# Influence of Genetic Variation in *PDE3A* on Endothelial Function and Stroke

Running Title: *PDE3A*, Endothelial Function, and Stroke

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## Abstract

We aimed to characterize the genetics of endothelial function, and how this influences risk for cardiovascular diseases such as ischaemic stroke. We integrated genetic data from a study of ultrasound flow mediated dilatation (FMD) of brachial artery in adolescents from ALSPAC (N=5214) with a study of ischaemic stroke (MEGASTROKE: N=60,341 cases and 452,969 controls) to identify variants which confer risk of ischaemic stroke through altered endothelial function. We identified a variant in *PDE3A,* encoding phosphodiesterase 3A which was associated with flow mediated dilatation (FMD) in adolescents (9-12 years old; beta(SE)=0.38(0.070); p=3.8x10-8) and confers risk of ischaemic stroke (OR(95% CI)=1.04(1.02-1.06) ;p=5.2x10-6). Bayesian colocalization analyses showed the same underlying variation is likely to lead to both associations (posterior probability=97%). The same variant was associated with FMD in a second study in young adults (age 24-27 years; beta(SE)=0.47(0.23); p=0.047), but not in older adults (beta(SE)=-0.012(0.13); p=0.89).We conclude thata genetic variant in *PDE3A* influences endothelial function in early life, and leads to increased risk of ischaemic stroke. Subtle, measurable changes to the vasculature that are influenced by genetics also influence risk of ischaemic stroke.

Keywords: Stroke, Genetics, Endothelial Function, Flow Mediated Dilation, ALSPAC

## Introduction

Genome-wide associations studies (GWAS) have identified numerous variants underlying cardiovascular diseases including stroke and coronary heart disease. 1, 2 However, in the main, the mechanism of these variants on disease risk has been elusive. A complementary approach to the standard GWAS design of clinical endpoints such as stroke is to integrate data with GWAS on intermediate phenotypes of disease risk such as carotid intima-media thickness or plaque. 3 Identifying variation that is common to an intermediate phenotype and disease outcome has the potential to identify mechanism-specific associations with disease and to illuminate causal pathways.

Endothelial function is one such phenotype of importance to stroke. 4 The endothelium is a group of cells lining blood vessels that functions both as a barrier, controlling the passage of materials into and out from the blood stream; and as a signal transducer, regulating vessel structure and function. 5 Impaired endothelial function is involved in the initiation of atherosclerosis, as well as latter plaque instability, 6 and promotion of small vessel arteriopathy. 7, 8 Several techniques exist for measuring endothelial function *in vivo*. 5 One validated method, ultrasound flow mediated dilatation (FMD), measures the response of the arterial endothelium to reactive hyperaemia via inflation and subsequent deflation of a blood flow constricting cuff (Sphygmomanometer). 5

Here, we perform a genome-wide association study of FMD in adolescents from the Avon Longitudinal Study of Parents and Children. We integrate the results with a large-scale GWAS of Stroke in over 60,341 cases and 452,969 controls (MEGASTROKE),2 and use genome-wide colocalization approaches to identify genetic variation which contributes to stroke through impaired endothelial function in adolescents.

## Methods

Data used in this study are available to all researchers through application to Avon Longitudinal Study of Parents and Children (<http://www.bristol.ac.uk/alspac/researchers/>) and UK Biobank (<https://www.ukbiobank.ac.uk/register-apply/>). Publicly available GWAS data pertaining to cardiovascular risk factors and traits used in this study are available from <http://megastroke.org> (stroke), <https://www.cardiomics.net/download-data> (coronary heart disease), <http://www.diagram-consortium.org/downloads.html> (type 2 diabetes), <http://www.broadcvdi.org/> (atrial fibrillation), <http://lipidgenetics.org/> (lipids), and <https://conservancy.umn.edu/handle/11299/201564> (Smoking status).

*Study Subjects*

Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the Avon Longitudinal Study of Parents and Children (ALSPAC) study, a prospective observational study of the genetic and environmental determinants of development and health from the prenatal period into adulthood. 9, 10, 11 The initial number of pregnancies enrolled was 14,541, which was later increased to 15,247 by retrospective recruitment. A total of 15,656 foetuses were included in further studies, of which 14,889 were alive at 1 year of age. Please note that the ALSPAC study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (<http://www.bristol.ac.uk/alspac/researchers/our-data/>). We studied endothelial function in 7,557 of these children aged between 9-12 years old (mean(SD) 10.7(0.25) years). Age, Sex, Body Mass Index (BMI), blood pressure and environmental factors were collected as previously described. 9 Room and skin temperatures were assessed using a commercial digital thermometer immediately before the vascular examination. Brachial artery endothelial function was successfully measured in 88% of children by FMD. 11 The right brachial artery was imaged using high-resolution ultrasound (ALOKA 5500) 5–10 cm above the antecubital fossa with the probe held in a stereotactic clamp. Edge detection software (Brachial Tools, MIA, IA, USA) was used to measure the brachial artery diameter at 3 s intervals throughout the 11 min recording protocol. Brachial artery FMD was induced by a 5 min inflation of a pneumatic cuff to 200mmHg, around the forearm immediately below the medial epicondyle followed by rapid deflation using an automatic air regulator (Logan Research, UK). We used FMD expressed as a percentage calculated using peak diameter in response to reactive hyperaemia in relation to the baseline diameter. 12

*Genotyping and Quality Control in ALSPAC*

We used imputed genotypic data of the ALSPAC. Genotyping, quality control, and imputation has been described previously. 13 GWAS data was generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. Imputation was carried out using the complete reference panel from the third phase of the 1000 Genomes Project. 14 5,297 Children had both genotyping information and FMD measurements. We excluded 83 cryptically related samples with PI-HAT >0.1875, determined using PLINK2, 15 meaning the final analyses were performed on 5,214 samples. We analysed all SNPs that were polymorphic (MAF>1%) in European samples and had an imputation info value >0.5. PLINK2 was used to estimate IBD and to perform ancestry-informative principal components analysis.15

*MEGASTROKE Genome-Wide Summary Statistics*

We used summary statistics, downloaded from <http://megastroke.org>, derived from MEGASTROKE, a trans-ethnic genome-wide meta-analysis of stroke.2 Our primary analysis was for all ischaemic stroke cases versus controls (60,341 cases and 452,969 controls). We also explored associations with ischaemic stroke subtypes in MEGASTROKE: cardioembolic stroke (9,006 cases, 426,629 controls), large artery stroke (6,688 cases, 345,446 controls) and small vessel stroke (11,710 cases, 346,101 controls).

*Genome-Wide Analyses in adolescents from ALSPAC*

Per-allele beta coefficients and standard errors for FMD were generated in a regression model that included age, sex, room temperature, body temperature, and eight ancestry-informative principal components. Covariates were selected based on their significant association with FMD in previous ALSPAC publications. 11 For sensitivity analysis, we performed analysis of a second model that was additionally adjusted for heritable covariates: BMI, systolic, and diastolic blood pressure. All statistical tests conducted were two-sided and SNPTEST v2.5.4-beta3 was used to perform the analysis. We used a *P*-value threshold of 5.0x10-8 to determine statistical significance. We discarded significant low-frequency SNPs (MAF<0.05) without substantial LD-support (one region).

*Validation Datasets*

We explored validation of the FMD associated novel SNP in independent cohorts of FMD measured in both younger and older cohorts of subjects.

We sought replication in younger subjects in the Young Finns Study (YFS), a study of young subjects (age 24-45) 16 The YFS cohort is a Finnish longitudinal population study sample on the evolution of cardiovascular risk factors from childhood to adulthood. In the present study, we used the variables measured in 2001 and described in detail previously.17 For these subjects, genotyping was performed in 2009 using a custom-built Illumina Human 670k BeadChip at the Welcome Trust Sanger Institute and imputed to 1000 Genomes phase 3. 18 We attempted replication of a single SNP in the youngest quartile (ages 24-27) and overall (ages 24-45). All analyses included age, sex, center and ancestry informative principal components as covariates.

We sought replication of the novel SNP with FMD in older individuals of European ancestry in both the Framingham Heart Study (FHS) and the Multi-Ethnic Study of Atherosclerosis (MESA).

The Multi-Ethnic Study of Atherosclerosis (MESA) subjects analyzed were 1029: 50% male; mean age 61 years (standard deviation 10 years). Flow-Mediated Dilation (FMD) of the brachial artery mean (SD): 4.8 (3.1). Framingham Heart Study (FHS) subjects analyzed were 393: 38% male; mean age 41 years (standard deviation 8 years). FMD of the brachial artery mean (SD): 5.9 (3.7).

For the MESA cohort, analysis was restricted to subjects with European ancestry based on the self-reported race/ethnicity. MESA and FHS genotype panels are described elsewhere. 19, 20 Standard QC procedures for the genotype data were performed using PLINK. We excluded SNPs with a minor allele frequency (MAF) <5% or significant deviation from Hardy-Weinberg equilibrium (P<1.0x10-6). SHAPEIT and IMPUTE2 software were used to impute PDE3A region (chr 12; p12.2:18060181-23060180; GRCh v37), using the 1000 Genomes reference panel (GRCh v37, phase III). 18 Imputed SNPs with an imputation quality estimate (R2< 0.40) were removed for association tests. The first three principal components (PCs) for population structures were derived using the smartpca script in EIGENSTRAT and included as covariates in association analyses for both MESA and FHS. 21

For both cohorts, linear regressions analyses assuming an additive model were computed using two models: model 1 which included sex, age, and PCs 1-3; and model 2 where BMI, diastolic and systolic blood pressure at the time of the measurements were added to the covariates of model 1. Linear Mixed Effects Kinship Models (package lmekin in R) for family data were implemented in FHS.

*Further Analysis of Novel association*

We used a Bayesian test for colocalisation at the novel gene between FMD GWAS summary results and stroke to assess whether two association signals are consistent with a shared causal variant. 22 The gwas-pw package was used to perform all analyses (<https://github.com/joepickrell/gwas-pw>).

*Association with Cardiovascular Risk Factors, Outcomes and Coronary Artery Expression*

Using data from publicly available repositories and UK Biobank, we assessed the impact of the *PDE3A* rs11045239 variant on cardiovascular risk factors: systolic blood pressure (id 4080), diastolic blood pressure (id 4079), pulse pressure (derived from the former 2 variables), pulse wave arterial stiffness (id 21021), hypertension (self reported, id 200002=1465), hypercholesterolaemia (self reported: id 20002=1473), ever smoking; 23 as well as cardiovascular diseases: coronary artery disease, 24 type 2 diabetes, 25 and atrial fibrillation. 26

UK Biobank (http://www.ukbiobank.ac.uk) is a prospective study that recruited 500,000 community-dwelling participants aged 40–69 years from across the UK between 2006 and 2010. The study collects extensive data from questionnaires, interviews, health records, physical measures, biological samples and imaging. For all variables we considered in this analysis we excluded outlier readings which were more than 3 standard deviations from the median value.

The UK Biobank genotyping procedure has been described elsewhere. 27 In short, two custom genotyping arrays were used to genotype 49,950 participants (UK BiLEVE Axiom Array) and 438,427 participants (UK Biobank Axiom Array). 27, 28 Genotype data (805,426 markers) were available for 488,377 individuals, and were subsequently imputed to the HRC reference panel (39,131,578 autosomal SNPs). Imputed genotypes were available for 487,442 individuals in this study. 27 From the resulting imputed dataset, we excluded (1) individuals that did not segregate with European individuals based on principal component analysis, (2) individuals with high levels of heterozygosity or missingness (>5%), (3) individuals whose reported sex did not match with sex inferred from the genetic data.

All UK Biobank analyses included age, sex and ancestry-informative principal components as covariates. In analyses of blood pressure variables we additionally corrected for body mass index, as has been the convention in GWAS studies. 29

In addition, we investigated the association of rs11045239, and other variants in close LD (r2>0.8), calculated using LDlink, 30 with expression of *PDE3A* in coronary arteries from GTEx. 31 All analyses were performed using the GTEx portal (<https://gtexportal.org/home/> accessed 14th May 2019).

***Standard Protocol Approvals, Registrations, and Patient Consents***

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. UK Biobank received ethical approval from the research ethics committee (REC reference 11/NW/0382). All participants provided informed consent to participate. The present analyses were conducted under UK Biobank application number 36509.

## Results

We performed a genome-wide association analysis of FMD in 5,214 adolescents from ALSPAC. The inflation of test statistic using genomic control was 1.014, while the LD score regression intercept was 1.001 indicating no inflation of test statistics.1 We identified a SNP (rs11045239) on chromosome 12 (12:20579694) that was associated with FMD (beta(SE)=0.38(0.070); p=3.8x10-8). The risk allele (A) had a frequency of 40% among Europeans and the SNP was located in an intron of the *PDE3A* gene, which encodes Phosphodiesterase 3A, a member of the cGMP-inhibited cyclic nucleotide phosphodiesterase family.

In order to identify regions with evidence of shared genetic variation impacting on FMD and ischaemic stroke, we performed a genome-wide Bayesian colocalization analysis.22 This analysis highlighted one region around the same *PDE3A* gene where the underlying genetic variation was highly likely to be associated with both FMD and ischaemic stroke (Posterior Probability = 97%; Figure 1). The most likely causal SNP based on Bayesian colocalization was rs11045239, although this was not conclusive (Posterior probability = 65%). The 95% credible set contained four other SNPs: rs12811752, rs11045244, rs7489190, rs10841519. The same *PDE3A* locus was recently reported to be associated at genome-wide significance with ischaemic stroke in MEGASTROKE (lead SNP rs7304841, OR(95% CI)=1.05(1.03-1.07), p=4.9x10-8).2 Effects were similar across ischaemic stroke subtypes: cardioembolic stroke (OR(95% CI)=1.04(1.00-1.08)), large artery stroke (OR(95% CI)=1.05(1.00-1.10)), and small vessel stroke (OR(95% CI)=1.05(1.01-1.08)). No other regions were highlighted with posterior probability of shared genetic effects greater than 50%.

Having established that genetic variation in a single locus in *PDE3A* is associated with both ischaemic stroke and FMD, we sought validation of the association in other cohorts with FMD data. As no other cohorts with genetic data and FMD measurement in adolescents exist to our knowledge, we sought replication in adult populations. In the Young Finns Study, we first analysed the youngest individuals (the first quartile: 24-27 years, N=599) that most closely resemble the discovery cohort. In these individuals there was evidence at nominal significance that the variant was associated with disease (beta(SE)=0.47(0.23); p=0.047). Conversely, when considering the whole cohort (age 24-45, N=2337), we did not observe a significant effect (beta(SE)=0.14(0.13);p=0.25). We also explored whether the same variant was associated with FMD in older individuals from the Framingham Heart Study and Multi-Ethnic Study of Atherosclerosis (N=1,186). We found no evidence of an association in this older group (beta(SE)=-0.012(0.13); p=0.89). These results might indicate that the genetic variant identified in the study has different influence on endothelial function in adolescents compared to adults.

To establish whether variation in *PDE3A* was associated solely with endothelial function, or influenced other cardiovascular pathways, we looked at association of the *PDE3A* rs11045239 SNP with other cardiovascular risk factors and outcomes in large publicly available datasets and UK Biobank. The *PDE3A* rs11045239 variant was not associated with any other related cardiovascular traits or outcomes (all p>0.05, Figure 2), suggesting the association with ischaemic stroke is not mediated through alternative cardiovascular pathways.

In addition, we looked at the association of *PDE3A* SNP rs11045239 and its proxies with mRNA expression of *PDE3A* in coronary arteries from GTEx. Although rs11045239 was not significantly associated with *PDE3A* expression (p=0.075), all proxy SNPs showed association at p<0.05 (Table 2). The A allele association with increased FMD and risk of stroke was associated with lower levels of *PDE3A.* Therefore, although not conclusive, this finding is consistent with variants in the *PDE3A* locus influencing expression of *PDE3A* in relevant tissues*.*

## Discussion

We identified a genetic variant in the Phosphodiesterase 3A gene which was associated at genome-wide significance with both FMD in early life and ischaemic stroke. Colocalisation analyses indicated that the same genetic variation in *PDE3A* associated with ischaemic stroke is also associated with FMD, thereby showing the shared association is not merely coincidental. The association with variants in *PDE3A* was consistent across all stroke subtypes, which are presumed to have distinct aetiologies. It therefore seems probable that the variant acts via a risk factor common to all subtypes. Exploring association of the same genetic variant with multiple other cardiovascular risk factors and outcomes, we could find no association that the variant also acts via other independent processes. There was some suggestion that variants at the *PDE3A* locus influence expression of *PDE3A* in coronary arteries, although this was not conclusive. An interpretation consistent with this data is that the associated genetic locus influences expression of *PDE3A* in arterial tissues, which leads to altered endothelial function and subsequent risk of ischaemic stroke. Mediation analysis might help to shed light on whether this is a potential causal pathway.

Although it is not possible to determine the exact mechanism by which the *PDE3A* variant confers risk of ischaemic stroke and alters endothelial function without further experimental data, some speculation on potential pathways is warranted. In vascular smooth muscle, phosphodiesterases play a key role in the nitric oxide / c-GMP pathway, one of the most important regulators of vascular smooth muscle contraction and platelet activation. Nitric oxide (NO) activates soluble guanylyl cyclase (sGC), which activates cyclic guanosine monophosphate (c-GMP), activating many signalling molecules, in particular protein kinase G (PRKG), which in turn promotes vascular smooth muscle contraction. Phosphodiesterases decompose c-GMP as well as cyclic adenosine monophosphate (c-AMP), into GMP and AMP, respectively. This has the effect of monitoring the influence of c-GMP on downstream processes such as smooth muscle contraction and platelet activation. Inhibition of Phosphodiesterases has therefore been a target of multiple pharmaceuticals, with the intended effect of prolonging the influence of c-GMP and promoting vasodilation. One such pharmaceutical, Cilostazol, is a selective inhibitor of Phosphodiesterase type 3, and is used primarily to treat peripheral vascular disease. Studies in East Asian populations suggest it ameliorates endothelial dysfunction, and reduces recurrent stroke rates in patients with previous stroke,32 although not all studies have been positive, 33 and it is currently being trialled for use to prevent recurrence after lacunar stroke in European populations. 34 Off-label studies have also suggested it has the potential to prevent progression of intracranial arterial stenosis.35 However, *PDE3A* is also expressed in cardiac muscle and whether the variant might influence stroke risk (particularly of cardioembolic source) via altered expression in the heart cannot be ruled out.

Why we detected an association of the *PDE3A* locus with endothelial function in adolescence, but not in adults, deserves further consideration. Ageing has a considerable impact on endothelial biology; 36, 37 normal endothelial function in children has a different molecular basis to the (dysfunctional) endothelium of older adults. In particular, decreases in NO production, expression of endothelial NO synthase, 38 expression of cell adhesions molecules such as ICAM1 (intercellular adhesion molecule 1) and growth factors such as VEGF (vascular endothelial growth factor), as well as increases in levels of endothelin with age, contribute significant changes to endothelial biology. Whether these factors lead to a fundamental change in the relationship between the *PDE3A* locus and endothelial function, or simply influence the signal to noise ratio and therefore our ability to detect an effect, remains unclear. Nevertheless, the fact that the same *PDE3A* locus has a subsequent influence on stroke risk suggests that the changes that occur in adolescence have a lasting impact on the vasculature and subsequent pathological processes.

Our study has limitations. We demonstrate that genetic variation that influences levels of *PDE3A* influences endothelial function and subsequently, ischaemic stroke. As such we demonstrate a pathway by which risk of stroke conferred. However, we cannot rule out other horizontal pathways by which the *PDE3A* locus also lead to risk of ischaemic stroke. However, we note that our analysis of other cardiovascular risk factors showed no association. As we were not able to assess endothelium-independent vasodilation in response to a nitrate we cannot be absolutely conclusive that our FMD measure results reflect endothelium-dependent vasodilation. Rather, it is possible that they reflect non specific alterations in vascular reactivity.

**Perspectives**

In conclusion we show that genetic variation in Phosphodiesterase 3A leads to altered endothelial function in early life, mostly likely via expression of *PDE3A,* and also leads to increased risk of ischaemic stroke, thus elucidating a pathway by which risk of disease is likely conferred.

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**Author’s Contributions**

HSM and MT conceived the study and obtained funding. MT and AAAO designed the analysis plan; MT, AAAO, SM, JC, LPL performed the statistical analyses. MT and AAAO wrote the first draft of the manuscript. L-OL, TL and OR contributed data. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

All research participants contributing clinical and genetic samples for analysis in this study provided written informed consent. Ethical approval for the ALSPAC study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

**Availability of data and materials**

ALSPAC: http://www.bristol.ac.uk/alspac/researchers/

MEGASTROKE GWAS: <http://megastroke.org>

Coronary Artery Disease GWAS: <https://www.cardiomics.net/download-data>

Type 2 Diabetes GWAS: <http://www.diagram-consortium.org/downloads.html>

Atrial Fibrillation GWAS: <http://www.broadcvdi.org/>

UK Biobank: <https://www.ukbiobank.ac.uk/>

Smoking Status: <https://conservancy.umn.edu/handle/11299/201564>

**Conflicts of Interest/Disclosures**

Dr. Anderson has consulted for ApoPharma, Inc.

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**Novelty and Significance**

What is New?

* Using a large scale genetic study of stroke (MEGASTROKE) and a study of endothelial function in adolescents (ALSPAC), we identified a genetic locus in the *PDE3A* gene, encoding Phosphodiesterase 3A, that was associated with both endothelial function and ischaemic stroke. The genetic variant was not associated with any other cardiovascular risk factor suggesting its influence on stroke acts solely through altered endothelial function.

What is Relevant?

* Our results highlight a pathway that in adolescence is influenced by genetic variation, which influences risk of stroke in later life.

Summary

Genetic variation in *PDE3A* influences risk of stroke through altered endothelial function, as measured by flow mediated dilatation.

**Figure 1.** Plots of -log10(p-value) for association of SNPs in the *PDE3A* gene region with (A) Flow Mediated Dilation in adolescents and (B) Ischaemic Stroke

A close up of a map

Description automatically generated

Each point indicates a SNP association with the trait, with colour indicating correlation (r2)with the lead SNP, rs11045239. Red line indicates Recombination Rate (CM/Mb) at this region of the genome. A, SNP associations with Flow Mediated Dilatation by chromosome position; B, SNP associations with ischaemic stroke by chromosome position.

**Figure 2.** Plot of the association of each risk allele (effect size and 95% confidence interval) of the *PDE3A* rs11405239 SNP on (A) Cardiovascular Risk Factors and (B) Cardiovascular Disease Outcomes and Binary Risk Factor traits. A close up of text on a white background

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Note: Exact numbers of cases and controls were not available in publicly available data for ever smoking.

**Table 1.** Study Populations

|  |  |  |
| --- | --- | --- |
| **Phenotype** | **Study** | **Sample Size** |
| Ischaemic Stroke | MEGASTROKE | 60,341 cases  452,969 controls |
| FMD (young population) | ALSPAC | 5,214 |
| Young Finns Study (24-27 years)  (24-45 years) | 599  2,377 |
| FMD (older population) | Multi-Ethnic Study of Atherosclerosis (MESA) | 1,029 |
| Framingham Heart Study (FHS) | 393 |

**Table 2.** Association of SNPs in LD with rs11045239 with mRNA expression of *PDE3A* in coronary arteries from GTEx (N=152)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| SNP | BP on Chromosome 12 | Effect Allele | Other Allele | Beta | P-value | R2 with rs11045239 |
| rs10841524 | 20589183 | A | G | 0.13 | 0.0085 | 0.85 |
| rs10841523 | 20588575 | G | A | 0.13 | 0.012 | 0.85 |
| rs11045245 | 20589390 | A | G | 0.13 | 0.012 | 0.83 |
| rs12811752 | 20577805 | T | C | 0.11 | 0.026 | 0.93 |
| rs12367495 | 20585416 | C | T | 0.1 | 0.033 | 0.98 |
| rs10841519 | 20584767 | G | C | 0.1 | 0.037 | 1 |
| rs7489190 | 20585027 | G | A | 0.098 | 0.048 | 0.98 |
| rs11045239 | 20579694 | G | A | 0.089 | 0.075 | 1 |

Note: Beta refers to the estimated influence of the Effect allele of each SNP on mRNA expression of PDE3A; SNP, Single Nucleotide Polymorphism; BP, base position.