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Association mapping of the *PARK10* region for Parkinson's disease susceptibility genes

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Abstract

Background—Previous studies indicate that as many as six genes within the *PARK10* region (*RNF11*, *UQCRH*, *HIVEP3*, *EIF2B3*, *USP24*, *ELAVL4*) might modify susceptibility or age at onset in Parkinson's disease (PD).

Methods—We sought to identify new PD susceptibility genes and to validate previously nominated candidate genes within the *PARK10* region using a two-stage design. We used data from a large, publicly-available genome-wide association study (GWAS) in the discovery stage

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(n=2000 cases and 1986 controls) and data from three independent studies for the replication stage (total n=2113 cases and 2095 controls). Marker density was increased by imputation using HapMap3 and 1000 Genomes reference panels, and over 40,000 single nucleotide polymorphisms (SNPs) were used in the final analysis. The association between each SNP and PD was modeled using logistic regression with an additive allele dosage effect and adjusted for sex, age, and axes of geographical variation.

Results—Although the discovery stage yielded promising findings for SNPs in several novel genes, including *DAB1*, none of the results were validated in the replication stage. Furthermore, in meta-analyses across all datasets no genes within *PARK10* reached significance after accounting for multiple testing.

Conclusion—Our results suggest that common variation in the *PARK10* region is not associated with PD risk. However, additional studies are needed to assess the role of *PARK10* in modifying age at onset and to determine whether rare variants in this region might affect PD susceptibility.

Keywords

PARK10; Parkinson's Disease; Replication; GWAS

1. Introduction

Parkinson's disease (PD) is the second-most common neurodegenerative disorder with a lifetime risk estimated at 1.6% [1]. Linkage and association studies have implicated over 20 susceptibility loci for PD, though in many instances the specific disease gene has not been clearly identified [2, 3]. In 2002, two independent studies reported evidence of linkage to PD on chromosome 1p32; one to PD risk [4] and the other to age at onset [5]. This region, which was designated *PARK10*, spans 19.2 megabases (Mb) (40.2–59.4 Mb on NCBI build 36) and contains approximately 200 genes. Several subsequent studies [6–8] nominated potential PD genes within the *PARK10* region including the: (1) ring-finger protein 11 gene (*RNF11*), (2) ubiquinol-cytochrome c reductase hinge protein gene (*UQCRH)*, (3) human immunodeficiency virus enhancer-binding protein 3 gene (*HIVEP3*), (4) gamma-subunit of the translation initiation factor EIF2B gene (*EIF2B3*), (5) ubiquitin-specific protease 24 gene (*USP24*), and (6) embryonic lethal, abnormal vision, Drosophila-like 4 gene (*ELAVL4*). However, attempts to replicate these candidate genes have yielded mixed results [9–11] and no markers within the *PARK10* region have reached genome-wide significance in any of the recently published PD genome-wide association studies [3, 12–19]. Thus, there is considerable uncertainty as to whether the *PARK10* region actually harbors PD susceptibility genes.

We re-examined the *PARK10* region in the publicly available NeuroGenetics Research Consortium (NGRC) Genome-Wide Association Study (GWAS) dataset enriched with additional markers imputed from the HapMap 3 and 1000 Genomes reference panels. Furthermore, we utilized two other publicly available GWAS datasets [15, 18] and unpublished data from a third case-control study [20] for replication. Our primary goals were to identify new PD-associated genes that might have been previously missed due to low genotyping coverage, and to verify associations with the aforementioned candidate genes.

2. Methods

2.1 Studies

The discovery phase for novel risk variants used data from the NGRC Genome-Wide Association Study of Parkinson Disease: Genes and Environment (phs000196.v1.p1) with

2000 subjects with PD and 1986 controls that were recruited from movement disorder clinics in Oregon, Washington, Georgia, and New York [14]. All subjects were genotyped on the IlluminaHumanOmni1-Quad_v1-0_B array and data were downloaded from dbGaP. Details of the quality control processes employed in the analysis are provided (Appendix A. Supplementary methods).

The replication phase used two publicly available GWASs, the Center for Inherited Disease Research (CIDR) GWAS in Familial PD (phs000126.v1.p1) and the National Institute of Neurological Disorders and Stroke (NINDS) Genome-Wide Genotyping in PD Study (phs000089.v3.p2), and a population-based study of PD at the University of Washington and Group Health Cooperative (GHC-UW) [20]. Information on both the CIDR [15] and NINDS [18] GWAS datasets has been published elsewhere. Because controls for both GWASs came from the NINDS Human Genetics Repository (http://ccr.coriell.org/Sections/Collections/NINDS), we performed identity-by-descent (IBD)-estimation using 287,341 independent single nucleotide polymorphisms (SNPs) to elucidate any overlap in controls that showed evidence of being duplicates or were a result of cryptic relatedness (PI≥0.5). We found evidence that nine controls overlapped between the NINDS and CIDR GWAS datasets, and these individuals were subsequently omitted from the NINDS dataset. The GHC-UW sample consisted of 758 non-Hispanic, white subjects (321 cases, 437 controls) who were genotyped for 1,138 tagging SNPs spanning the *PARK10* region and 440 ancestry informative markers (AIMs) using custom Affymetrix GeneChip Universal 3K Tag Arrays. The AIMs were unlinked SNPs selected to distinguish intercontinental population structure [21, 22] as well as European substructure [23]. Before imputation, SNPs were omitted if Hardy-Weinberg equilibrium was violated ($P < 0.001$ using an exact test) in the combined sample or if the genotyping rate was less than 90%. The project was approved by the Veterans Affairs Puget Sound Health Care System and University of Washington institutional review boards, and all subjects provided written informed consent.

Patients in the NGRC, CIDR, and NINDS studies met UK PD Society Brain Bank clinical diagnostic criteria for PD [14, 15, 18]. Patients in the GHC-UW study met similar clinical diagnostic criteria for PD as previously described [20]. The age at onset of PD was similar across studies with the following mean +/− SD onset age: 58.3+/−11.9 years (NGRC), 61.9+/−10.9 years (CIDR), 58.4+/−13.2 years (NINDS). In the GHC-UW study, age at onset data were not collected, but the mean +/− SD age at diagnosis was 66.2 +/− 10.4 years.

2.2 Genotype enrichment and imputation

A subset of 499 subjects from the NGRC study population was previously genotyped using the same custom Affymetrix 3K Array as was used in the GHC-UW study. Prior to imputation, these genotype data were merged into the NGRC dataset using the default consensus genotype call approach in PLINK [24]. Additionally, standard data-cleaning methods (e.g. strand flipping) were performed. We then used IMPUTE2 [25] to enrich the *PARK10* region with imputed markers. To ensure that rare variants were adequately covered, we used two phased reference panels from both HapMap3 and the 1000 Genomes pilot data, with release dates of Feb 2009 and Jun 2010, respectively, and we imputed genotypes for every 5-Mb interval in the 40–60 Mb region of chromosome 1 for each study separately. We omitted SNPs with an information metric less than 0.30 and noted those SNPs with information metrics between 0.30 and 0.50. After genotype imputation, the number of SNPs ($N_{SNP\text{-}STUDY}$) analyzed in the *PARK10* region for the NGRC, CIDR, NINDS, and GHC-UW studies were: $N_{SNP\text{-}NGRC} = 43{,}799$, $N_{SNP\text{-}CIDR} = 43{,}243$, $N_{SNP\text{-}NINDS} = 43{,}362$ and $N_{SNP\text{-}GHC\text{-}UW} = 40{,}351$, respectively, with 43,744 SNPs common to two or more studies.

2.3 Statistical analysis

Failure to recognize population structure can lead to confounding results. Thus, we accounted for differences in ancestry between cases and controls in our analyses using a principal components analysis (PCA) approach as implemented in the EigenStrat program [26]. For the three GWASs, we obtained a subset of uncorrelated markers by pruning the genome-wide SNPs to approximate linkage equilibrium as described in the Supplement. These markers were then used to calculate the axes of geographical variance or principal components (PCs) that describe the genetic variation. The first 28, 10, and 9 PCs were found to be significant (Tracy-Widom *P*-value < 0.05) for the NGRC, NINDS, and CIDR studies, respectively. However, for the GHC-UW dataset, we used the 440 AIMs to perform PCA, and although Tracy-Widom statistics may not be applicable to AIMs, we conservatively chose the top six PCs (Tracy-Widom *P*-value < 0.05).

We used PLINK [24] to analyze the genotyped and imputed SNPs based on the genotype probabilities with an additive dosage model in a logistic regression analysis adjusted for sex, age, and the significant PCs from EigenStrat PCA analysis. The asymptotic *P*-value was obtained from the Z-test assessing the significance of the association with PD. SimpleM [27] was used to infer the effective number of independent tests (Meff) after accounting for LD between SNPs with a minor allele frequency (MAF) of at least 0.005; Meff was 15,572 in the NGRC study. Thus, after accounting for multiple testing using a Bonferroni adjustment on the effective number of tests, we set the significance threshold for the overall study to $P < 3.2 \times 10^{-6}$ (i.e., 0.05/15,572). However, in selecting SNPs from the discovery phase for replication we used a less stringent threshold of $P < 5 \times 10^{-4}$ to reduce the probability of false negative results. Additionally, we performed a meta-analysis for each SNP across all studies using the classical approach of pooling effect size estimates and standard errors using a random effects model in PLINK. Cochrane's Q statistic was used to test for the presence of heterogeneity, and I^2 was calculated to examine the degree of heterogeneity present, and values of 25%, 50%, and 75% generally represent low, moderate, and high levels of heterogeneity, respectively.

Power was calculated using Quanto (http://hydra.usc.edu/gxe) and assuming a 1.5% prevalence of PD, a significance of 5×10^{-4} and a rare variant under a log-additive genetic model with a minor allele frequency (MAF) of 0.05 and 0.25.

3. Results

In the NGRC dataset, SNPs in five genes (*DAB1*, *SLFNL1*, *OMA1*, *SSBP3*, and *AGBL4*) met the predefined, exploratory significance threshold of 5×10^{-4} (Figure 1). The two SNPs with the lowest *P*-values resided near *DAB1* (Table 1) (rs61781879, $P=1.4 \times 10^{-6}$; rs61781882, $P=1.8 \times 10^{-6}$). The next most significant marker occurred within *SLFNL1* (rs11576546, $P = 9.4 \times 10^{-5}$). In the NGRC dataset, we did not replicate the association findings of any of the previously nominated *PARK10* candidate genes (Table 2), though the *P*-values for two SNPs in *HIVEP3* approached the exploratory significance threshold (rs4600038, $P = 7.8 \times 10^{-4}$; rs6680824, $P = 9.3 \times 10^{-4}$). In the discovery phase for variants with a MAF of 0.05 and 0.25, there was at least 80% power to detect risk alleles with odds ratios (ORs) of 1.50 and 1.25, respectively, and protective alleles with ORs of 0.60 and 0.80, respectively.

Results from the replication phase for new variants are shown in Table 1. None of the SNPs discovered in the NGRC dataset were replicated in the CIDR, NINDS, or GHC-UW studies. Although two SNPs (rs4927084, rs2018903) in *SSBP3* were weakly associated with PD in the GHC-UW study, the direction of the effect was opposite to that seen in the NGRC study. Several of the imputed SNPs chosen for replication had marginal information metrics (0.3 –

0.5), including *DAB1* variants rs61781879 and rs61781882 (Table 1). In the meta-analysis, none of the SNPs examined were associated with PD ($P > 0.05$). However, we observed evidence of heterogeneity across studies as indicated by $I^2 > 50\%$ for all SNPs and a significant Cochran's Q statistic ($P_Q < 0.05$) for all but two SNPs (1-58580706 in *DAB1* and rs11209229 in *SLFNL1*).

We also examined previously nominated *PARK10* candidate genes in more detail. From each of these genes, we selected the two SNPs with the lowest *P*-values in the NGRC and candidate SNPs in previously published studies [7–11] to test for association with PD in the CIDR, NINDS, and GHC-UW datasets (Table 2). However, no significant associations were observed in any of the three studies or in the meta-analysis across studies. In the meta-analysis, there were varying levels of heterogeneity, with I^2 values ranging from 0–62%, but Cochran's Q statistic was not significant for any of the SNPs ($P_Q \geq 0.05$).

4. Discussion

We sought to identify PD susceptibility genes within the *PARK10* region using data on over 40,000 markers in a two-stage design. Despite promising results in the discovery phase for SNPs in several novel genes, especially *DAB1*, none of these findings were validated in the replication stage. Furthermore, in the meta-analyses across all datasets, no genes within *PARK10* reached significance after accounting for multiple testing. One consideration in interpreting the results observed for *DAB1* is that the top-ranked SNPs were all imputed and in most instances the information metric was between 0.30 and 0.50. Thus, findings for this gene might simply represent false positives due to inaccuracies in imputation.

Oliveira and colleagues performed association mapping of the *PARK10* region with 284 SNPs in 267 multiplex PD families [8]. Using both an orthogonal model (OM) and the Monks-Kaplan method (MKM) they observed an association with age at onset for two genes, *EIF2B3* (rs546354, $P_{OM} = 0.01$ and $P_{MKM} = 0.0004$) and *USP24* (rs287235, $P_{OM} = 0.001$ and $P_{MKM} = 0.004$). The authors also reported that SNPs in *HIVEP3* were associated with PD risk (rs648178, $P = 0.008$; rs661225, $P = 0.004$). *USP24* was later reported to associate with PD risk in a small case-control study [11]. In a sample containing both multiplex and singleton PD families (n=643), Noureddine et al reported an association between *ELAVL4* (located within the *PARK10* region) and age at onset (rs967582, $P = 0.006$) but not PD risk [7]. Subsequent attempts to replicate this finding in case-control studies have yielded mixed results. Markers within *ELAVL4* were found to associate with PD risk in the GenePD Study [9] and in an Irish PD cohort [10], but not in case-control series from Norway [10] or the United States [10]. Two genes, *RNF11* and *UQCRH*, have gained consideration as *PARK10* candidate genes based on indirect evidence. In a comprehensive analysis of gene expression patterns in substantia nigra, both genes were highly differentially expressed in PD patients versus controls (*RNF11*, $P = 8.9 \times 10^{-7}$; *UQCRH*, $P = 3.0 \times 10^{-6}$). Furthermore, *RNF11* is expressed at high levels in neurons and is contained within Lewy bodies [28]. However, SNPs in these two genes were not associated with PD risk or age at onset in the study by Oliveira and colleagues [8] and to our knowledge these genes have not been included in other published candidate gene analyses. Subsequent to the aforementioned studies, a number of PD GWASs have been published. Most focused on PD risk [12–19] but one examined age at onset [29]. However, no genes within the *PARK10* region reached genome-wide significance or were among the highest ranking genes listed in any study.

Overall, we did not observe evidence of association with PD risk for any of the previously nominated *PARK10* candidate genes (Table 2). There are several possible explanations for our failure to replicate these findings. First, because our study populations included only

unrelated cases, we chose to test for association with risk but not age at onset. Using this approach we might have missed genes that primarily modify age at onset but not susceptibility. Second, our study might have lacked adequate power to detect risk alleles of small effect or of low frequency. This limitation is especially relevant for rare variants that were imputed, as imputation accuracy tends to be lower for low frequency markers. Third, the subjects used to generate all of the datasets except CIDR represented a mixture of familial and sporadic PD which might have confounded results if the effects of *PARK10* variants are largely confined to familial PD. In contrast, the study which provided the most robust evidence in favor of specific candidate genes within the *PARK10* region utilized only multiplex PD families [8]. However, there is evidence to suggest that familial and sporadic PD share common genetic pathways in many instances [30]. Finally, it is possible that previous studies reporting that variants in the *PARK10* region affect PD risk or age at onset simply represent spurious findings.

Our results suggest that common variation in the *PARK10* region is not associated with PD risk. However, additional studies are needed to assess the role of *PARK10* in modifying age at onset and to determine whether rare variants in the *PARK10* region affect PD susceptibility. Family-based analyses utilizing whole exome or whole genome sequencing and possibly focusing on pedigrees with evidence of linkage to the region might have the highest likelihood of success.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary methods

Supplementary methods related to this project can be found online.

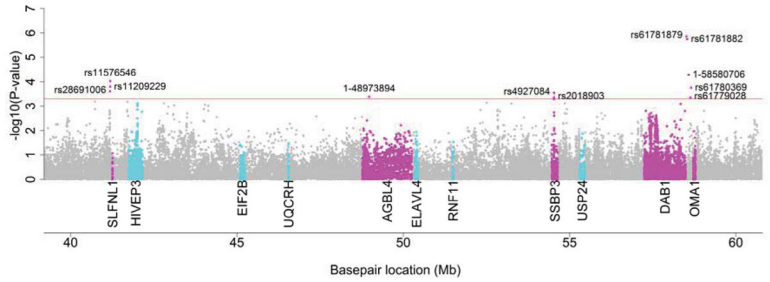

Figure 1. Manhattan plot of the *PARK10* region in the discovery phase

Each dot represents $-\log_{10}(P\text{-value})$ (y-axis) for a given SNP at a given location in 10^6 base pairs (Mb) in the *PARK10* region on chromosome 1 (x-axis). SNPs above the exploratory significance threshold ($P < 5 \times 10^{-4}$) are individually labeled. Grey dots represent SNPs from genes lacking any significant markers. SNPs from novel genes having one or more markers above the threshold are indicated by magenta dots. Cyan dots indicate SNPs from previously nominated candidate genes.

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Table 1

Association results for novel *PARK10* genes identified in the discovery phase

					Discovery				Replication				Meta-Analysis			
					NGRC (2000 cases/1986 controls)		GHC-UW (316 cases/436 controls)		CIDR (857 cases/867 controls)		NINDS (940 cases/ 792 controls)		All Studies (4113 cases/4081 controls)			
Gene	**SNP**	**Position**[a]	**MA**[b]	**MAF**[b]	**OR(95%CI)**	***P***	**OR(95%CI)**	***P***	**OR(95%CI)**	***P***	**OR(95%CI)**	***P***	**OR_R**	**P_R**	**P_Q**	**I^2**
DAB1	rs61781879	58514900	C	.04	.35(.23,.53)	1.4×10^{-6}	.51(.17,1.49)	.22	1.62(.78,3.37)	.20	.79(.45,1.39)	.41	.68	.28	.003	79
	rs61781882	58535050	T	.04	.35(.23,.54)	1.8×10^{-6}	.50(.17,1.47)	.21	1.6(.77,3.31)	.21	.79(.45,1.39)	.41	.68	.28	.003	78
	1-58580706	58580706	G	.02	.44(.29,.65)	5.2×10^{-5}	.66(.27,1.61)	.36	1.05(.54,2.01)	.89	.83(.47,1.46)	.52	.68	.08	.093	53
SLFNL1	rs11576546	41189495	G	.21	.78(.68,.88)	9.4×10^{-5}	.89(.68,1.16)	.38	1.09(.91,1.32)	.35	.83(.70,1.00)	.05	.88	.12	.031	66
	rs11209229	41187945	G	.20	.78(.69,.89)	1.6×10^{-4}	.87(.66,1.14)	.32	1.08(.89,1.3)	.44	.84(.71,1.01)	.06	.88	.09	.056	60
	rs28691006	41183208	C	.21	.80(.71,.90)	2.5×10^{-4}	.89(.69,1.15)	.39	1.09(.91,1.31)	.33	.84(.71,1.00)	.05	.89	.13	.041	64
OMA1	rs61780369	58653409	T	.02	.39(.23,.63)	1.8×10^{-4}	.60(.21,1.68)	.33	1.99(.73,5.4)	.18	.62(.29,1.33)	.22	.67	.24	.039	64
	rs61779028	58631461	A	.02	.50(.34,.73)	4.4×10^{-4}	.82(.33,2.03)	.67	1.42(.69,2.92)	.34	.96(.56,1.66)	.89	.82	.43	.046	63
SSBP3	rs4927084	54532654	G	.30	1.21(1.09,1.34)	2.9×10^{-4}	.77(.61,.96)	.02	1.05(.9,1.22)	.56	.96(.82,1.11)	.57	1.00	1.00	.001	81
	rs2018903	54531693	C	.30	1.21(1.09,1.34)	4.4×10^{-4}	.77(.61,.96)	.02	1.05(.9,1.23)	.55	.95(.82,1.11)	.55	1.00	.99	.001	81
AGBL4	rs72904830[c]	48973894	A	.02	.41(.25,.68)	4.1×10^{-4}	-	-	1.48(.64,3.44)	.36	.75(.41,1.36)	.35	.72	.35	.029	72

CI, confidence interval; OR, odds ratio; OR_R, pooled odds ratio for random effects model; P, *P*-value corresponding to *OR*; P_R, *P*-value corresponding to OR_R in random effects model; P_Q, *P*-value for Cochran's Q statistic for heterogeneity; I^2, percentage of the total variability in a set of effect sizes due to heterogeneity; MA, minor allele; MAF, minor allele frequency; SNP, single-nucleotide polymorphism

Results within grey cells are for SNPs with an information metric between 0.30 and 0.50. The information metric is a measure of the SNP imputation certainty ranging from 0 to 1 with increasing certainty.

[a] Based on NCBI build 36.

[b] In the NGRC study.

[c] The results for rs72904830 in the GHC-UW study were not shown because the information metric was less than 0.20, and the resulting meta-analysis only used results from the other three studies.

Table 2

Association results for previously nominated *PARK10* candidate genes

					Discovery		Replication						Meta-Analysis			
					NGRC (2000 cases/1986 controls)		GHC-UW (316 cases/436 controls)		CIDR (857 cases/867 controls)		NINDS (940 cases/ 792 controls)		All Studies (4113 cases/ 4081 controls)			
Gene	**SNP**	**Position**[a]	**MA**[b]	**MAF**[b]	**OR(95%CI)**	**P**	**OR(95%CI)**	**P**	**OR(95%CI)**	**P**	**OR(95%CI)**	**P**	**OR_R**	**P_R**	**P_Q**	**I^2**
HIVEP3	rs4600038[c]	42007887	A	0.42	.85(.77,.93)	7.8×10^{-4}	1.02(.82,1.27)	.84	1.00(.86,1.18)	.96	.96(.82,1.11)	.56	.93	.16	.16	41
	rs6680824[c]	42008591	T	0.45	1.17(1.07,1.29)	9.3×10^{-4}	.99(.81,1.22)	.93	1.03(.88,1.19)	.73	1.02(.89,1.18)	.75	1.08	.09	.22	32
	rs661225[d]	42082752	G	0.05	.98(.82,1.17)	.80	.88(.71,1.09)	.23	1.04(.90,1.21)	.58	1.04(.91,1.20)	.55	1.00	.94	.54	0
	rs648178[d]	41774750	G	0.10	.99(.88,1.11)	.81	.93(.74,1.17)	.55	.97(.81,1.15)	.73	1.03(.88,1.22)	.68	.99	.75	.90	0
ELAVL4	rs2480684[c]	50392177	G	0.29	.84(.73,.96)	.01	.97(.79,1.20)	.79	.92(.74,1.13)	.42	1.04(.85,1.27)	.73	.92	.08	.33	12
	rs7532927[c]	50397630	G	0.28	1.15(1.03,1.28)	.02	1.09(.83,1.42)	.54	1.11(.94,1.32)	.22	.98(.84,1.16)	.85	1.10	.02	.51	0
	rs967582[d]	50354759	C	0.35	1.07(.97,1.18)	.19	.84(.67,1.04)	.11	1.02(.88,1.18)	.81	.89(.77,1.03)	.13	.97	.58	.08	55
USP24	1-55362603[c]	55362603	C	0.05	.77(.62,.96)	.02	.80(.46,1.39)	.42	.91(.63,1.34)	.64	1.10(.78,1.54)	.59	.86	.08	.38	3
	rs17111652[c]	55363053	T	0.05	.77(.62,.96)	.02	.76(.45,1.28)	.30	.94(.67,1.32)	.72	1.13(.82,1.56)	.45	.89	.21	.25	28
	rs287235[d]	55451087	G	0.24	1.03(.93,1.15)	.56	1.11(.87,1.42)	.41	.99(.84,1.17)	.94	.90(.76,1.06)	.19	1.00	.99	.43	0
	rs1165226[d]	55380593	C	0.38	.99(.90,1.09)	.82	1.08(.88,1.34)	.46	1.00(.86,1.16)	1	.90(.78,1.04)	.17	.98	.57	.53	0
RNF11	1-51505913[c]	51505913	T	0.01	1.85(1.06,3.22)	.03	.26(.05,1.40)	.12	2.73(1.04,7.15)	.04	1.37(.6,3.11)	.46	1.50	.21	.11	50
	rs72692296[c]	51500183	T	0.01	.55(.31,1.00)	.05	.79(.24,2.59)	.70	.67(.33,1.37)	.27	1.11(.47,2.59)	.81	.70	.06	.62	0
UQCRH	rs55762739[c]	46554315	T	0.04	1.38(1.02,1.86)	.04	1.19(.5,2.82)	.70	1.43(.87,2.34)	.16	.82(.49,1.36)	.44	1.23	.09	.34	11
	1-46545090[c]	46545090	G	0.01	.65(.39,1.08)	.09	2.45(.93,6.5)	.07	1.63(.80,3.35)	.18	1.14(.58,2.23)	.71	1.20	.52	.05	62
EIF2B3	1-45102457[c]	45102457	T	0.02	1.54(1.02,2.33)	.04	1.35(.36,5.08)	.66	.76(.35,1.65)	.49	1.01(.56,1.83)	.96	1.23	.19	.38	2
	rs72214904[c]	45139896	T	0.01	1.96(1.01,3.79)	.05	.17(.04,.83)	.03	1.33(.59,3.00)	.49	1.63(.63,4.20)	.31	1.17	.69	.05	62
	rs546354[d]	45204251	G	0.18	.98(.87,1.11)	.77	1.09(.83,1.43)	.53	1.11(.92,1.34)	.28	.94(.79,1.13)	.54	1.01	.84	.58	0

CI, confidence interval; OR, odds ratio; OR_R, pooled odds ratio for random effects model; P, *P*-value corresponding to *OR*; P_R, *P*-value corresponding to OR_R in random effects model; P_Q, *P*-value for Cochran's Q statistic for heterogeneity; I^2, percentage of the total variability in a set of effect sizes due to heterogeneity; MA, minor allele; MAF, minor allele frequency; SNP, single-nucleotide polymorphism

Results within grey cells are for SNPs with an information metric between 0.30 and 0.50. The information metric is a measure of the SNP imputation certainty ranging from 0 to 1 with increasing certainty.

[a] Based on NCBI build 36.

[b] In the NGRC study.

[c] Among the top two SNPs for the corresponding gene in the discovery phase.

[d] SNP selected from previous candidate gene studies [7–11]. Note that *RNF11* and *UQCRH* were nominated as candidate genes based on results of a gene expression analysis [6] and thus for these two genes no SNPs were available for selection.