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


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 co-variate adjustment for smoking and sex, the most strongly associated variant at IRF5 was the rare variant rs62481981 (p_{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_{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 signaling 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 erythematosus (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 cases 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, PRDM1 and IRF5 increase risk of periodontitis

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Key words: inflammatory bowel disease; IRF5; periodontitis; PRDM1; rheumatoid arthritis; systemic lupus erythematosus

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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 automatically called by the GenomeStudio (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 \( p \leq 5 \times 10^{-7} \) 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 measurements 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 of 80% to detect an association with the probability of \( p < 0.05 \) at a dominant genetic model with \( \text{OR} = 2 \). Logistic regression analysis was performed to adjust for possible confounding of the covariates smoking and sex in the R statistical environment (http://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 fulfill 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, rs14294671 (\( \rho_{\text{dom}} = 0.0031 \)) and rs4625363 (\( \rho_{\text{dom}} = 0.0064 \)), 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 \( \rho_{\text{dom}} = 0.0052 \) (OR = 0.74, 95% CI = 0.6–0.9; Table 1, Table S1). One SNP in each group comprised three pairs of SNPs (MAF ≥231 SNPs (MAF ≥5% and with an average distance of 780 bp (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).

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 fulfill 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 strongest association with AgP (98% in cases vs 70% in controls, \( 0.0052 \), Table S1).
Table 1. Significant SNP associations in the German and Dutch AgP samples

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Population</th>
<th>p (allelic)</th>
<th>OR (95% CI)</th>
<th>p (best model)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL2RA</td>
<td>rs56855309</td>
<td>German</td>
<td>0.0078</td>
<td>0.81 (0.70–0.95)</td>
<td>0.0037 (dom)</td>
<td>0.75 (0.62–0.91)</td>
</tr>
<tr>
<td></td>
<td>rs10795738</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>0.0046 (dom)</td>
<td>0.75 (0.62–0.91)</td>
</tr>
<tr>
<td></td>
<td>rs4625363</td>
<td>Dutch</td>
<td>0.0127</td>
<td>0.79 (0.65–0.95)</td>
<td>0.0064 (dom)</td>
<td>0.74 (0.60–0.92)</td>
</tr>
<tr>
<td></td>
<td>rs12722489</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>0.0082 (dom)</td>
<td>0.74 (0.6–0.9)</td>
</tr>
<tr>
<td>PRDM1</td>
<td>rs1984224</td>
<td>German</td>
<td>0.0439</td>
<td>1.16 (1.004–1.3)</td>
<td>0.0296 (dom)</td>
<td>1.24 (1.02–1.51)</td>
</tr>
<tr>
<td></td>
<td>rs6923419</td>
<td>German</td>
<td>0.0019</td>
<td>0.71 (0.6–0.9)</td>
<td>allelic</td>
<td>allelic</td>
</tr>
<tr>
<td></td>
<td>rs6923608</td>
<td>German</td>
<td>0.0132</td>
<td>0.77 (0.6–0.95)</td>
<td>allelic</td>
<td>allelic</td>
</tr>
<tr>
<td></td>
<td>rs6924535</td>
<td>German</td>
<td>0.0017</td>
<td>1.16 (1.01–1.3)</td>
<td>0.0280 (dom)</td>
<td>1.24 (1.02–1.51)</td>
</tr>
<tr>
<td>IRF5</td>
<td>rs56303857</td>
<td>German</td>
<td>0.0325</td>
<td>1.36 (1.03–1.8)</td>
<td>allelic</td>
<td>allelic</td>
</tr>
<tr>
<td></td>
<td>rs62481981</td>
<td>German</td>
<td>0.0095</td>
<td>2.20 (1.2–4)</td>
<td>allelic</td>
<td>allelic</td>
</tr>
<tr>
<td></td>
<td>rs6924535</td>
<td>German</td>
<td>0.0129</td>
<td>1.37 (1.1–1.8)</td>
<td>0.0076 (dom)</td>
<td>1.62 (1.1–2.3)</td>
</tr>
<tr>
<td></td>
<td>rs56855309</td>
<td>Dutch</td>
<td>0.0132</td>
<td>1.70 (1.1–2.6)</td>
<td>0.0036 (het)</td>
<td>1.93 (1.2–3.0)</td>
</tr>
<tr>
<td></td>
<td>rs62481981</td>
<td>Dutch</td>
<td>0.0132</td>
<td>1.70 (1.1–2.6)</td>
<td>0.0036 (het)</td>
<td>1.93 (1.2–3.0)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Sample</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>IL2RA</td>
<td>rs56855309</td>
<td>German</td>
<td>347</td>
<td>211</td>
</tr>
<tr>
<td></td>
<td>rs10795738</td>
<td>German</td>
<td>347</td>
<td>214</td>
</tr>
<tr>
<td></td>
<td>rs4625363</td>
<td>German</td>
<td>443</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>rs12722489</td>
<td>Dutch</td>
<td>445</td>
<td>138</td>
</tr>
<tr>
<td>PRDM1</td>
<td>rs1984224</td>
<td>German</td>
<td>232</td>
<td>294</td>
</tr>
<tr>
<td></td>
<td>rs6923419</td>
<td>German</td>
<td>474</td>
<td>115</td>
</tr>
<tr>
<td></td>
<td>rs6923608</td>
<td>German</td>
<td>457</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>rs6924535</td>
<td>Dutch</td>
<td>232</td>
<td>294</td>
</tr>
<tr>
<td></td>
<td>rs1984224</td>
<td>Dutch</td>
<td>55</td>
<td>87</td>
</tr>
<tr>
<td>IRF5</td>
<td>rs56303857</td>
<td>German</td>
<td>524</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>rs62481981</td>
<td>German</td>
<td>580</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>rs56303857</td>
<td>Dutch</td>
<td>524</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>rs62481981</td>
<td>Dutch</td>
<td>131</td>
<td>33</td>
</tr>
</tbody>
</table>

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%.

PRDM1 and IRF5 increase risk of periodontitis

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),

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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 ($r^2 = 0, D^2 = uninformative$; 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-
allelic genetic model.

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>Sample</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRDM1</td>
<td>rs6923419</td>
<td>Pooled</td>
<td>664</td>
<td>160</td>
</tr>
<tr>
<td>IRF5</td>
<td>rs62481981</td>
<td>Pooled</td>
<td>773</td>
<td>28</td>
</tr>
</tbody>
</table>

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

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

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 genome-wide association with RA 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, Joslin 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 larger 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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**References**


association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. Nature Genetics 41, 1234–1239.


## Supporting Information

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

Figure S1. LD structure of SNPs at IL2RA, IRAF and PRDM1, which showed significant associations in the German Aep case-control sample and were selected for replication. LD was calculated with 1000 healthy individuals from North-Germany (pop- gen biobank) by using the software Haplovie. See text for details (Green diamonds – tagging SNPs that capture alleles at r² > 0.8, yellow squares – GWAS lead SNPs, orange square – rare variant, numbers = r²).

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 the better understanding of 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.