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Vitamin D Receptor Gene as a Candidate Gene for Parkinson Disease

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Summary

Vitamin D and vitamin D receptor (*VDR*) have been postulated as environmental and genetic factors in neurodegeneration disorders including multiple sclerosis (MS), Alzheimer disease (AD), and recently Parkinson disease (PD). Given the sparse data on PD and *VDR*, we conducted a two-stage study to evaluate the genetic effects of *VDR* in PD. In the discovery stage, 30 tagSNPs in *VDR* were tested for association with PD risk as a discrete trait and age-at-onset of PD as a quantitative trait in 770 Caucasian PD families. In the validation stage, 18 *VDR* SNPs were tested in an independent Caucasian cohort (267 cases and 267 controls) constructed from a genome-wide association study (GWAS). In the discovery dataset, SNPs in the 5' end of *VDR* were associated with both risk and age-at-onset with more significant evidence of association with age-at-onset (nominal $p=0.0008$ for the most significant SNPs). These SNPs were also associated with AD in a recent GWAS. In the validation dataset, SNPs in the 3' end of *VDR* were associated with age-at-onset (nominal $p=0.003$ for the most significant SNPs but not risk). The most significant 3' end SNP has been associated with both MS and AD. Our findings suggest *VDR* as a potential susceptibility gene and support an essential role of vitamin D in PD.

Keywords

VDR; vitamin D; Parkinson Disease; genetics; age-at-onset

INTRODUCTION

Parkinson disease (PD) is a progressive neurodegenerative disorder that affects roughly 1.5 million people in the US. The Mendelian forms of PD comprise <10% of all cases and involve well-defined exonic mutations in the genes *PARK2*, *SNCA*, *DJI*, *PINK1*, *ATP13A2* and *LRRK2*. The majority of PD cases result from complex interplay between environmental and genetic factors (Thomas, Beal 2007). Several genetic risk factors and gene-environment interactions for PD have been reported by us and others (Hancock et al. 2006, Li et al. 2003, Oliveira et al. 2005, Mizuta et al. 2008, van der Walt et al. 2004, van der Walt JM et al. 2005, McCulloch et al. 2008, Maraganore et al. 2006, Mizuta et al. 2006, Winkler et al. 2007, Hancock et al. 2008b). Vitamin D level is an environmentally modifiable factor as it is largely determined by diet and sunlight exposure. The effects of

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vitamin D and genetic variants in vitamin D receptor (VDR) gene have recently gained interest in PD and neurodegenerative research in general (Evatt et al. 2008, Knekt et al. 2010, Smolders et al. 2009). It was first noted in Japan that PD patients had lower serum vitamin D levels and higher prevalence of vitamin D deficiency than their age-matched controls (Sato et al. 2005). This observation was recently confirmed in a European Caucasian population (Evatt et al. 2008). In a longitudinal study of more than 3000 participants in Finland, higher serum vitamin D level was associated with reduced risk for PD: people in the highest quartile had one third of the risk comparing to people in the lowest quartile (Knekt et al. 2010). The serum vitamin D level was also negatively correlated with PD severity as measured by Hoehn and Yahr stages and motor symptom as measured by the motor part of the Unified Parkinson's Disease Rating Scale III (UPDRS III) (Sato et al. 2005, Sato, Kikuyama & Oizumi 1997).

To exert its biological functions, vitamin D is first converted to the active metabolite 1,25-dihydroxy vitamin D3. Upon binding to 1,25-dihydroxy vitamin D3, VDR is activated and interacts with vitamin D responsive elements in the promoters of vitamin D target genes to regulate their expression (Garcion et al. 2002). VDR is the primary mediator of vitamin D's biological actions. VDR and 1 α -hydroxylase, an essential enzyme to convert vitamin D to 1,25-dihydroxy vitamin D3 are expressed in human brain. Within the brain, the highest expression was found in hypothalamus and in the large neurons (likely to be the dopaminergic neurons) of the substantia nigra (SN) (Eyles et al. 2005). The expression pattern of VDR and 1 α -hydroxylase supports an important role of vitamin D in the etiology of PD. In addition, *VDR* null mice have impaired locomotor activity (Burne et al. 2005). Recently, the expression level of *VDR* mRNA was identified as a potential blood biomarker for PD (Scherzer et al. 2007).

Genetic studies on *VDR* polymorphisms also have suggested involvement of *VDR* with several neurodegenerative diseases, including multiple sclerosis (MS) and Alzheimer disease (AD). Motivated by the striking correlation between MS incidence rates and latitude, vitamin D status and *VDR* polymorphisms have been an active research topic in MS. SNPs in *VDR* have been associated with both MS risk and degree of disability after disease onset (Smolders et al. 2009). In AD, one candidate gene study reported a significant association at the 3' end of *VDR* in a Turkish population (Gezen-Ak et al. 2007). A recent genome-wide association study (GWAS) of late-onset AD has reported strong evidence for association in a cluster of SNPs near the 5' end of *VDR* in a sample of non-Hispanic Caucasians. (Beecham et al. 2009) (Beecham GW, Martin ER, Slifer MA, Gilbert JR, Haines JL, Pericak-Vancem MA 2009). In PD, Kim et al. examined the BsmI polymorphism (rs1544410) in a Korean population and found that the *b* allele was overrepresented in 85 PD patients compared to 231 controls (Kim et al. 2005). Given the growing body of evidence for vitamin D and VDR's involvement in several neurodegenerative disorders including PD, and the lack of any published study evaluating association between *VDR* and PD in Caucasians, we sought to thoroughly examine *VDR* polymorphisms in a large Caucasian sample of PD families and validate the association using publicly-available GWAS data.

MATERIALS AND METHODS

Subjects

Affected individuals and family members were collected by the Morris K. Udall Parkinson Disease Research Center of Excellence (PDRCE) at Duke University and then at the University of Miami (J.M. Vance, PI), and the 13 centers of the Parkinson Disease Genetics Collaboration. A standard clinical evaluation has been described elsewhere (Hancock et al. 2006). Individuals were classified as affected if he or she had at least two cardinal signs of PD (resting tremors, rigidity, and bradykinesia), asymmetry of symptom onset, and absence

of atypical signs. Unaffected individuals had no signs of PD. Individuals who showed only one cardinal sign and/or atypical signs were classified as unclear and were not used in the final analysis. Age-at-onset was defined as the age at which affected individuals recalled the development of one of the cardinal signs. We used denature HPLC, sequencing and genotyping to screen probands from all families for exonic mutations in *PARK2*. Forty-two families carrying *PARK2* mutation were excluded from the analysis. We also screened the proband of all families for the G2019S mutation in *LRRK2* and the N370S and 84 GG mutations in *GBA*. Given the low prevalence of those mutations in our dataset (2% for G2019S, and less than 1% for *GBA* mutations) and therefore small impact of those mutations, we did not exclude additional families based on *LRRK2* and *GBA* screening. To reduce population substructure, only non-Hispanic Caucasian families (by self-report) were used in the statistical analysis. The final family dataset used in the analysis included 770 families comprising 1,068 affected individuals, 1,282 unaffected relatives and 436 individuals with unclear PD status. These 436 individuals were used to infer genotype for ungenotyped parents but were not used directly in the association analyses. All individuals or their legal representative gave informed consent prior to this study. All ascertaining protocols were approved by institutional review board of PDRCE and each of 13 centers of the Parkinson Disease Genetics Collaboration (Oliveira et al. 2003).

SNP selection and genotyping

We used UCSC genome browser (www.genome.ucsc.edu), and the HapMap project (www.hapmap.org) to identify SNPs in and around *VDR*. TagSNPs (r^2 threshold of 0.8) with a minor allele frequency 5% in Caucasians and all validated exonic SNPs were examined. Genomic DNA was extracted from peripheral blood using the PureGene system (Gentra systems). We genotyped all SNPs using the Taqman Allelic DiscriminationR assay (Applied Biosystems) as described before (Hancock et al. 2006). All SNPs examined were successfully genotyped for 95% or more of the individuals in the study.

GWAS dataset

To further validate the association between *VDR* SNPs and PD AAO (the most significant finding in our family study), we examined publically available GWAS datasets. Three GWAS on PD have been deposited in the db Genotypes and Phenotypes (dbGAP) database (<http://www.ncbi.nlm.nih.gov/sites/entrez?dp=gap>): the National Institute of Neurological Disorders and Stroke (NINDS) study, the Progeny/GenePD study and the Linked Efforts to Accelerate Parkinson's Solutions (LEAPs). The Progeny/GenePD study have recently published a genome-wide analysis on AAO (Latourelle et al. 2009). No evidence for association was found in or near *VDR* (Supplemental Materials of Latourelle et al). The SNPs used in the LEAPs study is sparse (<200,000 SNP) and less informative (uniformly spaced). Therefore, the LEAPs GWAS data are not suitable for reliable imputation and comparison with our dataset. Genotype and phenotype data for the NINDS study were downloaded from dbGAP database. Detailed data cleaning has been reported elsewhere (Edwards et al. 2010). Briefly, imputation of SNP genotypes was performed using Impute (Marchini et al. 2007). Samples with genotyping efficiency < 0.98 and SNPs with genotyping call rate < 0.98 were removed from analysis. In addition, SNP with MAF < 0.01 or HWE $p < 10^{-7}$, were excluded (Edwards et al. 2010).

Statistical Analysis

Tests for deviations from HWE were performed using Genetic Data Analysis software. HaploView software (Barrett et al. 2005) was used to estimate linkage disequilibrium (LD) between SNPs. Family-based association analyses were performed using the test for association in the presence of linkage (APL) which infers genotypes of ungenotyped parents and therefore utilizes all families, including singleton and multiplex families, in the analysis

(Martin et al. 2000). The Monks-Kaplan method was used to evaluate association with age-at-onset (AAO) as a quantitative trait (Monks, Kaplan 2000). To explore potential genetic heterogeneity introduced by different AAO, we also stratified the dataset based on AAO for analysis of PD risk using APL. In order to have well-powered subsets, we started the stratification analysis by using the mean AAO of PD, i.e. AAO of 60, to define earlier and later onset subsets. (Destefano et al. 2002, Maher et al. 2002). Different AAO cutoff was explored to further examine the effect of AAO after the initial analysis. A similar strategy and AAO cutoff was implemented by Rocca and colleagues in their efforts to evaluate possible genetic heterogeneity in PD (McDonnell et al. 2006). For the GWAS dataset, linear regression analysis was used to test association between SNP genotypes and AAO using PLINK version 1.06 (Purcell et al. 2007).

To correct for multiple testing of SNPs in the gene, we applied SimpleM proposed by Gao et al. (Gao, Starmer & Martin 2008). This method takes into account of the non-independence between SNPs due to linkage disequilibrium (LD) and infers the number of independent tests such that a standard Bonferroni correction can be applied to correct for multiple testing.

RESULTS

The *VDR* gene has nine exons and multiple alternative first exons (Figure 1). Thirty tagSNPs within the *VDR* exonic boundaries and the 5 kilobase (kb) flanking regions were genotyped to cover most of the common genetic variations surrounding *VDR* (Figure 1). Using the SimpleM test, the effective number of independence test was reduced from thirty SNPs to twenty four. One coding SNP in exon 9 (rs731236) is in perfect LD ($r^2=1$) with the BsmI polymorphism previously reported by Kim et al (Kim et al. 2005). Therefore, rs731236 was used as the surrogate for the BsmI polymorphism. LD between the thirty SNPs is shown in Figure 2.

SNP associations with AAO as a quantitative trait (Table 1) and with risk as a discrete trait (Figure 3) were evaluated using family-based association tests. The AAO analysis revealed strong evidence of association at several SNPs with the most significant association at rs4334089 (nominal $p=0.0008$, corrected $p=0.02$, Table 1). The risk analysis found marginal evidence for association at rs2853559 (nominal $p=0.02$), which was not significant after multiple testing correction (Figure 3). Given the strong effect of AAO, we further examined SNP association with risk in subsets with different AAO. Using AAO of 60 as the cutoff value, the overall family dataset was stratified into 459 earlier onset families and 311 later onset families. Five SNPs were significantly associated with PD risk in the earlier onset subset (nominal $p<0.05$) but none in the later onset subset (Figure 3). All five SNPs overlapped with the significant SNPs in AAO analysis including rs4434089. Further stratification using younger AAO (AAO<40) did not reveal any significant results (data not shown), probably due to the small sample size (78 families with AAO<40). The previously reported association with PD at BsmI polymorphism was not significant in any analysis as indicated by association tests at rs731236.

All significant SNPs in the family dataset are located in the 5' end of the gene. The majority of them are located in the intron 1A_1B and intron 1B_1C, between the alternative exon 1A, 1B, 1C that generate alternative splicing isoforms of *VDR* (Figure 1). This cluster of SNPs are in moderate LD between each other (pairwise $r^2=0.14$ to 0.74 to rs4334089, Figure 2). Haplotype analysis of these 5'end SNPs did not define a haplotype that could explain the association better than single SNP analysis (data not shown).

Given the association between *VDR* and AAO in our family dataset, we further tested the association using the NINDS GWAS data deposited in dbGAP. Eighteen SNPs in and around *VDR* were either genotyped or imputed in the NINDS dataset (N=534). Sixteen of them overlapped with the SNPs studied in the family dataset, either by the SNP itself or by a tagSNP. The effective number of independence test as estimated by SimpleM for the eighteen SNPs is fifteen. In the NINDS dataset, three SNPs were significantly associated with AAO (Table 2) but none was associated with PD risk (data not shown). The strongest association was found at rs7968585 (nominal $p=0.003$, corrected $p=0.045$), which remained significant after correction for multiple testing in the NINDS dataset. None of the 5' end SNPs or SNPs in LD with them was significant in the NINDS dataset.

DISCUSSION

We conducted a comprehensive genetic analysis of *VDR* in PD. Previous studies of *VDR* in general have focused mainly on four restriction fragment length polymorphisms (RFLPs): TaqI (rs731236), ApaI (rs7975232), BsmI (rs1544410) and FokI (rs10735810) (Niino et al. 2000, Partridge et al. 2004, Tajouri et al. 2005, Mamutse et al. 2008, Uitterlinden et al. 2004). Herein, we systematically chose tagSNPs which cover all common variants in and around *VDR*, including the four previously described RFLPs. We examined these SNPs in a large dataset of Udall PD families and validated the association in the NINDS GWAS case-control cohort. Since a genetic component for the age-dependent penetrance of PD has been demonstrated (Destefano et al. 2002, Maher et al. 2002, Li et al. 2002), we also analyzed SNP association with AAO in addition to risk. Evidence for association between PD AAO and *VDR* SNPs were found in both family dataset and case-control cohort. .

The significant SNPs in the NINDS dataset are not in LD with the significant SNPs in the Udall family dataset, suggesting allelic heterogeneity, which is not unexpected for complex diseases (Schrauwen et al. 2009, Horne et al. 2007). The associations at different markers could be related to the same one or more underlying causative variants yet to be identified, although the significant markers themselves are not in strong LD with each other. Alternatively, these findings could suggest each of the significant markers or polymorphisms in LD with them has a distinct effect on the *VDR* gene expression/function (as discussed below), but these functional changes lead to the same phenotype.

The most significant SNP in our family study, rs4334089, is also associated with increased AD risk in a recent GWAS of AD (Beecham et al. 2009, Gilbert et al. 2009). The most significant SNP in the validation NINDS dataset, rs7968585, is in high LD with the ApaI polymorphism ($r^2=0.92$), which has been associated with AD risk in a Turkish cohort (Gezen-Ak et al. 2007) and MS risk in multiple studies (Smolders et al. 2009). The mechanisms underlying the association between *VDR* SNPs and multiple neurodegenerative diseases are not clear. Given that vitamin D is a well-documented anti-inflammatory molecule (Garcion et al. 2002), one explanation could be the inflammatory pathways that have been reported to be important in all three disorders. Another possibility is related to *VDR*'s role as a transcription factor. In that role, *VDR* regulates the transcription of many genes that are implicated in different diseases. The AD and MS studies corroborate the association we found in PD and suggest that the significant SNPs in *VDR* have functional consequences contributing to inter-individual variations of disease susceptibility.

In our family dataset, all the significant SNPs located in introns are between the alternatively spliced first exons, which generate alternative transcripts with different 5' untranslated region (UTR) (Figure 1). Although the functions of alternative transcripts of *VDR* in brain have not been extensively studied, a potential mechanism underlying the intronic SNP association is the SNP-mediated allelic-specific alternative splicing. Indeed, we have

observed this phenomenon in a previous study on coronary artery disease. In the limbic system associated membrane protein (LSAMP) gene, we have found that a risk haplotype located with the intron between alternative exon 1A and 1B was correlated with preferred usage of exon 1A, whose expression was associated with higher atherosclerosis burden (Wang et al. 2008). In the NINDS dataset, the significant SNP is in strong LD with the 3' UTR SNP rs739837. 3'UTR polymorphism, when located within miRNA target site, can modulate miRNA binding efficiency and affects translation/transcription of the gene. We have shown this is the case for the FGF20 gene (Wang G et al. 2008). We did not find any predicted miRNA binding site around rs739837 but we cannot exclude the existence of such a site unless the entire 3'UTR of *VDR* is carefully characterized by functional tests.

Although we did not replicate the BsmI polymorphism previously reported in a Korean cohort (Kim et al. 2005) and no evidence for association was reported for PD AAO near *VDR* in the Progeny/GenePD GWAS study (Latourelle et al. 2009), the strength of our study lies in providing evidence for association in the *VDR* gene in two independent datasets. It has been shown that any replications considerably increase the positive predictive value of a research finding despite negative results in replication efforts (Moonesinghe, Khoury & Janssens 2007). An important factor that could influence the effect size of *VDR* polymorphism and therefore association result is the vitamin D status. It has been found that vitamin D status modulated the association between *VDR* polymorphisms and type I diabetes mellitus incidence. The odds ratio of the risk allele increased with higher vitamin D level in the studied population (Ponsonby et al. 2008). It has been speculated that a poor vitamin D status would outpace the effect of *VDR* polymorphism and the *VDR* polymorphisms only manifest phenotypic variations in the presence of certain vitamin D level. This notion seems to be supported by the genetic studies in MS: positive association between *VDR* and MS was found in the studies conducted in regions with lower latitude but not in regions with higher latitude (Smolders et al. 2009). Therefore, incorporating vitamin D level in future study is crucial to fully characterize the genetic effects of *VDR* polymorphisms in PD.

In the family dataset, we found evidence for association with AAO. However, the association was not detected in our case-control cohort constructed using probands and unrelated controls from the family dataset (Edwards et al. 2009). This might be attributed to the different study design or properties of the test statistics: family-based associations versus case-control association. It is worthy pointing out that many of our initial reports of association with AAO in our family dataset have been replicated by other groups as risk associations, such as the ELAVL4, GSTO1 and USP24 genes (Oliveira et al. 2005, Li, Abecasis 2006, Li et al. 2006, MA et al. 2005, Destefano et al. 2008, Wahner et al. 2007, Li et al. 2003).

Many studies have demonstrated a beneficial role of vitamin D in PD in animal and cell culture studies. (Wang et al. 2001, Smith et al. 2006). There are several plausible mechanisms for the *VDR*-mediated vitamin D effects on PD. In addition to its anti-inflammatory property which plays a role in neurodegenerative diseases in general, (Garcion et al. 2002, Deluca, Cantorna 2001), , vitamin D regulates the expression of glial cell line-derived neurotrophic factor (GDNF) (Garcion et al. 2002, Smith et al. 2006, Evans 1988, Ferrari et al. 1998, Naveilhan et al. 1996). Administration of GDNF has been shown to alleviate PD symptoms in non-human primates model of PD and in PD patients (Gill et al. 2003, Gash et al. 1996, Kordower et al. 2000). Lastly, vitamin D is well known for its role in Ca^{2+} homeostasis. Chan et al has suggested that the SN dopaminergic neuron is particularly vulnerable to cell death due to its sustained opening of L-type Ca^{2+} channels for its pacemaker activity (Chan, Gertler & Surmeier 2009). Maintaining proper intracellular Ca^{2+} concentration in the face of extended Ca^{2+} influx puts SN dopaminergic neurons under

substantial cellular stress. It is intuitive that any genetic or environment changes tampering with Ca^{2+} homeostasis will accelerate SN dopaminergic neurons loss.

CONCLUSION

Our data suggest that common genetic variations in *VDR* modulate AAO of PD. The evidence of *VDR* as a genetic risk factor for PD supports the potential importance of vitamin D in PD. Given that vitamin D status is an environmentally modifiable factor, vitamin D presents a potential preventive/therapeutic strategy of this debilitating neurological disorder. Our findings warrant the need for future studies of *VDR* as well as its interaction with vitamin D levels in PD.

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Figure 1. Diagram of *VDR* gene structure with relative positions of genotyped SNPs

The *VDR* gene is located on the bottom strand of genomic DNA and therefore is displayed 3' to 5', left to right. Coding exons are shown as higher blocks while non-coding exons are shown as shorter blocks, introns are shown as straight lines, and the dotted line suggests alternative splicing of exons. Thirty tagSNPs were chosen and genotyped in the family data set. The locations of them are displayed in the context of *VDR* gene structure. SNP shown in bold was the proxy marker for the most significant SNP ($p=0.003$) in NINDS data set using linear regression; underlined SNP was the proxy marker for the previously reported significant SNP in the Korean study; SNP shown in bold and underlined is the most significant SNP ($p=0.0008$) in the family data set using Monks Kaplan analysis.

Figure 2. Pairwise LD plot for examined VDR SNPs

Pairwise r^2 was estimated in unrelated individuals with no PD and is displayed by gray-shaded square with the hundredths of r^2 value inside (HaploView) (Barrett et al. 2005). The shades of grey are proportional to the r^2 value with darker color representing higher r^2 value.

Figure 3. SNP association tests with PD risk as a discrete trait

Each bar represents an association test with PD risk in different datasets: overall (white), earlier onset (gray), and later onset (black). The dotted line depicts the p value of 0.05. The association tests were performed using APL. AAO of 60 was used to stratify the overall families (N=770) into earlier (N=459) and later (N=311) onset family subsets.

Table 1

Monks-Kaplan SNP association tests with PD AAO in the family dataset.

SNP	Location (bp)	Minor Allele Frequency*	P values
rs2853563	46522005	0.03	0.4019
rs3858733	46524234	0.03	0.6453
rs3847987	46524335	0.12	0.5563
rs11574119	46524359	0.04	0.1939
Rs739837	46524488	0.45	0.5951
Rs731236	46525024	0.40	0.5117
rs2239182	46541678	0.49	0.6099
rs2107301	46541837	0.26	0.1168
rs1540339	46543593	0.35	0.9943
rs2239179	46544033	0.43	0.7076
rs2189480	46550095	0.34	0.0439
rs3819545	46551273	0.38	0.5050
rs3782905	46552434	0.33	0.9517
rs2239186	46555677	0.18	0.8133
rs10735810	46559162	0.38	0.1861
rs2254210	46559981	0.38	0.1358
rs2238136	46563980	0.27	0.4991
rs4760648	46566932	0.42	0.0634
rs2853559	46569072	0.40	0.2514
rs11168287	46571681	0.49	0.4486
rs4334089	46572282	0.25	0.0008
rs4237855	46573470	0.39	0.1321
rs10783219	46581755	0.37	0.4302
rs10083198	46582232	0.28	0.0046
rs7299460	46582535	0.28	0.0016
rs4760658	46582753	0.34	0.0175
rs7976091	46590819	0.21	0.0229
rs10875708	46620017	0.20	0.0072
rs1015390	46630305	0.15	0.1413
rs4760673	46642376	0.16	0.3049

* Minor allele frequency was calculated in the overall dataset. SNPs with corrected p values less than 0.05 are in bold.

Table 2

Linear regression-based SNP association tests with PD AAO in the NINDS GWAS dataset

SNP	Location (bp)	Beta	Lower 95% confidence interval	Upper 95% confidence interval	p value
rs7968585	46518360	1.9940	0.6905	3.2970	0.0030
rs757343	46525942	-2.3860	-4.2990	-0.4728	0.0152
rs1544410	46526102	-1.0920	-2.5030	0.3192	0.1305
rs2239182	46541678	1.3080	-0.0228	2.6390	0.0551
rs2107301	46541837	-0.0969	-1.5830	1.3900	0.8984
rs2239181	46542216	-1.7170	-3.7060	0.2708	0.0916
rs1540339	46543593	0.5490	-0.8670	1.9650	0.4480
rs2239179	46544033	-1.7180	-3.1140	-0.3221	0.0165
rs886441	46549231	1.3690	-0.3218	3.0590	0.1137
rs2189480	46550095	-1.1150	-2.4890	0.2597	0.1131
rs3819545	46551273	0.0683	-1.3990	1.5350	0.9273
rs2239186	46555677	0.5753	-1.2150	2.3660	0.5294
rs2254210	46559981	0.1515	-1.1870	1.4900	0.8245
rs2238136	46563980	-0.3045	-1.8170	1.2080	0.6936
rs2853564	46564754	-0.0372	-1.3920	1.3180	0.9571
rs4760648	46566932	0.0858	-1.2300	1.4010	0.8984
rs4334089	46572282	0.5517	-0.9062	2.0100	0.4589
rs3890733	46575640	-0.2609	-1.6470	1.1260	0.7126