP patients will develop arthritis [50]. Moreover, the association between IFIH1 variants and PsA has been previously reported. For instance, a large-scale study by Stuart et al described a significant association between the rs1990760 T allele and psoriatic disease with higher odds ratio for PsA (OR=1.585; $p=1x10^{-14}$) than for cutaneous disease (OR=1.425; $p=7.6x10^{-10}$) [45]. Julia et al. also found a

significant association between PsA and rs17716942, a variant in strong linkage disequilibrium with rs1990760 [67].

Our findings highlight the relevance of IFIH1/MDA5 in the risk of developing psoriatic disease with a significant increased risk for EOPs and PsA among carriers of the high expression genotypes. This association was supported by studies that showed increased expression of interferon system proteins, including IFIH1, in skin lesions from psoriasis patients compared with healthy skin [18,45]. These findings point to IFIH1/MDA5 as a pharmacological target whose inhibition could be effective in treating psoriatic disease.

Our study has several limitations. First, it was based on a limited number of patients and from a single Spanish region and would thus require replication in larger cohorts from different populations. The rs35744605 and rs35337543 are predicted to be likely pathogenic by introducing a premature stop codon and an alternative mRNA. The two deleterious alleles were very rare in our population, and no homozygous was found in our cohort. Moreover, based on the observed allele frequencies homozygotes would have a frequency lower than 1 per 1,000 among Europeans. This makes difficult to stablish a significant conclusion about the increased risk for psoriasis among wild-type homozygotes, that would require much larger cohorts.

In conclusion, we found a significant association between a common *IFIH1* variant that has been linked to increased gene expression and EOPs. The effect on early-onset disease risk was more pronounced among Cw6-negative patients. The common rs1990760 T allele was also an independent risk factor for PsA in our cohort. This risk allele was in linkage disequilibrium with other variants previously associated with the risk of psoriasis and PsA as well. Our study reinforces the widely reported role of *IFIH1* gene variants on psoriatic disease and other immune mediated diseases.

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Data Availability Statement: The materials and raw data described in the manuscript will be freely available to any researcher without breaching participant´s confidentiality. To facilitate the revision of the results by other researchers, a file with the patient´s data is available as an excel file upon request to the corresponding author.

Conflicts of Interest: None of the authors have competing interests related to this work.

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