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Analysis of PTPRK polymorphisms in association with risk and age at onset of Alzheimer's disease, cancer risk, and cholesterol

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Abstract

The human receptor-type protein-tyrosine phosphatase kappa (*PTPRK*) gene is highly expressed in human brain and is previously associated with neuropsychiatric disorders and cancer. This study investigated the association of 52 single nucleotide polymorphisms (SNPs) in the *PTPRK* with the risk and age at onset (AAO) of Alzheimer's disease (AD) in 791 AD patients and 782 controls. Five SNPs (top SNP rs4895829 with p=0.0125) were associated with the risk of AD based on a multiple logistic regression ($p<0.05$); while 6 SNPs (top SNP rs1891150 with $p=8.02\times10^{-6}$) were associated with AAO by using a multiple linear regression analysis. Interestingly, rs2326681 was associated with both the risk and AAO of AD ($p=4.65\times10^{-2}$ and 5.18×10^{-3}, respectively). In a replication study, the results from family-based association test - generalized estimating equation (GEE) statistics and Wilcoxon test showed that seven SNPs were associated with the risk of AD (top SNP rs11756545 with $p=1.02\times10^{-2}$) and 12 SNPs were associated with the AAO (top SNP rs11966128 with $p=1.39\times10^{-4}$), respectively. One additional sample showed that four SNPs were associated with risk of cancer (top SNP rs1339197 with $p=4.1\times10^{-3}$), 12 SNPs associated with LDL-cholesterol (top SNP rs4544930 with $p=3.47\times10^{-3}$), and 8 SNPs associated with total cholesterol (top SNP rs1012049 with $p=6.09\times10^{-3}$). In addition, the AD associated rs4895829 was associated with the gene expression level in the cerebellum ($p=7.3\times10^{-5}$). The present study is the first study providing evidence of several genetic variants within the *PTPRK* gene associated with the risk and AAO of AD, risk of cancer, LDL and total cholesterol levels.

Keywords

Alzheimer disease; Age at onset; *PTPRK*; Polymorphisms; Gene expression; Cancer; Cholesterol

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1. Introduction

Alzheimer's disease (AD), as the most common type of dementia, is a chronic neurodegenerative disease that slowly destroys memory and thinking skills (Burns and Iliffe, 2009). The irreversible and progressive course of disease possibility leads to loss of the ability to carry out the simplest tasks (Querfurth and LaFerla, 2010). In 2013, approximately 5 million Americans aged 65 years or older were living with AD; while this number is projected to rise to 13.8 million, a nearly three-fold increase, by 2050 (Hebert et al., 2013). In 2010, the costs associated with AD were projected to fall between $159 and $215 billion; whereas these costs are estimated to be between $379 and more than $500 billion annually by 2040 (Hurd et al., 2013). Worldwide, the number of individuals living with AD was 26.6 million in 2006 and this number will quadruple and 1 in 85 persons worldwide will be living with the disease by 2050 (Brookmeyer et al., 2007). The genetic heritability of AD ranges from 49% to 79% based on reviews of twin and family studies (Gatz et al., 2006). Age at onset (AAO) is also genetically controlled. Previous studies showed that the estimated heritability of 42% for AAO of AD and 57–78% of the variance of AAO was related to genetic effects (Daw et al., 2000; Pedersen et al., 2001; Li et al., 2002).

With advances of technology developed, a number of genes have been suggested to be associated with AD. In the current study, we are interested in human receptor-type protein-tyrosine phosphatase kappa (*PTPRK*) gene, which is located at 6q22.2-q22.3 (Zhang et al., 1998). The protein encoded by this gene is a member of the protein tyrosine phosphatase (PTP) family. PTPs are known to be signaling molecules that regulate a variety of cellular processes including cell growth, differentiation, mitotic cycle, and oncogenic transformation (Yang et al., 1997). *PTPRK* is expressed in a number of tissues such as brain, spleen, prostate, and ovary. Some studies showed that *PTPRK* may play a role in the regulation of processes involving cell contact and adhesion (Fuchs et al., 1996). Previous genetic studies have shown that several single nucleotide polymorphisms (SNPs) such as rs17461290 and rs11753871within the *PTPRK* gene are associated with three adult psychiatric disorders: schizophrenia, major depressive disorder, and bipolar disorder (Hamshere et al., 2009; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium et al., 2015). It has been found that there is a significant relationship between the presence of *PTPRK* mutations and short malignant glioma patient survival time (Assem et al., 2012). Another study suggested that there was an association between Alzheimer's disease prevalence and malignant brain tumor incidence (Lehrer, 2010). In addition, it has been demonstrated that the *PTPRK* gene is a potential deletion target in primary central nervous system lymphomas that can present as progressive dementia (Nakamura et al., 2003). Increasing evidence suggests that total cholesterol levels are associated with AD and cognitive impairment (Ahmed et al., 2014; Giudetti et al., 2016). Thus, we hypothesize that the *PRPTK* genetic variants may play a role in cholesterol metabolism.

However, no study has focused on the relationship between of *PTPRK* gene and AD, especially AAO of AD. This study aimed to investigate the association of *PTPRK* gene with the risk and AAO of AD by using a case-control sample, followed by a replication using a

family-based study design. In addition, a third sample was used to examine the associations with risk of cancer, LDL- and total cholesterol levels.

2. Materials and Methods

2.1. Subjects

2.1.1. GenADA case-control study—Eight hundred and six patients with AD and 782 controls with complete genotype and phenotype information in a Canadian sample (Table 1) were selected from the Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's disease and the Neuroimaging component of Genotype-Phenotype Associations in Alzheimer's disease (GenADA) - Study Accession: phs000219.v1.p1. The details of these subjects were described elsewhere (Li et al., 2008; Filippini et al., 2009). Genotyping was conducted using the Affymetrix technique. There were 52 SNPs within the *PTPRK* gene.

2.1.2. NIA-LOAD family study—In total, 3007 individuals were available from the National Institute on Aging - Late Onset Alzheimer's Disease (NIA-LOAD) Family Study: Genome-Wide Association Study for Susceptibility Loci – Study Accession: phs000168.v1.p1. The details about these subjects were described elsewhere (Lee et al., 2008). Genotyping was conducted by the Center for Inherited Disease Research (CIDR) using the Illumina Infinium II assay protocol. Totally, 1266 AD cases and 1279 non-AD individuals (including 1070 with AAO values) from 1386 pedigree (589 nuclear families) (Table 1) were included in this study. There were 88 SNPs within the *PTPRK* gene.

2.1.3. The Marshfield sample—The Marshfield sample is from the publicly available data in A Genome-Wide Association Study on Cataract and HDL in the Personalized Medicine Research Project Cohort - Study Accession: phs000170.v1.p1 (dbGaP). The details about these subjects were described elsewhere (McCarty et al., 2005, 2008). Cancer cases were defined as any diagnosed cancer excluding minor skin cancer; while age at onset of cancer was defined by date of the earliest cancer diagnosis in the registry. Genotyping data using the ILLUMINA technique are available for 3564 Caucasian individuals (716 cancer cases and 2848 controls). Adjusted (age 59, BMI 29, no estrogen) baseline LDL values (mean ± SD = 149.1±26.9) and total cholesterol level (mean ± SD = 216.2±28.1) available for 2273 individuals were treated as continuous variables. Within the *PTPRK* gene, 79 SNPs were available.

2.2. Statistical methods

2.2.1. Genotype quality control—Hardy-Weinberg equilibrium (HWE) was tested using Golden Helix Software (http://www.goldenhelix.com/SNP_Variation/HelixTree/index.html). To deal with population stratification, the principal component analysis approach (Price et al., 2006) in Golden Helix was used to identify outlier individuals for the case-control data. Then, minor allele frequency (MAF) was determined for each SNP using HAPLOVIEW software (Barrett et al., 2005).

2.2.2. Multiple logistic regression models in PLINK software—For the case-control designs, the multiple logistic regression analyses of risk of AD and cancer as binary traits, adjusted for age and sex, were performed. The asymptotic p-values for the logistic regression models were observed while the odds ratio (OR) and its 95% confident interval (CI) were estimated using PLINK v1.07 (Purcell et al., 2007). Multiple linear regression analysis was used to examine the associations of SNPs with AAO of AD in the GenADA Canadian sample and the LDL and total cholesterol in the Marshfield sample after adjusting for age and sex. The asymptotic p-values were observed. The OR and its standard error for the logistic models, and the regression coefficient (β) for the linear models, were estimated using PLINK v1.07. To deal with multiple testing, Bonferroni correction ($\alpha=0.05/52=9.62\times10^{-4}$) for the discovery in the Marshfield sample was used for statistical significance.

2.2.3. Family-based association study—A family-based association analysis for AD was performed using PBAT version 36.1 (Van Steen et al., 2005). The advantages of using a family based association include that the design accommodates nuclear families with missing parental genotypes, extended pedigrees with missing genotypic information and contains analysis of SNPs, haplotype analysis, quantitative traits, and time to onset phenotypes. For the affection status of AD, the family-based association test - generalized estimating equation (FBAT-GEE) statistic was used to perform family-based association analysis (Lange et al., 2003). For testing time-to-onset trait (AAO), FBAT-Wilcoxon statistics were employed (Lange et al., 2004). The AAO values for healthy siblings were censored and age at entry into the study was used.

2.2.4. In silico analysis—We evaluated potential function of the disease associated SNP. First, we examined if these variants were located within the regions of the gene that might have potential functional importance. The sequences containing the associated SNPs were examined for microRNA binding sites, splicing sites, regulatory gene regions, and species-conserved regions using NIH-SNP Function Prediction (http://snpinfo.niehs.nih.gov/cgi-bin/snpinfo/snpfunc.cgi). Second, to determine if disease associated SNPs with *PRPRK* expression levels in human brain, we used publicly available data from the Genotype-Tissue Expression (GTEx) project (GTEx Consortium et al., 2015), in which, there is RNA sequencing on brain tissue from healthy donors available, resulting in genotype and expression phenotype data for ~100–120 normal individuals in multiple different brain regions. The information about subjects and RNA quality can be found in the GTEx website (www.gtexportal.org).

3. Results

3.1. Descriptive statistics

Based on the principal components analysis using the Golden Helix and missing values of AAO, we removed 15 individuals from the GenADA-case control sample. Consequently, 791 AD cases and 782 controls were left for further analysis from the Canadian sample (GenADA). The demographic characteristics of the subjects in these three samples are shown in the Table 1. The mean AAO for AD cases was 76.4 and 72.3 years in the NIA

sample and Canadian samples, respectively. The mean age at entry was 75.5 years for controls in NIA sample, and was 77.6 years in AD cases versus 73.4 years in controls in the Canadian sample. The mean age at entry was 71.1 years in cancer cases versus 65.1 years in controls in the Marshfield sample.

3.2. Case-control association analyses in the GenADA Canadian sample

Single marker analysis showed that five SNPs were associated with risk and six SNPs were associated with AAO ($p<0.05$) (Table 2). The strongest association was observed between SNP rs4895829 and risk of AD (OR=0.65, 95%CI=0.47–0.91, $p=1.25\times10^{-2}$). The top two SNPs showing significant associations with AAO were rs1891150 and rs1341597 ($p=8.02\times10^{-6}$ and 8.33×10^{-5}, respectively), remained significant after a Bonferroni correction ($p<9.62\times10^{-4}$). Interestingly, rs2326681 was associated with both the risk and AAO of AD ($p=4.65\times10^{-2}$ and 5.18×10^{-3}, respectively). Fig.1 shows the location of the SNPs showing association with AD and/or AAO.

3.3. Family-based association analyses with the NIA-LOAD data

Seven SNPs were associated with AD ($p<0.05$) by using FBAT-GEE analysis for affection status in the family-based study (Table 3). The most significantly associated SNP was rs1016015 ($p=2.3\times10^{-2}$) in an additive model and rs11756545 ($p=1.02\times10^{-2}$) in a dominant model. Our results further showed 12 SNPs associated with AAO ($p<0.05$) by using the FBAT-Wilcoxon test (Table 4). The most significantly AAO associated SNP was rs11966128 ($p=1.39\times10^{-4}$) in an additive model which remained significant after a Bonferroni correction ($p<0.05/88=5.68\times10^{-4}$). In addition, rs7748155 was associated with both the risk and AAO of AD in the family sample ($p=1.57\times10^{-2}$ and 2.07×10^{-2}, respectively).

3.4. Associations with cancer and cholesterol in the Marshfield sample

Table 5 showed that four SNPs were associated with the risk of cancer (top SNP rs1339197 with OR=0.84, 95%CI=0.74–0.95, $p=4.1\times10^{-3}$). We identified 12 SNPs associated with LDL-cholesterol and 8 SNPs associated with total cholesterol ($p<0.05$) in the Marshfield sample (Table 5). The first three most significant SNPs for LDL-cholesterol were rs4544930, rs1012049 and rs9372885 ($p = 3.47\times10^{-3}$, 5.31×10^{-3} and 6.6×10^{-3}, respectively). The top two SNPs associated with total cholesterol were rs1012049 and rs17352289 ($p=6.09\times10^{-3}$ and 8.87×10^{-3}, respectively). Interestingly, rs7767531 was associated with cancer, LDL-cholesterol and total cholesterol ($p=4.12\times10^{-2}$, 3.26×10^{-2}, 1.4×10^{-2}, respectively); while four SNPs (rs7767531, rs4533930, rs1012049 and rs17352289) were associated with both LDL-cholesterol and total cholesterol levels.

3.5. In silico analysis

To test if the sequences containing the associated SNPs were located at microRNA binding sites, splicing sites, regulatory gene regions, and species-conserved regions using NIH-SNP Function Prediction (http://snpinfo.niehs.nih.gov/cgi-bin/snpinfo/snpfunc.cgi). We found SNP rs7748155 associated with both AD and AAO and was located at the gene regulatory region and species-conserved region; while AAO-associated SNPs (rs17055612 and rs17055719) were located at the gene regulatory regions. The cholesterol associated SNP

rs17828130 was a coding nonsynonymous SNP and was located at the gene regulatory region; while rs9372885 was located at the gene regulatory region.

Having established strong associations of disease associated SNPs with AAO and risk of AD, we tested if the genotype at these SNPs are associated with levels of gene expression in the brain, based on the date from The Genotype-Tissue Expression (GTEx). We hypothesized that the effects of the SNP genotypes on AD risk may reflect genotypes based differences in levels of the gene expression in the brain. To investigate this, we analyzed recently released GTEx Consortium data. In postmortem samples from 100–120 normal individuals from the GTex dataset, among the disease associated SNPs, only rs4895829 genotype was associated with the expression level in the cerebellum ($p = 7.3\times10^{-5}$, Fig. 2), with GG genotype carriers showing the lowest levels of expression as compared with GC and CC genotypes (G is minor allele).

4. Discussion

In the present study, we examined the association of *PTPRK* gene with the risk and AAO of AD by using a case-control dataset and a family based-study sample for replication. In the case-control data, five SNPs were associated risk of AD and six SNPs were associated with AAO. Using FBAT-GEE and FBAT-Wilcoxon statistics in the family sample, we found that seven SNPs were significantly associated with the risk of AD and 12 SNPs were associated with the AAO of AD in the family-based dataset; while one SNP (rs7748155) was associated with both risk and AAO. There were few SNPs in the *PTPRK* gene that overlapped between these two data sets, which may be due to different arrays used for genotyping. The findings of the case-control design were confirmed by the results found using a family sample at the gene level in our current study. We also demonstrated homozygous disease associated genotype (GG) of rs4895825 displayed the lowest levels of expression as compared to other genotype groups (CG and CC) in human cerebellum brain tissue (Fig.2). In addition, one additional sample showed that several SNPs were associated with the risk of cancer and cholesterol levels.

To the best of our knowledge, this is the first study to investigate the association of *PTPRK* gene with AD, especially with AAO of AD. A previous study has identified the *APOE* e4 allele with AAO of AD (Williamson et al., 2009). However, *APOE* genotyping was neither fully specific nor sensitive (Bird, 2008). Genetic factors for AAO play an important role in the prevention and early treatment intervention of AD. A multi-gene approach will be effective in the screening and prevention of AD. The *PTPRK* gene investigated in this study is highly expressed in the human brain. Although the biological functions of *PTPRK* in neoplastic cells are still poorly characterized, *PTPRK* mediates highly specific intercellular homophilic interactions suggesting that it can directly sense cell-cell contact and thereby mediate contact inhibition of cell growth (Yang et al., 1997). The *PTPRK* is known to be up-regulated by transforming growth factor-beta (TGF-β), and therefore likely involved in mediating TGF-β dependent anti-proliferative and cell migration effects (Wang et al., 2005). Previous studies have already found that an overproduction of TGF-β can cause cerebral amyloid angiopathy, which is frequently associated with AD (Wyss-Coray et al., 1997; Ueberham et al., 2005). Other studies have also shown that several SNPs within *PTPRK*

gene are associated with three adult psychiatric disorders: schizophrenia, major depressive disorder and bipolar disorder (Hamshere et al., 2009; Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium et al., 2015). In the present study, the AD-associated SNP rs17461290 and AAO-associated SNP rs10872331 were previously associated with bipolar schizoaffective disorder (p=0.0165 and 0.049, respectively) (Hamshere et al., 2009); while the AD-associated rs11753971 and AAO-associated rs7767531 were previously associated with across three adult psychiatric disorders: schizophrenia (p=0.024 and 0.0949, respectively), major depressive disorder (p=0.0204 and 0.0343, respectively) and bipolar disorder (p=0.0207 and 0.0579, respectively) (Network and Pathway Analysis Subgroup of Psychiatric Genomics Consortium et al., 2015).

In the present study, four SNPs (rs1339197, rs9491931, rs9402020 and rs7767531) were associated with cancer; especially, the rs1339197 was also associated with AAO of AD in the family-bases sample, which suggested that *PTPRK* may play a role in AD and cancer. The *PTPRK* gene is involved in the processes related to many tumors, and the locus 6q22–23 is a common region of allelic deletion at chromosome 6 in several cancers (Yang et al., 1997). Previously, *PTPRK* as a potential tumor suppressor gene has been investigated by many cancer researchers. Some of these cancers were associated with AD or had a high prevalence in patients with AD in a number of studies. For example, Nakamura and his colleague reported that *PTPRK* may be a putative tumor suppressor, and appear to be relevant to the pathogenesis and prognosis of primary central nervous system lymphomas (PCNSLs) (Nakamura et al., 2003). The PCNSLs were reported to be present in progressive dementia that is a major form of AD (Burns and Iliffe, 2009). The study by Agarwal and colleagues indicated that *PTPRK* is significantly relevant to glioma pathogenesis (Agarwal et al., 2013). Furthermore, previous studies demonstrated that Alzheimer's disease and glioblastoma shared a yet unknown pathway that can promote the progression of both diseases (Lehrer, 2010; Deutsch and Mendez, 2015). Another study suggested *PTPRK* was the most likely candidate tumor suppressor gene for endocrine pancreatic tumors (Barghorn et al., 2001). Recent studies also reported that *PTPRK* was a key factor in coordinating apoptosis in prostate cancer cells (Sun et al., 2013). An epidemiological study which used National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program data showed the higher prevalence of pancreatic cancer and prostate cancer in patients with AD than that in control subjects (Burke et al., 1994). Stevenson and colleagues' study suggested PTPRK-mediated cell signaling pathway may be targeted with epigenetic therapies in acute lymphoblastic leukemia (Stevenson et al., 2014). Another study also found a relationship between acute lymphoblastic leukemia and AD by an immunological method (Sato et al., 1991). Therefore, the PTPRK gene may play a similar role in the progression of these cancers and AD.

Previous studies demonstrate that cholesterol levels are associated with dementia related (Ahmed et al., 2014; Giudetti et al., 2016). Our results further showed that 12 SNPs associated with LDL-cholesterol and 8 SNPs associated with total cholesterol. Interestingly, rs7767531 was associated with cancer, LDL-cholesterol and total cholesterol; while the same SNP is also associated with AAO in the family sample. However, future study is required to validate our current findings using more SNPs in the *PRPRK* genes and a large sample.

Moreover, based on the results of the in Silico analysis, we found four SNPs (rs7748155, rs17055612, rs17055719 and rs17828130) were located at the gene regulatory regions; while rs7748155 was also located at species-conserved region suggesting potential functional importance of the *PTPRK* gene. The cholesterol associated SNP rs17828130 was a coding nonsynonymous SNP and was located at the gene regulatory region; while rs9372885 was located at the gene regulatory region. In addition, individuals carrying minor allele (disease associated G allele) of AD risk SNP, rs4895829, demonstrated having significantly lower gene expression of the *PTPRK* as compared with non-carriers. Thus, the in Silico analysis adds additional evidence of supporting *PTPRK* gene in association with AD phenotypes.

There are several strengths of this study. First, we used population-based case control sample for initial study and then a family-based sample for replication. The family-based design provided a robust and powerful approach to identify a full range of disease susceptibility variants and confirmation of the results of case-control study. Second, several AD and its AAO associated SNPs (rs17461290, rs10872331, rs11753971, and rs7767531) were previously associated with psychiatric disorders. Third, we conducted association studies of *PTPRK* with cancer and cholesterol levels. In addition, we performed functional analyses.

There are a number of limitations in this study. For example, the small number of SNPs of the *PTPRK* gene in the GenADA sample led to a little overlap of the SNPs in the two samples. Some disease and AAO associated SNPs in the PTPRK gene were different between in the two sample sets indicating that phenotypic and genotypic heterogeneity exists in AD and AAO. Therefore, our replication results in AD and its AAO are gene-based rather than SNP-based. Furthermore, current findings might be spurious or subject to type I error. Future confirmatory studies, or targeted genome sequencing the *PTPRK* gene in AAO of AD in the current sample sets, may provide an opportunity to dissect the genetic complexity of this gene in this disorder more accurately.

5. Conclusion

We discovered a significant association between *PTPRK* genetic variants and the risk and AAO of AD in two independent samples. To our knowledge, this finding of AD associated *PRPRK* variants has not been previously reported. Furthermore, we provided initial evidence of several genetic variants in *PTPRK* influencing the risk of cancer and cholesterol levels. These results suggest a potential role of *PTPRK* in the pathogenesis of AD, cancer and cholesterol metabolism. These findings may serve as a resource for replication in other ethnic populations. In addition, future studies of this gene may help to characterize the genetic function of AD risk and AAO and the biological pathway of pathogenesis and prognosis of AD, cancer, and cholesterol levels.

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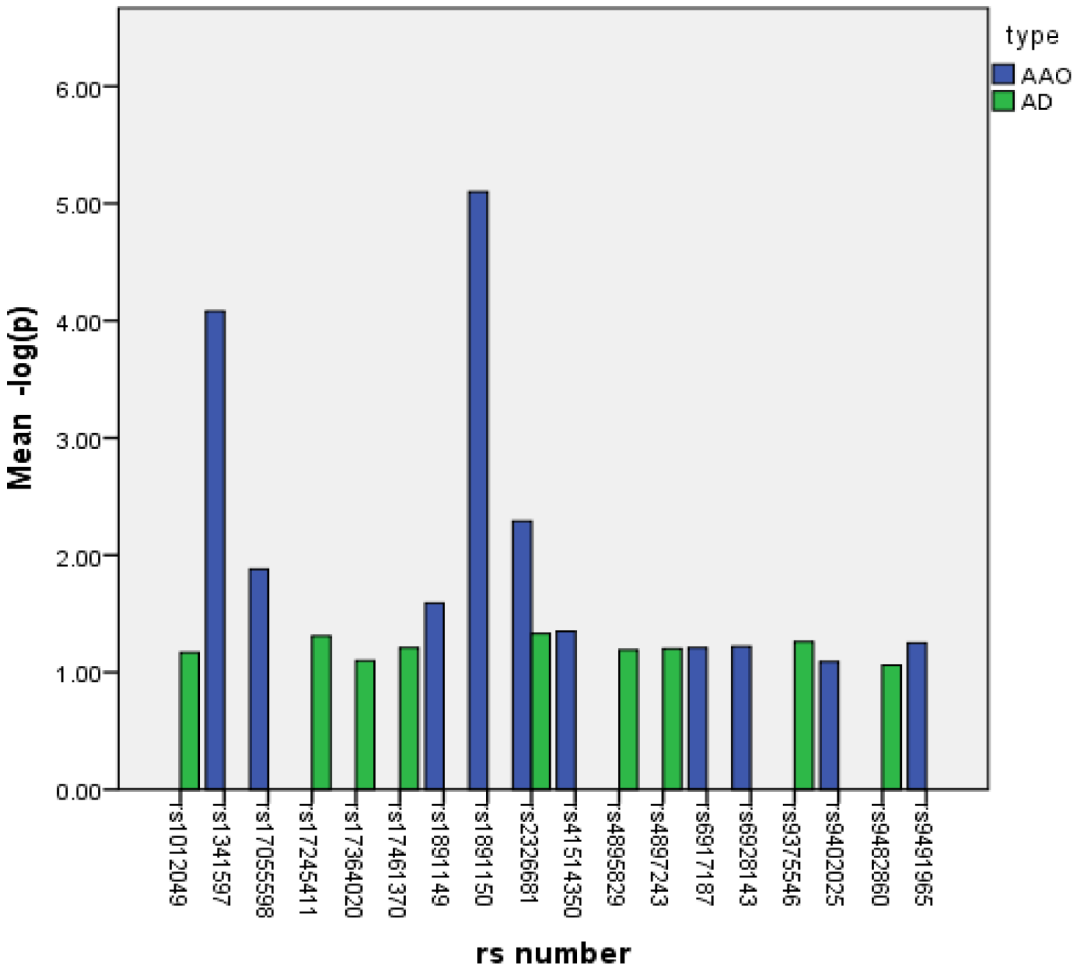

Figure.1.

The results of –log(p) values for single SNP analysis of risk and AAO of AD in the GenADA sample.

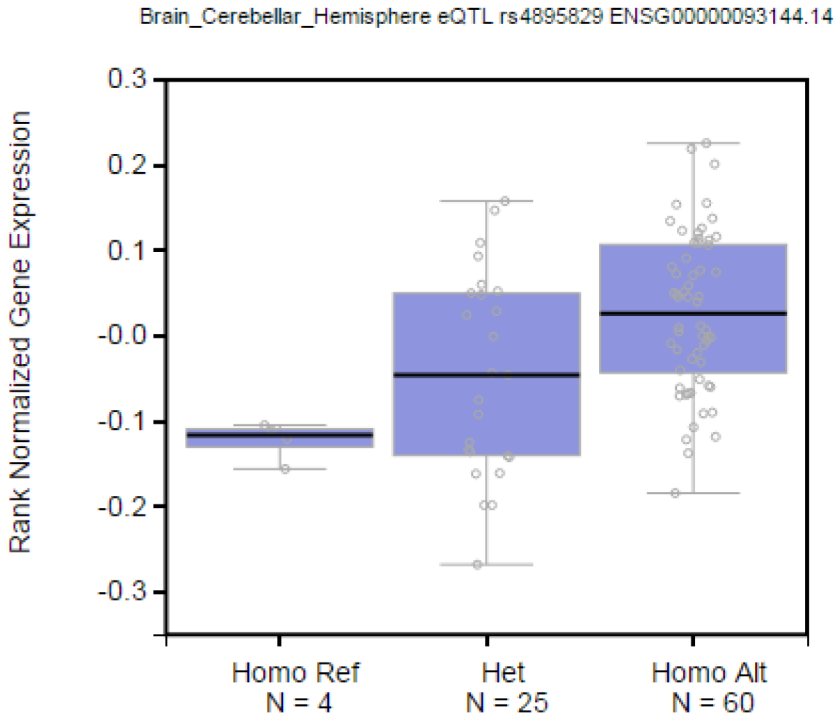

Figure 2.

Genotype at rs4895829 associates with gene expression in the brain and defines a clinically important AD phenotype in eQTL Boxplot showing the association between rs4895829 genotype and gene expression in the cerebellum in 89 healthy postmortem samples (P = 0.000073) from the GTEx Consortium, with GG (Home Ref, N=4) genotype carriers showing the lowest levels of expression. Medians and interquartile ranges are indicated. GC genotype (Het, N=25) and CC genotype (Homo Alt, N=60) are shown.

Table 1.

Descriptive characteristics of cases and controls.

Variable	Family Study (NIA sample)		Case-control study (Canadian sample)		Marshfield sample	
	AD Patients	Controls	AD Patients	Controls	Cancers	Controls
Sample size (n)	1266	1279	791	782	716	2848
Mean AAO (years±SD[a])	76.4±6.7	-	72.3±8.5	-	64.2±12.8	-
Range of age at onset (years)	50-98	-	40-97	-	40-97	-
Mean age at entry (years±SD)	-	75.5±8.1	77.6±8.6	73.4±7.9	71.1±10.3	65.1±11.3
Range of age at entry (years)	-	42-103	43-100	48-94	46-90	46-90

[a]SD refers to the standard deviation of the mean.

Table 2.

Single marker analysis of risk of AD and its AAO in the GenADA sample.

SNP	Position[a]	AL[b]	MAF[c]	HWE[d]	OR-AD[e]	p-AD[f]	β-AAO[g]	p-AAO[h]
rs4895829	128420786	G	0.17	0.145	0.65(0.47, 0.91)	0.0125	0.12(−0.34, 0.59)	0.6106
rs9375546	128417097	C	0.17	0.085	0.68(0.49, 0.93)	0.0151	0.16(−0.31, 0.61)	0.5168
rs4897243	128430767	T	0.17	0.132	0.68(0.49, 0.94)	0.0186	0.19(−0.27, 0.66)	0.419
rs2326681	128691100	C	0.01	0.843	2.11(1.01, 4.38)	0.0465	−1.86(−3.16, −0.56)	0.00518
rs17245411	128387064	C	0.05	0.532	0.69(0.48, 0.99)	0.0482	−0.22(−1.12, 0.67)	0.6238
rs1891150	128805122	C	0.03	0.397	0.86(0.56, 1.33)	0.5177	−2.19(−3.14, −1.23)	8.02E-06
rs1341597	128820851	T	0.03	0.452	0.93(0.60, 1.46)	0.7682	−1.97(−2.95, −0.99)	8.33E-05
rs17055598	128669758	A	0.01	0.759	1.53(0.78, 2.99)	0.2172	−1.81(−3.23, −0.38)	0.01324
rs1891149	128805026	A	0.06	0.775	1.17(0.86, 1.60)	0.313	−0.76(−1.43, −0.09)	0.02572
rs41514350	128527278	C	0.02	0.013	1.42(0.79, 2.55)	0.2392	1.27(0.03, 2.50)	0.0447

[a] Physical position (bp);

[b] Minor allele;

[c] Minor allele frequency;

[d] p-value for Hardy-Weinberg equilibrium test;

[e] Odds ratio for AD;

[f] p-value for AD;

[g] Regression coefficient for AAO;

[h] p-value for AAO.

Table 3.

Single marker analysis of risk of AD based on FBAT-GEE ($p<0.05$).

SNP	Position (bp)[a]	AL[b]	MAF[c]	HWE[d]	Fam#[e]	$p_{FBAT-GEE}$[f]
rs1016015	128869961	T	0.01	$>10^{-4}$	19	0.023(a) 0.023(d,r)[g]
rs11753971	128614517	T	0.10	0.71	129	0.427(a) 0.0372(d,r)
rs11756545	128855588	C	0.09	0.63	146	0.0937(a) 0.0102(d,r)
rs17461290	128870929	T	0.16	0.96	194	0.265(a) 0.0332(d,r)
rs4341027	128348811	C	0.30	0.25	258	0.0504(a) 0.027(d,r)
rs7748155	128733046	C	0.19	0.19	183	0.696(a) 0.0157(d,r)
rs9398863	128362605	C	0.10	0.65	112	0.0233(a) 0.0611(d,r)

[a] Physical position is based on NCBI Genome Build 36.3.

[b] Minor allele.

[c] Minor allele frequency.

[d] p-value of Hardy-Weinberg equilibrium test.

[e] The number of informative families using an additive model.

[f] p-value based on FBAT-GEE analysis for affection status.

[g] Letters in parentheses indicate the genetic models used for analysis (a, additive; d, dominant; r, recessive model).

Table 4.

Single marker analysis of AAO based on FBAT-Wilcoxon (p<0.05).

SNP	Position (bp)[a]	AL[b]	MAF[c]	HWE[d]	Fam#[e]	p-FBAT-Wilcoxon[f]
rs10428737	128781777	A	0.10	0.03	63	0.024(a) 0.032(d,r)[g]
rs11966128	128650841	G	0.08	0.72	62	0.000139(a) 0.000778(d,r)
rs1339197	128649904	T	0.46	0.03	219	0.0135(a) 0.0108(d,r)
rs17055612	128674033	C	0.08	0.74	62	0.00302(a) 0.00177(d,r)
rs17055628	128677748	C	0.07	0.96	62	0.00185(a) 0.00106(d,r)
rs17055719	128694187	G	0.07	1.00	60	0.00353(a) 0.0021(d,r)
rs17456385	128668324	T	0.07	0.87	58	0.00799(a) 0.00499(d,r)
rs3822945	128782080	A	0.29	0.01	161	0.095(a) 0.0442(d,r)
rs7748155	128733046	C	0.19	0.19	132	0.0488(a) 0.0207(d,r)
rs7767531	128535684	G	0.35	0.09	190	0.01(a) 0.0236(d,r)
rs7773248	128682710	G	0.08	0.97	63	0.000685(a) 0.000369(d,r)
rs9402035	128702994	T	0.11	0.31	73	0.0108(a) 0.00708(d,r)

[a] Physical position is based on NCBI Genome Build 36.3.

[b] Minor allele.

[c] Minor allele frequency.

[d] p-value of Hardy-Weinberg equilibrium test.

[e] The number of informative families using an additive model.

[f] p-values based on FBAT-Wilcoxon analysis for age at onset.

[g] Letters in parentheses indicate the genetic models used for analysis (a, additive; d, dominant; r, recessive model).

Table 5.

Associations between SNPs and cancer and cholesterol levels in the Marshfield sample.

SNP	Position[a]	AL[b]	MAF[c]	HWE[d]	OR-Cancer[e]	p-Cancer[f]	β-LDL[g]	p-LDL[h]	β-Chol[i]	p-Chol[j]
rs1339197	128649904	T	0.441	0.75	0.84(0.74, 0.95)	0.0041	1.38(−0.13, 2.89)	0.07436	1.10(−0.36, 2.56)	0.14
rs9491931	128614570	C	0.246	0.648	1.19(1.03, 1.36)	0.0157	−0.64(−2.42, 1.13)	0.4757	−0.89(−2.59, 0.81)	0.306
rs9402020	128505339	G	0.051	0.042	0.71(0.53, 0.95)	0.0229	2.14(−1.25, 5.53)	0.216	1.19(−2.02, 4.42)	0.469
rs7767531	128535684	G	0.334	0.018	0.87(0.76, 0.99)	0.0412	1.81(0.15, 3.48)	0.0326	1.99(0.40, 3.59)	0.01402
rs4544930	128436582	T	0.204	0.016	0.97(0.83, 1.13)	0.677	−2.86(−4.77,−0.94)	0.00347	−2.30 (−4.14, 0.47)	0.014
rs1012049	128572000	A	0.275	0.417	0.92(0.80, 1.06)	0.236	2.41(0.72,4.100	0.00531	2.28(0.65, 3.91)	0.00609
rs9372885	128517784	T	0.021	0.313	0.68(0.43, 1.08)	0.0991	6.84(1.91,11.8)	0.0066	4.63(−0.17, 9.43)	0.0588
rs3813372	128555088	G	0.016	0.446	0.65(0.37, 1.12)	0.118	7.81(1.74,13.9)	0.0118	4.85(−0.93,10.6)	0.1
rs9402030	128602695	G	0.015	0.488	0.55(0.29, 1.02)	0.0557	8.39(1.82,14.9)	0.0124	5.70(00.55, 12.03)	0.0739
rs9372887	128607471	A	0.013	0.531	0.59(0.32, 1.12)	0.107	8.01(1.20,14.8)	0.0213	5.71(−0.75, 12.17)	0.0834
rs6912749	128438700	T	0.229	0.033	0.98(0.85, 1.13)	0.767	−2.03(−3.85, −0.19)	0.0301	−1.56(−3.32, 0.20)	0.0829
rs12528715	128588870	G	0.049	0.019	1.16(0.90, 1.51)	0.258	3.61(0.27, 6.94)	0.0342	2.55(−0.69, 5.79)	0.123
rs17055441	128573344	A	0.017	0.436	0.63(0.36, 1.09)	0.095	6.60(0.43, 12.7)	0.0362	4.52(−1.34, 10.4)	0.131
rs13213933	128590678	A	0.049	0.019	1.17(0.90, 1.52)	0.241	3.53(0.19, 6.88)	0.0383	2.57(−0.68, 5.83)	0.121
rs17352289	128656785	A	0.072	0.184	0.87(0.69, 1.10)	0.252	2.90(0.08,5.73)	0.0439	3.69(0.93,6.44)	0.00887
rs9398869	128783169	A	0.082	0.218	1.08(0.87, 1.33)	0.505	2.21(−0.42,4.84)	0.1	3.28(0.68, 5.88)	0.0134
rs17828130	128445438	A	0.365	0.024	0.90(0.80, 1.03)	0.117	1.57(−0.02, 3.16)	0.0535	1.70(0.18, 3.22)	0.0283
rs6914064	128824612	C	0.421	0.497	0.99(0.88,1.12)	0.871	0.94(−0.59,2.47)	0.23	1.49(0.28, 2.94)	0.0458

[a] Physical position (bp);

[b] Minor allele;

[c] Minor allele frequency;

[d] p-value for Hardy-Weinberg equilibrium test;

[e] Odds ratio for cancer based on logistic regression;

[f] p-value for canccer based on logistic regression;

[g] Regression coefficient for LDL based on linear regression;

[h] p-value for LDL based on linear regression;

[i] Regression coefficient for total cholesterol level based on linear regression;

[f] p-value for total cholesterol level based on linear regression.