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A large candidate-gene association study suggests genetic variants at IRF5 and PRDM1 to be associated with aggressive periodontitis

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Abstract

Aim: Epidemiological and clinical studies indicated a relationship of periodontitis with rheumatoid arthritis (RA). We aimed to identify shared genetic susceptibility loci of RA and periodontitis.

Materials and Methods: Forty-seven risk genes of genome-wide significance of RA and SLE were genotyped in a German case–control sample of aggressive periodontitis (AgP), using Immunochip genotyping arrays (Illumina, 600 cases, 1440 controls) and Affymetrix 500 K Genotyping Arrays (280 cases and 983 controls). Significant associations were replicated in 168 Dutch AgP cases and 679 controls and adjusted for the confounders smoking and sex.

Results: Variants at *IRF5* and *PRDM1* showed association with AgP. Upon covariate adjustment for smoking and sex, the most strongly associated variant at *IRF5* was the rare variant rs62481981 ($p_{\text{pooled}} = 0.0012$, odds ratio [OR] = 3.1, 95% confidence interval [95% CI] = 1.6–6.1; 801 cases, 1476 controls).Within *PRDM1* it was rs6923419 ($p_{\text{pooled}} = 0.004$, OR = 0.7, 95% CI = 0.6–0.9; 833 cases, 1440 controls). The associations lost significance after correction for multiple testing in the replication. Both genes are implicated in beta-interferon signalling and are also genome-wide associated with SLE and inflammatory bowel disease.

Conclusion: The study gives no definite evidence for a pathogenic genetic link of periodontitis and RA but suggests *IRF5* and *PRDM1* as shared susceptibility factors.

Conflict of interest and source of funding

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Epidemiological and clinical studies observed that periodontitis (PD) is present and frequently severe in rheumatoid arthritis (RA) patients (Mercado et al. 2003, Detert et al. 2010, Scher et al. 2012), independent of the confounder smoking (Potikuri et al. 2012). Although a causal relationship between both diseases has not been proved (Linden et al. 2013), it was reported that the presence of PD was associated with increased joint damage (Mikuls et al. 2014). Citrullinated antigens drive adaptive immune responses that are nearly exclusive to RA, and the oral pathogen *P. gingivalis* is the only known pathogen that is able to catalyse citrullination. Thus, infection with the oral pathogen *P. gingivalis* may influence disease-specific autoantibody responses. Accordingly, a significant relationship between PD and established anti-citrullinated protein antibodies (ACPA) -positive RA, independent of smoking and supragingival plaque levels, was demonstrated (Mikuls et al. 2014).

A relationship of PD to other autoimmune disease has not been well established. PD shares some pathogenetic similarities with systemic lupus erythrematosus (SLE) (Kobayashi et al. 2003) and some studies described a greater propensity of individuals with SLE to also have PD (Rhodus & Johnson 1990, Novo et al. 1999), but this is not unequivocally observed (Mutlu et al. 1993). Notably, recent results from genome-wide associations studies (GWAS) showed that RA and SLE share several common genetic risk factors (Cotsapas et al. 2011, Ramos et al. 2011), implying shared molecular mechanisms that may underlie the observed clustering of these autoimmune diseases.

We hypothesized that genetic risk loci of RA may also be shared by PD and systematically analysed all 45 non-HLA rheumatoid arthritis loci, which were known at the time of the design of the study. (Eyre et al. 2012) and additionally all then known 30 SLE risk loci (Guerra et al. 2012). We focused on patients of aggressive periodontitis (AgP) because this phenotype allows a better control of confounding effects such as age and accumulating life-style factors and due to the strong severity and early onset, it is assumed that genetic factors play a prominent role in disease susceptibility.

Material and Methods

Study population

Cases and controls of this study consisted of unrelated subjects and were recruited across Germany and the Netherlands between 2002 and 2010. The AgP case–control sample, which was genotyped by the Immunochip was described before (Schaefer et al. 2010). In brief, inclusion criteria for all AgP cases ($N = 600$) were of age ≤ 35 with parents and grandparents born in Germany and having ≥ 2 teeth with at least 30% alveolar bone loss. The controls were 1441 population representative individuals from the region of Kiel, Germany. The Dutch AgP case–control sample was also described before (Schaefer et al. 2010, 2013). AgP cases ($N = 164$) had ≥ 2 teeth with $\geq 50\%$ alveolar bone loss and were ≤ 35 years of age. Six hundred and seventy-nine ethnically matched Dutch controls ($N = 679$) were blood donors collected at the University Medical Center Groningen, NL. For these controls, no data on smoking was available. Three hundred and sixty-eight Dutch blood donors together with a second sample of 189 periodontitis-free blood donors, both collected at the bloodbank Sanquin, Amsterdam, NL were genotyped for covariate adjustment. For these, data on smoking and gender were available.

Analysis of candidate genes (Immunochip)

All candidate genes were genotyped in 600 German AgP cases and 1441 German controls, using the Immunochip (Illumina, San Diego, USA), a custom made Illumina Infinium genotyping array, designed to perform deep replication and finemapping of established GWAS loci from major inflammatory and autoimmune diseases, including RA and SLE.(Cortes & Brown 2011) The array contains about 3000 single-genetic polymorphisms (SNPs) for each disease, which were selected from available GWAS data for deep replication in other disease samples to allow the identification of pleiotropic genes, which are associated with more than one of those diseases for which the chip was designed. For finemapping, the chip contains all known SNPs of the dbSNP database (Bhagwat 2010), from the 1000 Genomes project (February 2010 release) (Abecasis et al. 2010). To further improve genotype coverage, seven RA loci (*ARID5B, CD5, GATA3, IKZF3, POU3F1, RCAN1*, and *RUNX1*) were additionally analysed using the Affymetrix 500K Array set. The following genes were finemapped:

RA ($N = 36$): *AFF3, ANKRD55, ARID5B, CCL21, CCR6, CD2, CD28, CD40, CD5, CTLA4,*

DDX6, DNASE1L3, FCGR2A GATA3, GIN1, IKZF3, IL2-IL21, IL2RA, IL2RB, IL6R, KIF5A, MMEL1, PADI4, POU3F1, PRKCQ, PTPRC, RASGRP1, RBPJ, RCAN1, REL, RUNX1, SPR
ED2, TAGAP, TLE3, TRAF1, TRAF6.
SLE (N = 19): *BANK1, CD44, ETS1, HLA-DRB1, IFIH1, IKZF1, IRF7, ITGAM, JAZF1, LRRC18-WDFY4, LYN, NCF2, RasGRP, SLC15A4, TNFSF4, TNIP1, UBE2L3, UHRF1BP1, XKR6*.
RA and SLE (N = 9): *BLK, ETS1, IRF5, IRF8, PRDM1, PTPN22, PXK, STAT4, TNFA IP3, TYK2*.

Genotyping

Immunochips were genotyped with the Infinium BeadChips Scanner iScan (Illumina, San Diego, USA) as previously described (Schaefer et al. 2013). Genotype data were automatically called using the GenomeStudio Data analysis software package (Illumina, San Diego, USA). Affymetrix 500 K genotyping arrays were analysed as described before (Schaefer et al. 2010). GWAS genotype data were automatically called by the BRLMM algorithm (Affymetrix, High Wycombe, UK). All SNPs with a minor allele frequency (MAF) ≥5% were included.

The SNPs rs6923419 (*PRDM1*) and rs62481981 (*IRF5*) were genotyped on 384-well plates on the TaqMan genotyping system (Applied Biosystems, Foster City, USA) as described before (Hampe et al. 2007, Schaefer et al. 2009).

Statistical analysis

SNP associations with a $p \leq 5 \times 10^{-3}$ were taken into replication, when this association was flanked on both sides by an additional significant marker with $p < 0.05$. Markers were tested for deviations from Hardy–Weinberg equilibrium in controls ($\alpha = 0.05$) and for a callrate of >98% in cases and controls before inclusion in the analysis. Genotypes were analysed using the software PLINK v2 (Purcell et al. 2007). Correction for multiple testing was performed by the method of Bonferroni in the replication experiment. To be independent, SNPs had to show a linkage disequilibrium (LD) $r^2 < 0.8$. LD measures were calculated with Haploview 4.1 (Barrett et al. 2005). Power calculations were performed using PS Power and Sample Size Calculations software (Dupont & Plummer 1998) The explorative study had a statistical power to detect an association with the probability of $p > 0.8$ at MAF ≥ 15% and with an OR ≥ 1.5. Logistic regression analysis was performed to adjust for possible confounding of the covariates smoking and sex in the R statistical environment (htttp://www.r-project.org).

Results

Candidate gene association study of 44 known RA risk loci in a large German AgP sample

Of all loci, SNPs within three genetic regions, i.e. *IL2RA*, *PRDM1,* and *IRF5* fulfilled the pre-assigned significance threshold and suggested association with AgP.

At the chromosomal region of *IL2RA*, 89 kb were covered on the immunochip by 165 SNPs with an MAF ≥ 5% and with an average distance of 539 bp (Table S1). The GWAS lead SNP of RA (rs10795791) (Eyre et al. 2012) was not associated with AgP. Instead, GWAS lead SNPs of type 1 diabetes (T1D) (Plagnol et al. 2011), Crohn's disease (CD) (Jostins et al. 2012), multiple sclerosis (MS; rs12722489) (Sawcer et al. 2011) and generalized vitiligo (rs706779) (Jin et al. 2010) showed nominal significant association with AgP. However, these SNPs did not fulfil our pre-assigned selection criteria for replication (Table S1). Instead, two groups of three neighbouring SNPs fulfilled the selection criteria. Of these two groups, one SNP in each case, rs41294671 ($p_{dom} = 0.0031$) and rs4625363 ($p_{dom} = 0.0064$), was in LD to the CD- and MS-lead SNP rs12722489 ($r^2 > 0.8$; Fig. S1), which showed the smallest p-value at the dominant genetic model with $p_{dom} = 0.0052$ (OR = 0.74, 95% CI = 0.6–0.9 (Table 1, Table S1, MAF cases = 14.2%, MAF controls = 17.6%, Table 2).

At the chromosomal region of *PRDM1*, 181 kb were covered by 231 SNPs (MAF ≥ 5%) with an average distance of 780 bp (Table S1). Within this region, genome-wide associations with RA (rs6911690) (Eyre et al. 2012), with inflammatory bowel disease (IBD, rs6568421, rs7746082, rs6911490) (Barrett et al. 2008, Franke et al. 2010, Anderson et al. 2011, Jostins et al. 2012), and with SLE (rs548234) (Han et al. 2009, Zhou et al. 2011) have been reported. However, none of these reported GWAS lead SNPs indicated nominal association with AgP (Table S1). Instead, a group of six neighbouring SNPs within intron 2 fulfilled the pre-assigned selection criteria. This group comprised three pairs of SNPs that were in almost complete LD to each other ($r^2 > 0.98$, Fig. S1, Table S1), with rs6923419 showing the strongest association with AgP ($p = 0.0019$) and a protective genetic effect of OR = 0.77 (95% CI 0.6–0.9; Table 1, MAF cases = 10.5%, MAF controls = 14.1%, Table 2). The effect size was similar to the risk allele that was reported for the strongest genome-wide association with RA (OR = 0.87, rs6911690), located upstream of *PRDM1* (Eyre et al. 2012).

At the chromosomal region of *IRF5*, 67 kb were covered by 81 SNPs (MAF ≥ 5%) with an average distance of 840 bp (Table S1). Within this region, SNP rs729302 showed genome-wide association with RA (Lee et al. 2012) and SLE (Yang et al. 2013), SNP rs4728142 with IBD and SLE (Han et al. 2009, Anderson et al. 2011, Jostins et al. 2012), SNP rs3807306 with RA (Eyre et al. 2012), and SNP rs10488631 showed genome-wide association with RA (Stahl et al. 2010), SLE (Radstake et al. 2010, Chung et al. 2011), systemic sclerosis (Hom et al. 2008, Allanore et al. 2011, Gorlova et al. 2011), and primary biliary cirrhosis (Hirschfield et al. 2009, Liu et al. 2010). All these SNPs except for rs10488631 showed nominal association with AgP in our sample, but did not fulfil the pre-assigned selection criteria for replication (Table S1). Instead, a group of 14 neighbouring SNPs upstream of the *IRF5* coding region fulfilled these criteria with rs4731531 showing the

Table 1. Significant SNP associations in the German and Dutch AgP samples

Gene	SNP	Population	*p* (allelic)	OR (95% CI)	*p* (best model)	OR (95% CI)
IL2RA	rs56855309	German	0.0078	0.81 (0.70–0.95)	0.0037 (dom)	0.75 (0.62–0.91)
	rs10795738*		0.0045	0.80 (0.68–0.93)	0.0033 (dom)	0.75 (0.62–0.91)
	rs4625363		0.0127	0.79 (0.65–0.95)	0.0064 (dom)	0.74 (0.60–0.92)
	rs12722489†		0.0082	0.78 (0.6–0.9)	0.0052 (dom)	0.74 (0.6–0.9)
	rs56855309	Dutch	n.s.	n.s.	0.0406 (dom)	0.70 (0.50–0.99)
	rs10795738*		n.s.	n.s.	0.0388 (dom)	0.70 (0.50–0.98)
	rs4625363		n.s.	n.s.	0.0210 (rec)	2.32 (1.12–4.84)
	rs12722489†		n.s.	n.s.	0.0146 (rec)	2.45 (1.2–5.1)
PRDM1	rs1984224	German	0.0439	1.16 (1.004–1.3)	0.0296 (dom)	1.24 (1.02–1.51)
	rs6923419		0.0019	0.71 (0.6–0.9)	allelic	allelic
	rs6923608		0.0132	0.77 (0.6–0.95)	allelic	allelic
	rs6924535		0.0417	1.16 (1.01–1.3)	0.0280 (dom)	1.24 (1.02–1.51)
	rs1984224	Dutch	0.0087	1.39 (1.1–1.8)	0.0047 (dom)	1.67 (1.2–2.4)
	rs6923419		0.0246	0.65 (0.5–0.95)	allelic	allelic
	rs6923608		0.0246	0.65 (0.5–0.95)	allelic	allelic
	rs6924535		0.0129	1.37 (1.1–1.8)	0.0076 (dom)	1.62 (1.1–2.3)
IRF5	rs56303857	German	0.0325	1.36 (1.03–1.8)	allelic	allelic
	rs62481981‡		0.0095	2.20 (1.2–4.0)	0.0089 (het. dom)	2.22 (1.2–4.1)
	imm_7_128356335		0.0256	1.38 (1.04–1.8)	allelic	allelic
	rs56303857	Dutch	0.0132	1.70 (1.1–2.6)	0.0036 (het)	1.93 (1.2–3.0)
	rs62481981‡		n.s.	n.s.	0.0355 (het. dom)	2.70 (1.03–7.1)
	imm_7_128356335		n.s.	n.s.	0.0188 (het)	1.73 (1.1–2.7)

n.s., not significant; allelic, allelic genetic model; rec, recessive model; het, heterozygous model; dom, dominant model.
*3.7 kb from GWAS lead SNP for lipid lowering.
†GWAS lead SNP of CD, MS, located 2.5 kb upstream the GWAS lead SNP of RA (rs7090512).
‡Rare variant with a MAF < 1%.

Table 2. Genotypes and minor allele frequencies of the significant SNPs in the German and Dutch AgP samples

Gene	SNP	Sample	Cases					Controls				
			11	12	22	Total	MAF (%)	11	12	22	Total	MAF (%)
IL2RA	rs56855309	German	347	211	42	600	24.6	732	592	117	1,441	28.7
	rs10795738*		347	214	38	599	24.2	732	595	114	1441	28.6
	rs4625363		443	140	17	600	14.5	976	420	45	1441	17.7
	rs12722489†		445	138	16	599	14.2	980	414	46	1440	17.6
	rs56855309	Dutch	88	56	20	164	29.27	304	311	64	679	32.33
	rs10795738*		88	56	20	164	29.27	303	315	60	678	32.08
	rs4625363		109	43	12	164	20.43	464	192	22	678	17.40
	rs12722489†		108	44	12	164	20.73	463	195	21	679	17.5
PRDM1	rs1984224	German	232	294	74	600	36.8	632	650	158	1440	33.5
	rs6923419		474	115	5	594	10.5	1063	345	31	1439	14.1
	rs6923608		457	121	5	583	11.2	1064	346	31	1441	14.2
	rs6924535		232	294	74	600	36.8	633	649	158	1440	33.5
	rs1984224	Dutch	55	87	22	164	39.9	310	298	70	678	32.3
	rs6923419		130	32	2	164	11.0	480	182	17	679	15.9
	rs6923608		130	32	2	164	11.0	480	182	17	679	15.9
	rs6924535		56	86	22	164	39.6	310	298	71	679	32.4
IRF5	rs56303857	German	524	72	3	599	6.5	1306	130	5	1441	4.9
	rs62481981‡		580	20	0	600	1.7	1417	22	0	1439	0.8
	imm_7_128356335		524	72	3	599	6.5	1307	128	5	1440	4.8
	rs56303857	Dutch	131	33	0	164	10.1	598	78	3	679	6.2
	rs62481981‡		157	7	0	164	2.1	667	11	0	678	0.9
	imm_7_128356335		133	30	0	163	9.2	598	78	3	679	6.2

11 = homozygous common allele; 12 = heterozygous; 22 = homozygous rare allele; MAF, minor allele frequency.
*3.7 kb from GWAS lead SNP for lipid lowering.
†GWAS lead SNP of CD, MS, located 2.5 kb upstream the GWAS lead SNP of RA (rs7090512).
‡Rare variant with MAF < 1%.

strongest association ($p = 0.0011$) and a genetic effect of OR = 1.25 (95% CI = 1.1–1.4; MAF cases = 46.4%, MAF controls = 40.9%, Table S1). This region spanned the reported genome-wide associated RA and SLE lead SNP rs729302, which was nominally significantly associated in our AgP sample ($p = 0.0238$),

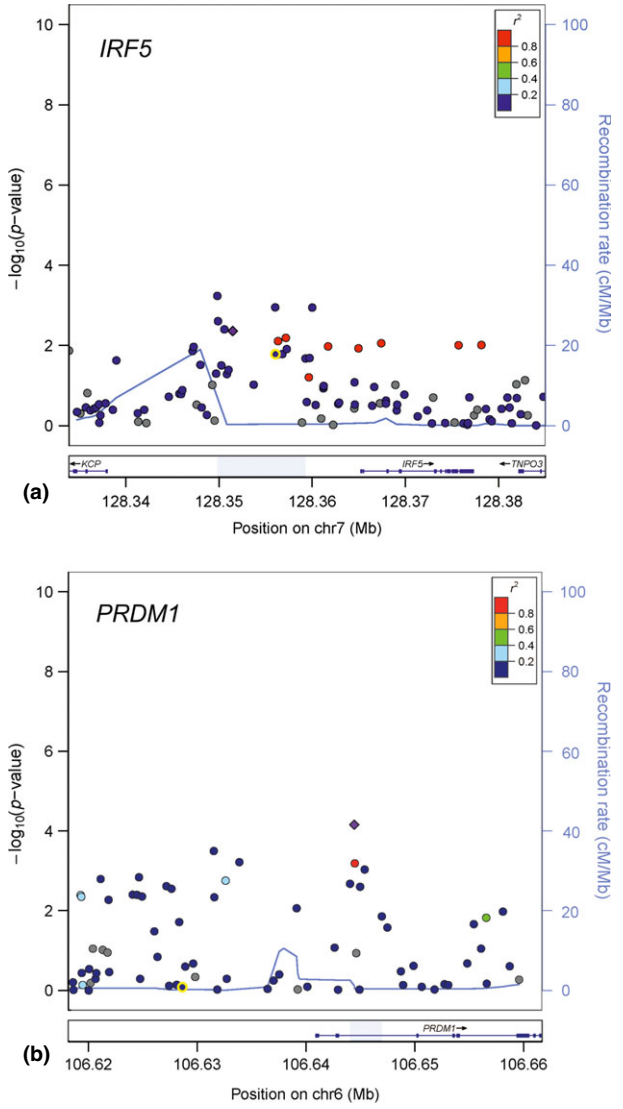

Fig. 1. Association plots of immunochip data for *IRF5* and *PRDM1*. Regional association plots of immunochip data for (a) *IRF5* and (b) *PRDM1* in the pooled AgP case–control samples (N = 768 cases, 2119 controls). The $-\log^{10}$ p-values of the analysed SNPs were plotted as a function of the genomic SNP position (NCBI build 36). The chromosomal localization of the SNPs, which were significant in both individual German and Dutch AgP samples are indicated in the gene track by a light blue box (SNP annotation provided by LocusZoom databases). Purple diamond = index SNP, red dots indicate SNPs that are in complete linkage disequilibrium (LD) to the index SNP ($r^2 \geq 0.8$). See details in the text. (a) purple diamond = index SNP rs56303857, yellow circle = RA-GWAS lead SNP rs729302. (b) purple diamond = index SNP rs6923419, yellow circle = RA- and ulcerative colitis-GWAS lead SNP rs6911490.

with a genetic effect of the same direction (OR = 1.40, 95% CI = 1.1–1.9, Table 1, MAF cases = 31.6%, MAF controls = 35.3%, Table 2) (Lee et al. 2012, Yang et al. 2013). The polymorphism that is located closest to rs729302 in European genomes is the rare variant rs62481981 (168 bp upstream, MAF = 0.6%; 1000 Genome phase 1 genotype data), with no evidence of LD (r^2 = 0, D′ = uninformative; Fig. S1). This rare variant was significant under the dominant genetic model in our AgP sample (p = 0.0089, OR = 2.22, 95% CI = 1.2–4.1, Table 1, MAF cases = 1.7%, MAF controls = 0.8%, Table 2).

We further observed several single SNP associations ($p < 0.009$) upstream of the coding region of *FCGR2A* (Eyre et al. 2012). Of these *FCGR2A* SNPs, the strongest association was observed for rs6698806, with p = 0.0007 (OR = 0.79, 95% CI = 0.7–0.9, Table S1), upstream of the RA and IBD associated SNPs. Furthermore, we observed several single-SNP associations ($p < 0.008$) from 20 kb downstream to the coding region of *SPRED2* with SNP rs17755105, located within *SPRED2*, showing the smallest p-value (p = 0.0039, OR = 0.8, 95% CI = 0.6–0.9), located 11 kb upstream to the RA-GWAS lead SNP rs6546146 (Table S1). These SNP associations were not replicated as they did not comply with our pre-assigned selection criteria and chances of false positive associations were high.

Replication of the associations of *IL2RA*, *PRDM1*, and *IRF5* in an independent AgP case–control sample of Dutch descent

The observed associations of the chromosomal regions of *IL2RA*, *IRF5*, and *PRDM1* were replicated with immunochip data from an independent, although smaller sample of 164 Dutch AgP cases and 679 ethnically matched healthy controls.

In the replication of *IL2RA*, GWAS lead SNP rs12722489 (Hafler et al. 2007, Franke et al. 2010) showed the lowest p-value of the seven tested SNPs (Fig. S1), with the smallest p-value under the recessive genetic model (p = 0.0146) and a genetic effect of OR = 2.45 (95% CI = 1.2–5.1, Table 1). The effect was reversed to that shown in the German explorative panel.

Of the six SNPs within *PRDM1* that fulfilled the selection criteria, four SNPs were significant in the Dutch replication panel, with genetic effects of the same direction as in the German explorative panel. In this sample, SNP rs6923419 was significantly associated with p = 0.0246 (OR = 0.65, 95% CI = 0.45–0.95, Table 1). The best association with the Dutch AgP sample was shown by SNP rs1984224 (tagging SNP rs6924535; Fig. S1) under the dominant genetic model with p = 0.0047 (OR = 1.657, 95% CI = 1.2–2.4, Table 1).

Of the significant group of 14 neighbouring common variants at *IRF5*, three SNPs flanking GWAS lead SNP rs729302 up- and downstream (rs56303857, imm_7_128356335, and imm_7_128357166; Table 1, Fig. S1) were borderline significantly associ-

Table 3. Genotypes and minor allele frequencies of the significant SNPs in the pooled populations used for covariate adjustment

Gene	SNP	Sample	Cases					Controls				
			11	12	22	Total	MAF (%)	11	12	22	Total	MAF (%)
PRDM1	rs6923419	Pooled	664	160	9	833	10.7	1078	322	40	1440	14.0
IRF5	rs62481981	Pooled	773	28	0	801	1.7	1461	15	0	1476	0.5

11 = homozygous common allele; 12 = heterozygous; 22 = homozygous rare allele; MAF, minor allele frequency.

Table 4. Association statistics after covariate adjustment for the confounders smoking and sex in the single and pooled population

Gene	SNP	Sample	*p* (allelic)	OR (95% CI)
PRDM1	rs6923419	Pooled	0.0039	0.74 (0.6–0.9)
		German	0.0153	0.74 (0.6–0.9)
		Dutch	0.2453	0.78 (0.5–1.1)
IRF5	rs62481981	Pooled	0.0012	3.1 (1.6–6.1)
		German	0.0215	2.6 (1.2–5.8)
		Dutch	0.0233	4.73 (1.3–19.9)

allelic, allelic genetic model.

ated in the Dutch AgP case–control sample, with rs56303857 showing the smallest *p*-value under the dominant genetic model ($p = 0.0036$, OR = 1.93, 95% CI = 1.2–3.0). The rare variant rs62481981 was significant under the dominant genetic model in the Dutch replication AgP case–control sample ($p = 0.0355$, OR = 2.70 95% CI = 1.03–7.1). GWAS lead SNP rs729302, located 168 bp downstream and not in LD (Fig. S1) was not significant in this small Dutch replication sample.

After Bonferroni correction for twelve independent simultaneous tests in the replication sample (Fig. S1), the association of *IRF5* SNP rs56303857 remained significant at the threshold of $p = 0.05$ ($p_{corrected} = 0.043$). The association of *PRDM1* SNP rs1984224 was slightly above this significance threshold with $p_{corrected} = 0.056$.

The size of the replication sample was severely underpowered to clearly reject the null-hypothesis of no association. To obtain an overall picture, we pooled the German explorative and Dutch replication samples. In this enlarged German–Dutch pooled case–control population, the *p*-values for the *IRF5* and *PRDM1* associations indicated a higher evidence of association compared to that shown in the single samples (Fig. 1). E.g., for the best associated SNPs at *IRF5,* rs56303857 and rs62481981, it was $p = 0.0044$ (OR = 1.41, 95% CI = 1.1–1.8) and $p = 0.0011$ (OR = 2.29, 95% CI = 1.4–3.8), respectively. For the most strongly associated *PRDM1* SNP rs6923419, the pooled *p*-value was $p = 0.00007$ (OR = 0.69, 95% CI = 0.6–0.8).

The genetic effects of the variants of *IRF5* and *PRDM1* on the disease risk of AgP are independent of the confounding effects of smoking and sex

We tested the associations of the replicated and most strongly associated SNPs within *IRF5* and *PRDM1* for independence of the established periodontitis risk factor smoking and the confounder gender in a logistic regression analysis. Data for smoking were not available for all German population representative controls of the explorative study. Therefore, we used 469 population representative German controls of the explorative study, for which smoking data were available, and added 454 German blood donors with known smoking history to compensate for a loss of the statistical power. Likewise, no data on smoking were available for the entire Dutch control panel of the replication. Here, we used an independent control sample of Dutch blood donors ($N = 557$), which we genotyped for the selected SNPs. We pooled the German and Dutch samples, as in both populations, the genetic effect was of the same direction and the allele frequencies were very similar between both independent samples (Table 3). After covariate adjustment for smoking and gender, *IRF5* SNP rs62481981 was significantly associated with AgP under the allelic genetic model with $p = 0.0012$ (OR = 3.1, 95% CI = 1.6–6.1; Table 4). *PRDM1* SNP rs6923419 was significantly associated with AgP under both the allelic and recessive genetic models, with $p_{allelic} = 0.0039$ (OR = 0.74, 95% CI = 0.6–0.9; Table 4).

To avoid stratification from unaccounted effects of the single populations resulting by pooling, we repeated the logistic regression analyses adjusting for smoking and sex in the individual larger German and smaller Dutch case–control samples. In the individual study populations, *PRDM1* SNP rs6923419 was associated in the German panel under both models, with $p_{allelic} = 0.0153$ (OR = 1.36, 95% CI = 1.1–1.7), but not in the Dutch panel. *IRF5* SNP rs62481981 was associated in both, the German and the Dutch samples, with $p = 0.0215$ (OR = 2.6, 95% CI = 1.2–5.8) and $p = 0.0233$ (OR = 4.74, 95% CI = 1.3–19.9), respectively; however, after correction for multiple testing, the adjusted associations in the individual samples lost their significances.

Candidate gene association study of 20 known SLE risk loci in a large AgP sample

All established SLE risk loci (Guerra et al. 2012) were genotyped with the Immunochip in 600 German AgP cases and 1448 population representative German controls as described above. Nine further SLE loci were reported to be shared with RA (*BLK, ETS1, FCGR2A, IRF5, IRF8, PRDM1, PTPN22, STAT4, TNFAIP3, TYK2*) and had already been analysed

in the first step of the study. Of all analysed loci, only SNPs within the two genetic regions of *IRF5* and *PRDM1* described above, fulfilled the pre-assigned significance threshold and suggested association with AgP; no further SLE risk loci were associated with AgP.

Discussion

This study finemapped candidate genes, which had previously shown genome-wide association with RA and SLE, to identify putative associations of these genetic regions with AgP. We identified SNPs within *IRF5* and *PRDM1* to be associated in two independent AgP case–control samples. Both genes were also associated with IBD (Barrett et al. 2008, Franke et al. 2010, Anderson et al. 2011, Jostins et al. 2012). The observed effect sizes and effect directions were comparable to those reported for the associations with RA, SLE, and IBD, and were independent of the covariates smoking and sex.

The major limitation of our study was the lack of statistical power (SP). Although the SP of the explorative AgP sample was sufficient to detect a true positive association with a probability >0.8 for the common alleles at *PRDM1* (MAF > 14%), the SP was not sufficient to give evidence for the association of less frequent variants. Confidence in the findings is gained, if considered that the *p*-values became more significant in proportion to the increased sample size. In the case of false positive associations, the *p*-values were more likely to lose significance at an increased sample size.

At *IRF5*, the shared GWAS lead-SNP of RA, SLE and IBD, rs4728142, was associated with AgP with the same effect direction. At *PRDM1,* the best SLE and AgP associated variants were located within intron 1, whereas the variants that were best associated with IBD and RA were located upstream of the protein-coding sequence. However a recent whole exome sequencing study of CD identified two functional rare missense variants to be associated with CD and UC, which were located ~14 kb downstream of the best AgP-associated variants and showed the same genetic effect direction (Ellinghaus et al. 2013). If an overlap of genetic risk alleles between RA, SLE, IBD, and AgP exists, it should not necessarily be expected that the same risk alleles were associated. A recent study that analysed putative correlations of risk genes of immune disorders reported that although ~38% of the susceptibility genes of immune-mediated phenotypes showed pleiotropic effects in different disease classes, only ~8% of the SNPs that were associated with a specific disease had pleiotropic effects (Sivakumaran et al. 2011). Pleiotropy does not suggest direct pathological linkage of the diseases, but suggest multiple functions of the gene or variant, which may have different effects in different contexts.

The proteins IRF5 and PRDM1 play a role in interferon-beta (IFN-β) signalling. The transcription factor interferon regulatory factor (IRF5) is a coregulator of IFN-β (Steinhagen et al. 2013) with diverse roles, including virus-mediated activation of interferon (Barnes et al. 2001). It acts as a molecular switch that controls whether macrophages will promote or inhibit inflammation (Barnes et al. 2002). *PRDM1,* also known as B lymphocyte–induced maturation protein (Blimp-1), is a transcriptional repressor of IFN-β, which specifically binds to the IFN-β gene promoter (Keller & Maniatis 1991) and is known to be a master regulator of B- and T-cell differentiation (Crotty et al. 2010).

In conclusion, this study aimed to elucidate a shared genetic basis of RA or SLE with AgP and identified *PRDM1* and *IRF5* as suggestive candidate genes, which both play a role in IFN-β signalling and are also associated with an increased risk of IBD. The study indicates that the extent of shared risk loci is limited. The *p*-values of the associated variants do not propose *PRDM1* and *IRF5* as major risk genes of PD. Yet, the height of the *p*-values may be partly influenced by the moderate frequency of the associated alleles and the limited size of the study populations. Similarly, although a general role in the disease aetiology of PD cannot be assigned, these loci may be of importance for the individual patient. Because of the limited size of the replication sample, our findings require validation in a large case–control sample of the same phenotype and geographical background. After successful validation of the observed associations, these loci can guide focused pathway analyses and may underpin hypothesis-driven research into specific pathogenic mechanisms.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. LD structure of SNPs at IL2RA, IRF5 and PRDM1, which showed significant associations in the German AgP case–control sample and were selected for replication. LD was calculated with 1000 healthy individuals from North-Germany (popgen biobank) by using the software Haploview. See text for details (Green diamonds – tagging SNPs that capture alleles at $r^2 > 0.8$, yellow squares – GWAS lead SNPs, orange square – rare variant, numbers = r^2).

Table S1. SNPs, chromosomal positions and statistics of the loci that suggested significant associations.

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Clinical Relevance

Scientific rationale for the study: Epidemiological and clinical studies suggested associations of rheumatoid arthritis (RA) and periodontitis (PD). To better understand the underlying disease mechanisms, we aimed to explore shared genetic risk loci.

Principal findings: The genes *IRF5* and *PRDM1* showed associations with aggressive periodontitis. After adjustment for the covariates smoking and sex, the most strongly associated variant at *IRF5* was rs62481981 ($p = 0.0012$, odds ratio [OR] = 3.1, 95% confidence interval [95% CI] = 1.6–6.1) and at *PRDM1* it was rs6923419 ($p = 0.004$, OR = 0.7, 95% CI = 0.6–0.9). However, the associations lost significance after correction for multiple testing.

Practical implications: *IRF5* and *PRDM1* are proposed as candidate genes for the susceptibility to PD. This knowledge can be used to underpin further hypothesis-driven research into putative shared disease mechanisms.