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Further Genetic Evidence for Three Psoriasis-Risk Genes: *ADAM33*, *CDKAL1*, and *PTPN22*

Yonghong Li¹, Wilson Liao², Monica Chang¹, Steven J. Schrodi¹, Nam Bui¹, Joseph J. Catanese¹, Annie Poon², Nori Matsunami³, Kristina P. Callis-Duffin⁴, Mark F. Leppert^{3,5}, Anne M. Bowcock^{6,7,8}, Pui-Yan Kwok², Gerald G. Krueger³, and Ann B. Begovich^{1,9}

¹Celera, Alameda, California, USA

²Department of Dermatology, University of California, San Francisco, California, USA

³Department of Human Genetics, University of Utah, Salt Lake City, Utah, USA

⁴Department of Dermatology, University of Utah, Salt Lake City, Utah, USA

⁵LineaGen Research Corporation, Salt Lake City, Utah, USA

⁶Division of Human Genetics, Department of Genetics, Washington University School of Medicine, St. Louis, Missouri, USA

⁷Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA

⁸Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

Abstract

Predisposition to psoriasis is known to be affected by genetic variation in HLA-C, IL12B, and IL23R, and although other psoriasis-associated variants have been identified, incontrovertible statistical evidence for these markers has not yet been obtained. To help resolve this issue, we tested 15 single-nucleotide polymorphisms (SNPs) from 7 putative psoriasis-risk genes in 1,448 psoriasis patients and 1,385 control subjects; 3 SNPs, rs597980 in *ADAM33*, rs6908425 in *CDKAL1* and rs3789604 in *PTPN22*, were significant with the same risk allele as in prior reports (one-sided $P < 0.05$, false discovery rate < 0.15). These three markers were tested in a fourth sample set (599 cases and 299 controls); one marker, rs597980, replicated (one-sided $P < 0.05$) and the other two had odds ratios with the same directionality as in the original sample sets. Mantel–Haenszel meta-analyses of all available case–control data, including those published by other groups, showed that these three markers were highly significant (rs597980: $P = 0.0057$ (2,025 cases and 1,597 controls), rs6908425: $P = 1.57 \times 10^{-5}$ (3,206 cases and 4,529 controls), and rs3789604: $P = 3.45 \times 10^{-5}$ (2,823 cases and 4,066 controls)). These data increase the likelihood that *ADAM33*, *CDKAL1*, and *PTPN22* are true psoriasis-risk genes.

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Correspondence: Dr Yonghong Li, Discovery Research, Celera, 1401 Harbor Bay Parkway, Alameda, California 94502, USA. yonghong.li@celera.com.

⁹Current address: Roche Molecular Diagnostics, Pleasanton, CA, USA

CONFLICT OF INTEREST

Authors with affiliations to Celera have personal financial interest in the company.

INTRODUCTION

Psoriasis is a common, chronic, T-cell-mediated inflammatory disease of the skin found in most ethnic groups, with a prevalence of 1.5–3% in Caucasians and <1.0% in Asians and Africans (Campalani and Barker, 2005). The disease is characterized by an inflammatory process and marked hyperproliferation of the epidermis, resulting in aberrant terminal differentiation of keratinocytes. Psoriasis occurs equally in men and women with ~75% of patients developing disease before the age of 40 years.

Twin studies suggest that approximately two-thirds of the variation in psoriasis risk is heritable. Disease concordance in monozygotic twins (65–72%) is higher than in dizygotic twins (15–30%), and the incidence is substantially increased in family members of affected individuals (e.g., 6% for first-degree relatives) (Bowcock and Cookson, 2004). Specific genetic variants, in the form of single-nucleotide polymorphisms (SNPs) and/or haplotypes in three genes, *HLA-C*, *IL12B*, and *IL23R*, have been consistently associated with psoriasis risk in multiple independent sample sets (Tsunemi *et al.*, 2002; Nair *et al.*, 2006, 2008; Capon *et al.*, 2007; Cargill *et al.*, 2007; Smith *et al.*, 2007; Liu *et al.*, 2008), and there is increasing evidence that variants in the *IL13/IL4* gene region also contribute to psoriasis risk (Chang *et al.*, 2008; Li *et al.*, 2008). However, the combined effects of these four loci do not fully account for the heritability of this disease.

Additional genes in inflammatory and other pathways have been implicated in the genetic etiology of psoriasis (Zhang *et al.*, 2007; Lesueur *et al.*, 2007b; Capon *et al.*, 2008; Hollox *et al.*, 2008; Liu *et al.*, 2008; Smith *et al.*, 2008; Wolf *et al.*, 2008); however, further testing in large, independent sample sets is required to ascertain whether these findings represent genuine associations. Here we tested 15 markers in 7 putative-risk gene regions including *ADAM33*, *IL15*, *SPATA2*, *CDKAL1*, *FLJ45139*, *PTPN22*, and a region on chr 1q24 in up to 2,047 individuals with psoriasis and 1,684 control subjects. We provide meta-analysis evidence from up to 3,206 cases and 4,529 controls suggesting three may be true psoriasis susceptibility genes.

RESULTS

We genotyped 15 candidate markers from 7 distinct gene regions in three white, North American psoriasis case–control sample sets (sample sets 1–3) described in detail elsewhere (Cargill *et al.*, 2007) (Table 1). These SNPs were chosen from recent candidate gene-based or genome-wide association studies; 13 markers were modestly associated with psoriasis in these previous studies whereas 2 SNPs, not significant on their own, were part of disease-associated haplotypes (Zhang *et al.*, 2007; Lesueur *et al.*, 2007b; Capon *et al.*, 2008; Smith *et al.*, 2008; Wolf *et al.*, 2008) (for details see “Materials and Methods”).

Genotype distributions in our sample sets showed no consistent or pronounced violation of Hardy–Weinberg equilibrium in either cases or controls (all Hardy–Weinberg equilibrium $P > 0.01$) except for g.96516 ($P = 0.003$ in sample set 2 cases) (Supplementary Table 1). The allele frequencies of all markers were similar to previous reports except for two *IL15* SNPs, rs10519613 and g.96516. SNP g.96516, the most significant marker in the Chinese case–

control study (Zhang *et al.*, 2007) with a control minor allele frequency of 23%, was rare in our white samples (minor allele frequency=0.4%), which is consistent with findings in another white sample set (Weger *et al.*, 2008).

We tested association of these SNPs with psoriasis risk using the same genetic model suggested in the original report—13 SNPs at the single marker level and 2 purported haplotypes in *ADAM33* and *IL15*. Because our individual sample sets had low power to replicate markers with a weak effect, we evaluated replication in the three sample sets combined (1,448 psoriasis patients and 1,385 control subjects). On the basis of a Mantel–Haenszel analysis, three markers replicated (one-sided $P < 0.05$): rs597980 in *ADAM33*, rs6908425 in *CDKALI*, and rs3789604 in *PTPN22* (Table 2). This is more than one would expect under the null hypothesis (13 markers tested $\times 0.05 = \sim 1$ marker), suggesting that some of these significant SNPs are likely to be genuine psoriasis markers. These three SNPs all had a false discovery rate of less than 0.15, indicating that one in six of these markers may be false positive (Table 2).

Although the *ADAM33* SNP, rs597980, was significant, the three-marker *ADAM33* haplotype (defined by rs512625, rs2280089, and rs535964), which showed the most significant association in the original report ($P = 0.00004$) (Lesueur *et al.*, 2007b), was not significant in our sample sets (best haplotype $P = 0.28$, global $P = 0.34$). Similarly, we did not observe significant association of the four marker (rs10519613, g.96516, rs1057972, and rs10833) *IL15* haplotype in our sample sets (best haplotype $P = 0.37$, global $P = 0.52$), even though this haplotype was associated with both psoriasis and increased *IL15* transcriptional activity in the Chinese case–control study (Zhang *et al.*, 2007).

Next, we tested the three replicated SNPs in a fourth sample set consisting of 599 psoriasis cases and 299 controls. The *ADAM33* marker replicated (one-sided $P = 0.031$), and, although the other two markers were not significant in this sample set, the directionality of the odds ratios was the same as reported in the original sample sets (Table 3). A Mantel–Haenszel analysis of our four psoriasis sample sets combined, showed that all three SNPs were significant (one-sided $P < 0.05$). A meta-analysis of the *CDKALI* and *PTPN22* markers in our replication sample sets plus the original case–control reports showed that both were highly significant (rs6908425: $P = 1.57 \times 10^{-5}$ and rs3789604: $P = 3.45 \times 10^{-5}$). Because the initial study of *ADAM33* was family-based, we could not carry out a meta-analysis for rs597980.

DISCUSSION

These results suggest that variants in three distinct genes may be associated with psoriasis risk. Although evidence of replication for individual SNPs in our combined sample sets was modest (one-sided $P = 0.0057–0.015$), the overall observation is significant in the context of our study design—these three markers had false discovery rates < 0.15 suggesting at least two may be considered true positives. Furthermore, two of the three markers were highly significant in a meta-analysis of all sample sets combined ($P = 1.57 \times 10^{-5}$ and 3.45×10^{-5}). The observed effect sizes for the three variants, however, were modest, with odds ratios all less than 1.25. This is typical of other recently identified genetic variants that make

incremental contributions to disease risk in common, complex disorders (Wellcome Trust Case Control Consortium, 2007; Barrett *et al.*, 2008; Raychaudhuri *et al.*, 2008).

Given that all three variants are relatively frequent (control allele frequency >0.20), their population attributable risk cannot be discounted if these findings withstand replication in other sample sets. For example, assuming that the odds ratio and control allele frequency observed in the metaanalysis are correct, the allelic population attributable risk for the *CDKALI* marker would amount to 13.7%. Furthermore, carrying multiple-risk markers in these and the other four well-established genes, *HLA-C*, *IL12B*, *IL23R*, and *IL13/IL4* is expected to substantially augment an individual's susceptibility to psoriasis; conversely, individuals with multiple protective alleles may be at much reduced risk.

The association of these three markers with psoriasis further supports the observation of pleiotropic effects in inflammatory diseases—*ADAM33* has been proposed as a risk factor for asthma (Van Eerdewegh *et al.*, 2002), *CDKALI* for Crohn's disease (Wellcome Trust Case Control Consortium, 2007) and type 2 diabetes (Steinhorsdottir *et al.*, 2007), and *PTPN22* for rheumatoid arthritis, type I diabetes and others (Begovich *et al.*, 2004; Bottini *et al.*, 2004; Gregersen *et al.*, 2006). It should be noted, however, that the *PTPN22* variant associated with psoriasis risk is different from the major variant (R620W missense SNP) associated with rheumatoid arthritis and other diseases; previous studies have shown that R620W is not significantly associated with psoriasis in our sample sets (unpublished results) or other sample sets (Criswell *et al.*, 2005; Nistor *et al.*, 2005; Huffmeier *et al.*, 2006). These findings are consistent with evidence suggesting variants in noncoding regions of the *PTPN22* gene region are involved in psoriasis (Huffmeier *et al.*, 2006).

Interpretation of our negative results for the other putative psoriasis-risk variants should take into account various factors such as the overall sample size, marker effect sizes, the allele frequencies of the tested markers, and the possibility of genetic heterogeneity. Our three combined sample sets (1,448 cases and 1,385 controls) have >80% power to replicate allelic association for a marker with a 0.20 control allele frequency, as is the case for 11 out of the 13 markers tested here, and an odds ratio of 1.2. However, our three combined sample sets have less than 50% power to replicate markers with odds ratio of 1.1 or less, regardless of marker allele frequency. Not surprisingly, all three significant markers identified in this study had odds ratio > 1.1 in our sample sets.

In conclusion, our data suggest that three genes, *ADAM33*, *CDKALI*, and *PTPN22*, in addition to *HLA-C*, *IL12B*, *IL23R*, and *IL13/IL4*, may be psoriasis-risk factors. Given the modest effect sizes, further replication, followed by a meta-analysis, is required to confirm or refute these hypotheses and detailed fine mapping is required to pinpoint the causal variants. In addition, although we did not observe significant association of the other tested markers with psoriasis, we cannot rule out their involvement in the genetics of the disease, due to the modest power of our sample sets to detect small effect sizes. An unequivocal identification of unreported genetic risk factors should further our understanding of the underlying disease mechanism, provide fresh leads to drug discovery, and identify potential pharmacogenomic markers.

MATERIALS AND METHODS

Marker selection

The primary goal of this study was to replicate 15 genetic variants recently reported to be associated with psoriasis risk (see Table 1 for the complete list of SNPs).

ADAM33—Having confirmed the presence of a psoriasis susceptibility locus on chromosome 20p13 in a linkage study (Lesueur *et al.*, 2007a), Lesueur *et al.* (2007b) fine mapped a 17Mb region using a family-based association study and identified *ADAM33* as the putative psoriasis-risk gene. Five of the tested SNPs reached significance ($P=0.01-0.04$) and testing combinations of SNPs revealed a three-SNP haplotype that was highly significant ($P=0.0009$). Although these findings were not replicated in a second smaller family-based sample set (all $P>0.05$) (Lesueur *et al.*, 2007b), a recent French study replicated association of one *ADAM33* SNP, rs512625, with psoriasis (Siroux *et al.*, 2008).

IL15—Employing a candidate gene approach, Zhang *et al.* (2007) tested 12 SNPs in the *IL15* gene, which lies within the PSORS9 locus on chromosome 4q31.2–q32.1, in a Chinese case–control sample set (632 psoriasis patients/485 control subjects). Four markers were significant ($P<0.05$), with a reported 3'-untranslated region (UTR) SNP (g.96516A→T) showing the strongest association ($P_{\text{correction}}=0.00006$). Two haplotypes containing the minor T allele of g.96516 were highly correlated with disease susceptibility and increased *IL15* transcriptional activity. IL15, a proinflammatory cytokine affecting T-cell activation and proliferation, is involved in regulation of inflammatory events in several diseases including psoriasis (McInnes and Gracie, 2004). In addition, targeting the IL15 protein was efficacious in alleviating psoriasis pathology in an animal model (Villadsen *et al.*, 2003).

SPATA2—In a genome-wide association study testing 408,000 SNPs, Capon *et al.* (2008) identified strong association of a reported SNP, rs495337, with psoriasis risk ($P=1.4\times 10^{-8}$, 2,679 cases and 2,215 controls). rs495337 maps to the *SPATA2* transcript and is in perfect linkage disequilibrium with several SNPs in the adjacent *ZNF313* gene. On the basis of the association of rs495337 with *ZNF313* expression and a potential role for *ZNF313* in regulating T-cell activation, *ZNF313* was proposed as a risk factor for psoriasis.

CDKAL1, FLJ45139, and chr 1q24—Given that psoriasis and Crohn's disease share a common genetic etiology (Duerr *et al.*, 2006; Cargill *et al.*, 2007), Wolf *et al.* (2008) tested in their psoriasis sample set (1,256 cases/2,938 controls) 15 Crohn's disease-associated SNPs and reported that three may be involved in psoriasis (rs12035082 in 1q24, $P=0.009$; rs2836754 in *FLJ45139* on 21q22.2, $P=0.002$; rs6908425 in *CDKAL1* on 6p22.3, $P=0.00015$). We tested rs2836754 and rs6908425 and rs12037606, a proxy for rs12035802 ($r^2=1$, in the CEU samples; www.hapmap.org).

PTPN22—Smith and colleagues recently tested whether variants in *PTPN22*, a widely recognized risk factor for retinoic acid (Begovich *et al.*, 2004) and several other autoimmune diseases (Bottini *et al.*, 2004; Criswell *et al.*, 2005), were also associated with psoriasis (Smith *et al.*, 2008). Although the retinoic acid-associated rs2476601 (R620W) SNP was not

significant in their psoriasis sample set, agreeing with other reports (Criswell *et al.*, 2005; Nistor *et al.*, 2005; Huffmeier *et al.*, 2006), they found that two other SNPs, rs1217414 and rs3789604, were significantly associated with early onset disease ($P=0.003$ and 0.0002 , respectively; 647 cases vs 566 controls).

Clinical samples

Three white, North American psoriasis sample sets, totaling 1,448 individuals with dermatologist-confirmed psoriasis (cases) and 1,385 normal subjects (controls), have been described in detail elsewhere (Cargill *et al.*, 2007). Briefly, sample set 1, obtained from the University of Utah, consisted of 467 cases and 460 controls. Sample set 2, obtained from the Genomics Collaborative Division of SeraCare Life Sciences, consisted of 498 cases and 498 controls. Sample set 3 consisted of 483 cases and 427 control subjects; 293 of the cases and 292 of the controls were provided by Genomics Collaborative; BioCollections Worldwide provided the rest. All individuals were 18 years or older at the enrollment.

The fourth case–control sample set included 599 unrelated Caucasian patients of European descent recruited from outpatient clinics at the University of California, San Francisco and Washington University, St. Louis, MO. All subjects filled out a clinical questionnaire and received a skin examination by a dermatologist, who confirmed the diagnosis of plaque psoriasis. Controls ($n=299$) were unrelated white individuals of European descent recruited in San Francisco, who had no history of psoriasis, autoimmune disease, or cancer.

Clinical research was conducted according to the Declaration of Helsinki Principles. All protocols were approved by national and/or local institutional review boards and informed written consent was obtained from all subjects.

Genotyping

Genotyping of SNPs in sample sets 1–3 was carried out by allele-specific real-time PCR, with accuracy >99% (Chang *et al.*, 2008). For sample set 4, rs597980 (*ADAM33*) and rs6908425 (*CDKALI*) were genotyped by TaqMan, (Applied Biosystems, Foster City, CA, USA) and rs3789604 (*PTPN22*) by sequencing.

Statistical analysis

Hardy–Weinberg equilibrium testing was performed using the exact test of Weir (Weir, 1996). Allelic association of SNPs with psoriasis risk was determined by the χ^2 -test in individual sample sets and by meta-analysis using fixed effects of Mantel–Haenszel methods. Haplotypes were inferred from the genotypic data, and haplotype frequencies estimated and tested for association with disease status using a score test with haplotypes coded in an additive fashion (Schaid *et al.*, 2002). Power of replication was estimated using the PS:Power and Sample Size Calculation Program (<http://biostat.mc.vanderbilt.edu/wiki/bin/view/Main/PowerSampleSize>). False discovery rate (Benjamini and Hockberg, 1995), was estimated using one-sided P -values obtained in the combined sample sets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SNP	single-nucleotide polymorphism
UTR	untranslated region

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Table 1

Genotyped markers

Associated disease in prior studies	Publication	Putative risk gene/region	SNP ID	Chr	Position (bp) ¹	SNP type
Psoriasis	Lesueur <i>et al.</i> (2007b)	ADAM33	rs512625	20	3,596,378	Intergenic
			rs677044	20	3,597,431	3'-UTR ²
			rs2280089	20	3,598,127	Intron
			rs597980	20	3,599,165	Intron
			rs44707	20	3,599,226	Intron
	Zhang <i>et al.</i> (2007)	IL15	rs10519613	4	142,873,534	3'UTR
			g_96516	4	142,873,720	3'UTR
			rs1057972	4	142,873,882	3'UTR
			rs10833	4	142,873,997	3'UTR
	Capon <i>et al.</i> (2008)	SPATA2	rs495337	20	47,955,737	Synonymous
Psoriasis/Crohn's disease	Smith <i>et al.</i> (2008)	PTPN22	rs1217414	1	114,214,190	Intron
			rs3789604	1	114,156,465	Synonymous
			rs12037606	1	171,165,025	Intergenic
	Wolf <i>et al.</i> (2008)	CDKAL1	rs6908425	6	20,836,710	Intron
			rs2836754	21	39,213,610	Intron

SNP, single-nucleotide polymorphism; 3'-UTR, 3'-untranslated region.

¹ Positions according to genomic contig NT_011387.8 (Entrez Nucleotide) in the National Center for Biotechnology Information Genome Build 36.3.² 3' untranslated region.

Table 2

Association test of putative psoriasis risk markers in the three sample sets combined

Gene/region	SNP	Minor allele	Major allele	Case allele frequency	Control allele frequency	OR (95% CI)	Allelic P^1	FDR ²
ADAM33	rs512625 ³	A	G	0.298	0.310	0.94 (0.84–1.06)	0.176	0.286
ADAM33	rs677044	G	A	0.213	0.211	1.01 (0.89–1.14)	0.572	0.620
ADAM33	rs597980	A	G	0.475	0.450	1.10 (0.99–1.22)	0.030	0.136
ADAM33	rs44707	G	T	0.389	0.409	0.92 (0.82–1.02)	0.068	0.176
IL15	rs10519613	A	C	0.096	0.093	1.03 (0.86–1.23)	0.366	0.433
IL15	g-96516	T	A	0.0014	0.004	0.34 (0.11–1.09)	0.0580	0.176
IL15	rs1057972	T	A	0.472	0.476	0.98 (0.88–1.09)	0.626	0.626
SPATA2	rs495337	A	G	0.388	0.393	0.97 (0.88–1.09)	0.354	0.433
1q24	rs12037606	A	G	0.420	0.406	1.05 (0.95–1.17)	0.155	0.286
CDKAL1	rs6908425	T	C	0.200	0.220	0.88 (0.77–1.00)	0.031	0.136
FLJ45139	rs2836754	T	C	0.383	0.368	1.06 (0.95–1.18)	0.123	0.265
PTPN22	rs1217414	A	G	0.276	0.266	1.05 (0.93–1.18)	0.204	0.295
PTPN22	rs3789604	G	T	0.184	0.208	0.86 (0.75–0.98)	0.013	0.136

SNP, single-nucleotide polymorphism; FDR, false discovery rate.

Markers with $P < 0.05$ in boldface.

¹ One-sided, based on previous studies except for g.96516 whose allele frequencies were markedly different between the White and Asian populations.

² false discovery rate.

³ rs512625 was recently reported to be significant in another case-control study (Siroux *et al.*, 2008). A meta-analysis of this marker in our three sample sets and that of Siroux *et al.* showed that this SNP was not significant (Mantel-Haenszel $P_{\text{combined}} = 0.27$, $OR_{\text{combined}} = 0.94$ (95% CI: 0.85–1.05), Breslow-Day test for OR homogeneity $P = 0.99$).

Association test and meta-analysis of the three replicated markers with psoriasis risk in the fourth sample set and all case-control sample sets investigated

Table 3

Gene	SNP	Sample set	Case				Control				MAF	Allelic P ¹	OR (95%CI) ²	
			11	12	22	Sum	11	12	22	Sum				
ADAM33	rs597980 ³	SS1	98	243	117	458	0.479	105	217	136	458	0.466	0.287	1.05 (0.87–1.26)
		SS2	126	220	147	493	0.479	101	237	154	492	0.446	0.074	1.14 (0.95–1.36)
		SS3	105	240	137	482	0.467	82	208	136	426	0.437	0.099	1.12 (0.93–1.35)
		SS4	119	292	181	592	0.448	41	93	87	221	0.396	0.031	1.23 (0.98–1.54)
		SS1+2+3+4	448	995	582	2,025	0.467	329	755	513	1,597	0.442	0.0057	1.13 (1.02–1.24)
CDKAL1	rs6908425	SS1	21	135	309	465	0.190	26	150	281	457	0.221	0.052	0.82 (0.66–1.03)
		SS2	18	147	327	492	0.186	23	175	294	492	0.225	0.017	0.78 (0.63–0.98)
		SS3	18	179	285	482	0.223	26	130	270	426	0.214	0.686	1.05 (0.84–1.32)
		SS4	14	177	397	588	0.174	13	65	144	222	0.205	0.077	0.81 (0.62–1.07)
		SS1+2+3+4	71	638	1,318	2,027	0.192	88	520	989	1,597	0.218	0.010	0.87 (0.77–0.97)
UK ⁴	46	360	773	1,179	0.192	165	1,018	1,749	2,932	0.230	1.52E-04	0.79 (0.70–0.89)		
SS1+2+3+4+UK	117	998	2,091	3,206	0.192	253	1,538	2,738	4,529	0.226	1.57E-05	0.83 (0.76–0.90)		
PTPN22	rs3789604	SS1	10	136	315	461	0.169	23	152	284	459	0.216	0.0057	0.74 (0.58–0.93)
		SS2	21	161	311	493	0.206	17	177	298	492	0.214	0.321	0.94 (0.76–1.17)
		SS3	15	140	327	482	0.176	14	135	277	426	0.191	0.205	0.90 (0.71–1.14)
		SS4	14	159	379	552	0.169	13	52	154	219	0.178	0.341	0.94 (0.70–1.25)
		SS1+2+3+4	60	596	1,332	1,988	0.180	67	516	1,013	1,596	0.204	0.016	0.87 (0.77–0.98)
UK ⁵	23	199	613	835	0.147	84	765	1,621	2,470	0.189	9.94E-05	0.73 (0.63–0.86)		
SS1+2+3+4+UK	83	795	1,945	2,823	0.170	151	1,281	2,634	4,066	0.195	3.45E-05	0.81 (0.74–0.89)		

¹ Calculated by χ^2 method for individual sample sets and by Mantel Haenszel method for the combined sample sets; two sided for UK and SS1+2+3+4+UK and one sided for all other replication sample sets, individually or combined.

² Calculated by χ^2 method for individual sample sets and by Mantel Haenszel method for the combined sample sets.

³ Prior study used family-based samples; not included for meta-analysis.

⁴ Wolf *et al.* (2008).

⁵ Smith *et al.* (2008).