Calculating polygenic risk score for individuals with sporadic early onset Alzheimer's disease

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Abstract

Sporadic early onset Alzheimer's disease (sEOAD) exhibits the symptoms of late onset Alzheimer's disease (LOAD) but lacks the familial aspect of the early onset familial form. The genetics of Alzheimer's disease (AD) identifies the *APOE* ε4 allele to be the greatest risk factor; however, it is a complex disease involving both environmental risk factors and multiple genetic loci. Polygenic risk scores (PRS) accumulate the total risk of a phenotype in an individual based on variants present in their genome. We determined whether sEOAD cases had a higher PRS compared to controls. A cohort of sEOAD cases were genotyped on the NeuroX array and PRS were generated using PRSice. The target dataset consisted of 408 sEOAD cases and 436 controls. The base dataset was collated by the IGAP consortium, with association data from 17,008 LOAD cases and 37,154 controls, which can be used for identifying sEOAD cases due to having shared phenotype. PRS were generated using all common SNPs between the base and target dataset, PRS were also generated using only SNPs within a 500kb region surrounding the *APOE* gene. Sex and number of *APOE* ε2 or ε4 alleles were used as variables for logistic regression and combined with PRS. The results show that PRS is higher on average in sEOAD cases than controls, although there is still overlap amongst the whole cohort. Predictive ability of identifying cases and controls using PRSice was calculated with 72.9% accuracy, greater than the *APOE* locus alone (65.2%). Predictive ability was further improved with logistic regression, identifying cases and controls with 75.5% accuracy.

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1 Introduction

1.1 Alzheimer's Disease

Dementias are a group of brain diseases characterised by memory loss, changes in personality and behaviour, and difficulty with language and visuospatial skills beyond the normal considerations with aging. Globally, 46.8 million people are affected by dementia, a number that will rise with aging populations living longer (Prince, 2015). The most common form is Alzheimer's disease (AD) (Budson and Kowall, 2011). AD pathology is still unclear, however the presence of amyloid-β (Aβ) senile plaques and neurofibrillary tau tangles (NFTs) are used as biomarkers of disease in clinical diagnosis, appearing before symptoms of disease and present in post-mortem examination (Jack *et al*., 2016). Symptoms of AD increase in severity as the disease progresses, from mild to moderate and severe AD. AD is characterised by deterioration of working memory, anterograde episodic amnesia, and semantic memory; difficulty with language, visuospatial and perceptual skills are symptoms of moderate and severe AD.

Aging is a natural part of life and cognitive decline is a normal process, AD causes cognitive decline to occur at a rate greater than expected. Loss of neurones occurs three times faster in AD cases than the elderly (Barber, 2016). Aβ deposits can be present in aging brain tissue; however, in AD brains the Aβ deposits form oligomers and propagate in greater proportions in the parenchymal parts of the brain. The propagation of Aβ also occurs in the walls of arteries veins and capillaries within the brain, which is classed as cerebral amyloid angiopathy (CAA) (Thal *et al*., 2002). NFTs identified in post-mortem tissue are a result of hyper-phosphorylation of tau phosphoprotein (p-tau) deposits in the perikaryon, cell death can lead to extracellular presence of NFTs (Duyckaerts *et al*., 2009).

There is correlation between severity of disease and levels of NFTs, severity increases with increased levels of tau hyper-phosphorylation; correlation with Aβ deposition occurs only with Aβ oligomers and not deposition, as controls with high Aβ burden and AD with no deposits can occur (Bierer *et al*., 1995).

Disease progression in AD is highlighted by an increase in symptoms caused by neuronal loss in different regions of the brain. Cortical shrinkage is evident in the hippocampus, affecting memory storage and formation, symptoms of mild AD; damage to the frontal cortex and cingulate gyrus affect cognitive function, specifically language and emotional processing, evident as a change personality of individuals with severe AD entirely.

Post-mortem examination remains the definitive method of diagnosis for AD. Diagnosis for AD is completed with varying methods, the recommended diagnosis tool was to follow criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRD). Testing biomarkers provides qualitative indicators for the likelihood of AD in an individual, an individual can be diagnosed based on the results of either amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) $A\beta_{42}$ as an indicator of higher levels of Aβ deposition; CSF p-tau or tau PET as an indicator of tau pathology; and one of three

biomarkers which indicate neurodegeneration or neuronal injury with total tau (CSF t-tau), measure cerebral glucose metabolism rates with fluorodeoxyglucose PET (FDG-PET) or structural MRI scans (Jack *et al*., 2016).

Mild cognitive impairment (MCI) is a condition present at an early age which differs from normal aging (Hodges, 2006). When MCI is diagnosed in individuals, many go on to develop AD whilst the remainder are classed as non-converters (Hodges, 2006). The likelihood of developing AD is greater amongst individuals with MCI than healthy individuals (Hodges, 2006).

1.1.1 Genetics of AD

Onset of AD usually occurs in individuals 65 years of age or older, however 5% of cases are early-onset AD (EOAD) with symptoms being seen before the age of 65 (Minati *et al*., 2009). EOAD can be characterised into two further subtypes, early-onset familial AD (EOFAD) and the sporadic form (sEOAD) which shares genetic aetiology with late-onset AD (LOAD). EOFAD often occurs in individuals with a family history of AD, due to autosomal dominant inheritance. Many variants within the genes Amyloid precursor protein (*APP*), Presenilin 1 (*PSEN1*) and Presenilin 2 (*PSEN2*) have been identified and confirmed to cause EOFAD (Liu, C. *et al*., 2013). LOAD has a more complex aetiology and is considered to be caused by multiple variants rather than a single cause (Wingo *et al*., 2017).

LOAD has an estimated heritability of 70%, whereas this estimate for sEOAD is 90-100% (Barber, 2016; Wingo *et al*., 2017). Genome wide association studies (GWAS) have identified 20 genetic loci which affect the risk of developing LOAD (Lambert *et al*., 2013). Next-generation sequencing (NGS) has uncovered many more variants affecting this risk, such as those found within the *TREM2* gene (Guerreiro *et al*., 2013; Jonsson *et al*., 2013). The discovery of variants, with a spectrum of varying effect size and allele frequency, implicates alternative processes which are involved in the aetiology of AD. The spectrum of genetic variants which affect risk of AD are shown in Figure 1.

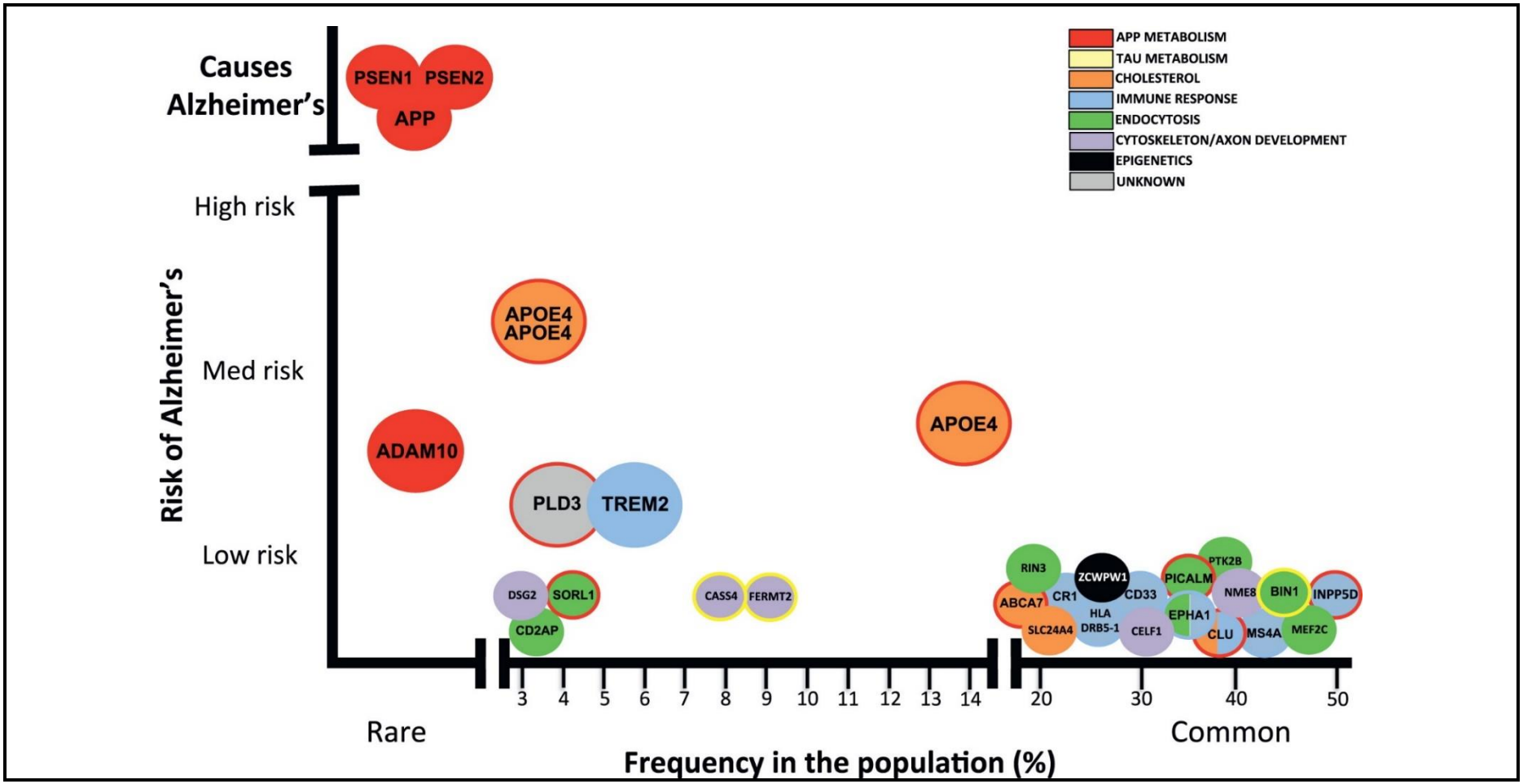


Figure 1 – The range of genes identified to affect risk of AD

The figure identifies genes containing variants implicated in AD, discovered using genome wide association studies (GWAS), whole genome and whole exome sequencing. The genes are distributed by increasing risk on AD and allele frequency in the population. Most common variants were identified in GWAS, and rarer variants were found by NGS. Genes are coloured by the processes they are known to be involved in. The figure is taken from Karch and Goate (2015).

1.2 Genotyping Arrays

Genotyping arrays are an alternative to whole-genome or whole-exome sequencing. The process is more cost-effective, quicker to deploy, and results are easily analysed with accessible tools (Nalls *et al*., 2015). Arrays can be adaptable and contain thousands of markers that have been previously implicated in specific diseases. Using an array for genotyping individuals to calculate polygenic risk scores (PRS) can provide a greater coverage of the heritable risk of disease without the expense of sequencing.

The NeuroX is an array designed to capture genetic risk variants identified in many neurodegenerative diseases including AD, frontotemporal dementia, Parkinson's disease, Amyotrophic lateral sclerosis, and multiple sclerosis (Nalls *et al*., 2015). Some of the variants included on the array have not been fully researched and understood, as they were not identified as significant in GWAS.

1.3 Polygenic Risk Scoring

PRS are calculated using the cumulative effects of variants across the genome to identify an individual's overall risk for a given phenotype. Complex disorders are thought to be caused by an accumulation of many common, low-risk variants. A greater number of risk variants harboured by an individual increases their PRS. By producing a model which identifies individuals with high-risk for AD, the potential for early screening, diagnosis and greater definition of disease severity becomes possible (Eusden, *et al*., 2014).

In a recent study by Escott-Price *et al*. (2015) PRS were calculated for a cohort of LOAD cases and controls. The study used genotype information from the cohort to identify common variants that affect the risk of developing AD. PRS generated were used to form a risk prediction model, which achieved predictive ability of 78.2%. The study was followed up recently with the calculation of risk in LOAD cases diagnosed post mortem, and alternative methods to improve predictive ability (Escott-Price *et al*., 2017a; Escott-Price *et al*., 2017b).

PRSice was first used in a study for major depressive disorder (MDD) using schizophrenia as a base phenotype (The International Schizophrenia Consortium, 2009). The study highlights the ability to predict MDD using genetic risk of schizophrenia, identifying the two complex disorders to be concordant. The results mean that risk variants in one disorder can be pleiotropic and affect the risk of another disorder. Therefore, a base dataset using effect scores based on LOAD can be used for identifying risk in sEOAD, as they share genetic aetiology.

1.3.1 PRSice

The PRSice software package generates PRS from genotype information of individuals in a target dataset based on the effect scores of variants in an independent base dataset (Eusden *et al*., 2014). The program uses R to define parameters and PLINK for the computational analysis (Purcell *et al.*, 2007; R Core Team, 2013). PRSice is a command line program that allows specific parameters to be considered when generating PRS. The output

includes a list of individual scores at the best-fit threshold for predicting disease risk and a list of each tested threshold with its corresponding Nagelkerke's R^2 value, quantifying the level of predictability with that threshold (Eusden *et al.*, 2014).

1.3.2 Considerations

Linkage disequilibrium (LD) describes the association of alleles at different loci which are inherited together in a population. LD is often considered when SNPs are scored based on their weighted effect and allele frequency amongst cases and controls of a disease. The alleles of two SNPs present on the same chromosome can be commonly inherited together. The recurrence of an index SNP with another SNP at a locus is an indicator of the degree of LD between variants (Bush and Moore, 2012). Given two SNPs in tight LD, both could be perceived as contributing to the disease risk in a functional haplotype, however it may be that only one polymorphism is responsible for the phenotypic effect. Implicating a variant affecting risk of developing a disease which has no phenotypic effect reduces the accuracy of results and presents a false positive in discovery. This can be controlled for with PRSice by limiting the correlation allowed between any two SNPs present on the same chromosome to ensure each SNP included in the analysis has phenotypic effect, the SNP with no phenotypic effect can be pruned out.

1.4 Aims of the Study

The aim of this study was to develop a model to distinguish between sEOAD cases and controls. This is completed by using a genotyped dataset of sEOAD cases and controls and generating PRS using PRSice and a base dataset of LOAD cases and controls. Predictive ability of the PRS at correctly identifying cases vs controls was calculated and compared with alternative models to find the greatest predictive ability.

2 Methods

2.1 Samples

Individuals were recruited from seven centres across the UK (Belfast, Bristol, Leeds, Manchester, Nottingham, Oxford, and Southampton) and one centre in Germany (Bonn), DNA was collected from 451 sEOAD cases and 528 controls. The demographics of the cases and controls in the cohort are described in Table 1. To minimise inclusion of familial cases, all sEOAD cases were screened for variants implicated in EOFAD in *PSEN1*, *PSEN2* and exons 16 and 17 of *APP*. All sEOAD cases had a documented or predicted age of onset below 65 to rule out LOAD. Guidelines set by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), the Alzheimer's disease and Related Disorders Association (ADRDA) and the Consortium to Establish a Registry for Alzheimer's disease (CERAD) were used to diagnose definite (post-mortem confirmed) or probable AD. Experimental procedures were completed by I. S. Barber, with informed consent in concordance with guidelines approved by the local ethics committee (Nottingham Research Ethics Committee 2 (REC reference 04/Q2404/130). A standard phenol chloroform DNA extraction method was used on blood (2ml) or brain (100mg) tissue. DNA was quantified on the NanoDrop 3300 spectrometer and assessed for quality using gel electrophoresis (Barber *et al*., 2017).

A

Centre	N	Mean age at onset	Females (%)	*APOE* ε4+ (%)	*APOE* ε4ε4 (%)
Bristol	24	53.5	11 (45.8)	12 (50.0)	3 (12.5)
Manchester	356	57.3	171 (48.0)	211 (59.3)	49 (13.8)
Nottingham	37	58.5	18 (48.6)	17 (45.9)	2 (5.4)
Oxford	34	55.5	19 (55.9)	20 (58.8)	4 (11.8)
All sEOAD Cases	**451**	**57.0**	**219 (48.6)**	**260 (57.6)**	**58 (12.9)**

B

Centre	N	Mean age at death	Females (%)	*APOE* ε4+ (%)	*APOE* ε4ε4 (%)
Belfast	47	73.8	33 (70.2)	9 (19.1)	0 (0.0)
Bonn	134	74.9	74 (55.2)	41 (30.6)	3 (2.2)
Leeds	191	78.4	98 (51.3)	39 (20.4)	4 (2.1)
Manchester	3	83.7	2 (66.7)	0 (0.0)	0 (0.0)
Nottingham	111	77.4	41 (36.9)	22 (19.8)	0 (0.0)
Oxford	15	81.5	11 (73.3)	3 (20.0)	0 (0.0)
Southampton	27	77.1	12 (44.4)	6 (22.2)	0 (0.0)
All Controls	**528**	**76.9**	**271 (51.3)**	**120 (22.7)**	**7 (1.3)**

Table 1 – Sample demographics for sEOAD cases and controls in the cohort.

(A) The sEOAD cases are recruited from four centres within the UK, the age of onset is either documented or estimated (based on disease duration and age at death), the proportion of female individuals, and the number of individuals harbouring at least one APOE ε4 allele was recorded as well as the number individuals with the ε4ε4 genotype. **(B)** The controls were recruited from several centres across the UK as well as Bonn, Germany. The age at death is given and the number and proportion of females from each centre. The number of controls harbouring at least one *APOE* ε4 allele is given along with the number and proportion of controls with the ε4ε4 genotype. The *APOE* ε4 minor allele frequency (MAF) for all sEOAD cases was 0.51 and estimated as 0.12 for controls.

2.2 NeuroX array

Data quality control (QC) was carried out by I. S. Barber. The first stage of QC was performed in Illumina GenomeStudio 2011.1, shown in Figure 2. Results produced on the microarray were given as raw fluorescent signal reads (.idat). Reads were imported into the program each marker formed clusters based on genotypes for individuals with a sample call rate >0.99; individuals with low sample call rate were 'zeroed', made inactive by the program, to produce more accurate cluster regions. The clustering process was completed automatically by the program or assisted using a cluster file specific to the microarray, provided by the CHARGE consortium. Of the total 267,607 markers on the NeuroX array, 218,600 were clustered using the cluster file and the remainder were clustered by the program (Barber *et al*., 2017). Clusters were assessed to determine if an individual's DNA quality was too poor for producing accurate results or if any assays were poorly designed for markers. Markers of non-autosomal SNPs, on chromosomes X, Y, and the pseudo autosomal region, were assessed by individual chromosome, whilst all autosomal SNPs were assessed together. Individuals with low sample call rate, zeroed before QC, were re-introduced as call rate improved once clustering had been assessed.

The second stage of QC was performed in PLINK (Purcell, *et al*. 2007). Individuals with a call rate of <95% were removed and SNPs with a call rate of <90% were removed. Other assessments were based on identifying any individuals who would affect results by being too closely related, or not of European ancestry. SNPs were also filtered by whether they adhered to Hardy-Weinberg equilibrium (HWE) using a Bonferroni corrected p-value of 1×10^{-6}, and fall within the expected level of heterozygosity of ±3 standard deviations (Barber, 2016).

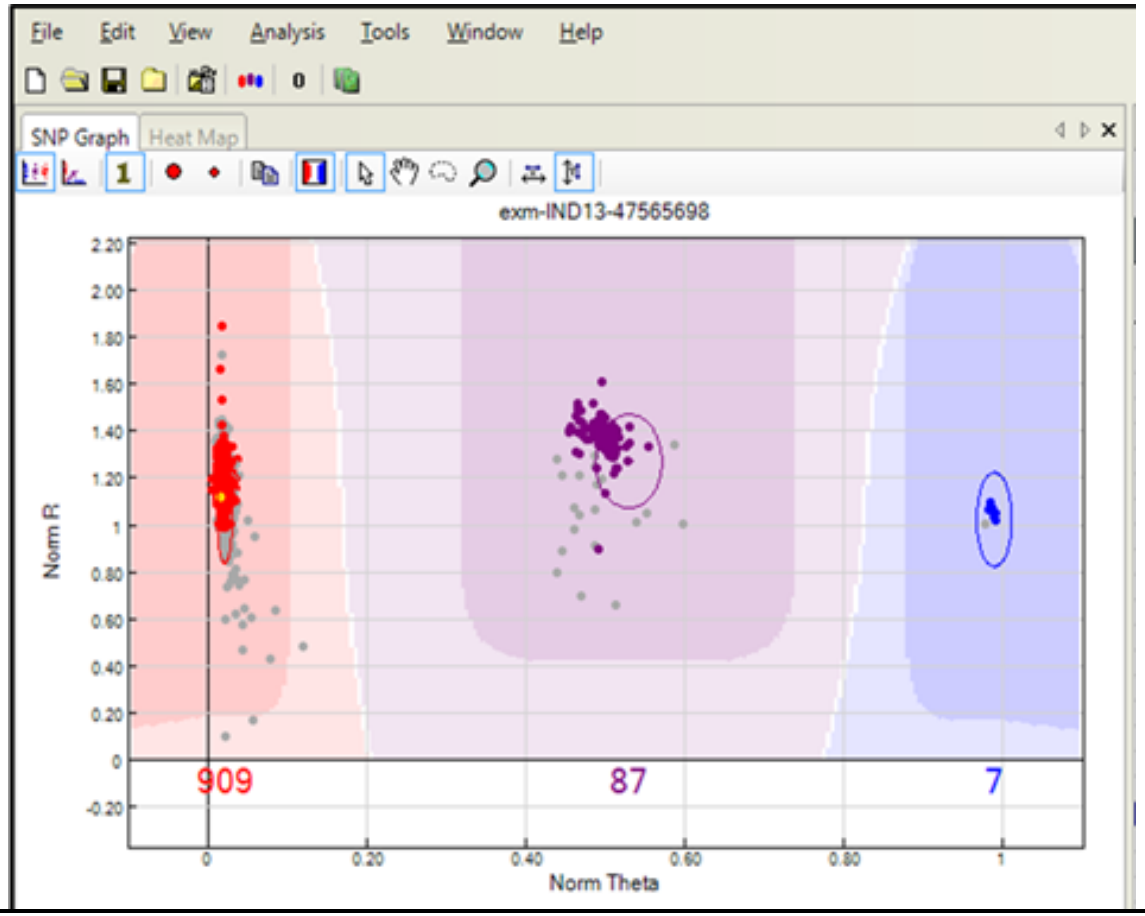


Figure 2 – Cluster assessment in GenomeStudio 2011.1

The figure represents the clustering process of the marker exm-IND13-47565698. The automatic clustering identified 909 individuals homozygous for the major allele (red), 87 individuals with a heterozygous genotype (purple) and 7 individuals homozygous for the minor allele (blue). The remaining individuals (grey) had been zeroed and were inactive when forming the cluster bounds. Clusters were expected to form as tightly packed regions with high intensity, close to the centre of the cluster. The positions at which clusters form were determined by which alleles were present and if there were any heterozygotes, the clusters should also be distant from one another.

Centre	N	Mean age at onset	Females (%)	*APOE* ε4+ (%)	*APOE* ε4ε4 (%)	Definite AD	Probable AD
Bristol	21	53.3	9 (42.9)	10 (47.6)	3 (14.3)	21	0
Manchester	328	57.1	156 (47.6)	196 (59.8)	46 (14.0)	53	275
Nottingham	26	58.2	12 (46.2)	11 (42.3)	1 (3.8)	5	21
Oxford	33	55.6	19 (57.6)	19 (57.6)	3 (9.1)	24	9
Cases	**408**	**56.8**	**196 (48.0)**	**236 (57.8)**	**53 (13.0)**	**103**	**305**

Table 2 – Sample demographics of sporadic early onset Alzheimer's disease (sEOAD) cases after quality control in Illumina GenomeStudio 2011.1 and PLINK.

A total of 43 sEOAD cases failed QC and were removed, leaving 408 cases for analysis as outlined above.

2.3 Polygenic Risk Scoring

PRS for all individuals were calculated using PRSice (Eusden *et al*., 2014). PRSice is a command-line program which uses an R script to incorporate the SNP information from an independent base dataset and generate scores based on the genotypes of individuals in the target dataset. The base dataset consisted of IGAP association data for individuals with LOAD, in a text file (.txt or .assoc). information contained in the file included chromosomal location, identification of which allele affects risk, P-value, and effect score as either a β-value, θ-value, or odds ratio (OR).

The data accumulated by the IGAP consortium was derived from a meta-analysis of genome wide association studies (GWAS) performed by Genetic and Environmental Risk for Alzheimer's Disease (GERAD), European Alzheimer's Disease Initiative (EADI), Cohorts for Heart and Ageing Research in Genomic Epidemiology (CHARGE), and Alzheimer's Disease Genetics Consortium (ADGC).

The target dataset was in PLINK binary ped format (.bim, .bed and .fam), containing information for individuals with sEOAD. PRSice took the base dataset, target dataset and the PRSice_v1.25.R script as input arguments.

The requirements for PRSice included PLINK v1.9 and R v3.1 or later. PRSice produces results based on the parameters set. The following command was used to generate results. The script parameters are explained in Table 3.

```
R -q –file=./PRSice_v1.25.R –args \
base IGAP_stage_1.txt \
target NeuroX_sEOAD \
slower 0 \
supper 1 \
sinc 0.001 \
clump.snps F \
prune.snps T \
prune.kb.r2 0.8 \
best.thresh.on.bar F \
report.individual.scores T \
report.best.score.only F \
plink ~/plink2 \
figname PRS_NeuroX
```

Command	Parameter	Task
slower	0	Lower threshold of P-value testing
supper	1	Upper threshold of P-value testing
sinc	0.001	Increments of P-value testing
clump.snps	F	Clump SNPs in LD
prune.snps	T	Prune SNPs in LD
prune.kb.r2	0.8	R^2 value for LD pruning
best.thresh.on.bar	T	Produce best-fit bar plot
report.individual.scores	T	Produce individual scores list
report.best.score.only	F	Show results for best threshold or all thresholds
figname	PRS_NeuroX	Output file name

Table 3 – Script used in the command line for PRSice and the task performed.

The table identifies all the commands used in PRSice along with parameter set for them and the task performed by the command. The commands are either settings where a value is required, or queries indicated as either true or false. The P-value thresholds are controlled using `supper`, `slower` and `sinc`; all SNPs common to both datasets are tested based on their P-value to the thousandth. LD pruning is controlled using `clump.snps`, `prune.snps` and `prune.kb.r2`. PRSice requires either clumping or pruning to be turned on and the other to be turned off, SNPs in LD with an index SNP are tested on their r^2 value and SNPs with an r^2 value of 0.8 or greater are pruned out. The output file by default produces a series of individual scores at the best-fit threshold; however, turning `report.best.score.only` off produces individual scores at all tested thresholds.

2.4 Statistical Analysis

The results produced in PRSice were imported into Excel, the best fit p-value threshold was identified in one output file of PRSice and scores for each individual at each tested threshold were identified in another. A scatter graph was produced of scores for each phenotype for comparison. Individual PRS at the best-fit threshold are included as Appendix I.

Decile scoring was used to identify trends in the data. The range of scores were segmented into tenths and the number of cases and controls within each decile range were counted. Proportions of cases and controls were calculated and a bar graph was produced for identifying trends. Averages for cases and controls at each decile were also incorporated on the scatter graph.

Individual scores with phenotypes were exported to SPSS for statistical analysis. Logistic regression was performed to calculate sensitivity and specificity of the model. A receiver operating characteristic (ROC) curve was produced for the model, from which area under the curve (AUC) was calculated as a value of predictive ability of a model for identifying cases and controls.

2.5 The *APOE* locus

The *APOE* gene correlated with higher risk of AD when harbouring an ε4 allele. The genetic locus of *APOE* has numerous SNPs which have been implicated to affect this risk, and SNPs in genes neighbouring *APOE* (*APOC1* and *TOMM40*) have also been implicated by linkage studies. The *APOE* locus, which contains the LD block in which the variants are present, is extensive. To identify the effect of the *APOE* locus alone on risk of AD, a 500kb region surrounding the *APOE* gene was isolated for analysis. The region was identified in UCSC Genome Browser as chr19:45,160,844-45,660,844 (Kent *et al*., 2002). The variants within this region present on the NeuroX array were identified and extracted to form an alternative target dataset, NeuroX_sEOAD_APOE. The NeuroX_sEOAD_APOE dataset contained 198 SNP genotypes for 408 sEOAD controls and 436 cases. The *APOE* ε4 allele genotyping SNPs, rs7412 and rs429358, were both included in the custom content, however rs429358 failed QC and both SNPs were therefore genotyped manually using TaqMan assays. This dataset was tested in PRSice as with the NeuroX target dataset to produce risk scores. The results were imported into SPSS and sensitivity, specificity, and predictive ability to identify cases and controls using the *APOE* locus were calculated.

All individuals had their age at death, sex and the number of *APOE* ε2 and ε4 alleles documented, cases had an age at onset. Age was excluded as a covariate as the results were not collected for all individuals, controls would not have an age at onset and age at death is expected to be lower in sEOAD cases given age at onset is below 65 and healthy controls are all over 65 years old when sampling. The covariates were combined and tested in SPSS and sensitivity, specificity and AUC were calculated using logistic regression, the covariates were also combined with PRS to identify if predictive ability for identifying cases and controls improved.

A ROC curve was produced comparing the *APOE* locus risk score, PRS, covariates as a risk scoring model, and the combination of PRS with the covariates as a risk score model. Regression models were validated using the Hosmer-Lemeshow P-value. A significant value ($p \leq 0.05$) suggests that the model is poor and a non-significant value is indicative of a good model. Nagelkerke's R^2 value, used by PRSice to identify the best-fit, was also calculated as the greatest Nagelkerke's R^2 value identifies the best model for predicting disease status.

3 Results

3.1 NeuroX QC

The SNPs which failed QC in GenomeStudio were zeroed by the program and became inactive. A total of 2,462 markers were zeroed during the QC process in GenomeStudio. QC in PLINK removed 43 sEOAD cases and 92 controls, 2,558 SNPs were also removed which included 2,462 SNPs zeroed in QC in GenomeStudio (Barber *et al*., 2017). The demographics of the remaining sEOAD cases are shown in Table 2. The base dataset collated by the IGAP consortium contained the SNP information accumulated from the association data of an independent cohort of 17,008 LOAD cases and 37,154 controls. The imputed dataset had statistics for 7,055,881 SNPs of which 28,538 SNPs were common with the target dataset.

3.2 PRS generated using PRSice

The output files of PRSice included a bar plot and a list of all the tested P-value thresholds, their corresponding P-values and Nagelkerke's R^2 values, and a list of the individuals and their PRS at each threshold. The best-fit P-value threshold was identified as $P \leq 0.302$, using 9,434 SNPs, from a Nagelkerke's R^2 value of 0.209, when $P=2.08\times10^{-26}$. P-values and Nagelkerke's R^2 values follow the same trends, the higher the Nagelkerke's R^2 value the lower the P-value; the number of SNPs increase with increasing Nagelkerke's R^2 values until a threshold is reached, then adding more SNPs results in a reduction of Nagelkerke's R^2. This is due to the analysis identifying the greatest predictive ability using the fewest SNPs. A list of some of the tested P-value thresholds with their P-values and Nagelkerke's R^2 values are given as Table 4. The graphs produced by PRSice as output files are shown as Figure 3.

P-value Threshold	P-value	Nagelkerke's R^2	Number of SNPs
≤0.001	3.26×10^{-20}	0.149	141
≤0.002	1.24×10^{-20}	0.154	203
≤0.005	1.01×10^{-21}	0.163	355
≤0.010	1.06×10^{-22}	0.172	546
≤0.020	5.06×10^{-23}	0.176	930
≤0.050	1.14×10^{-23}	0.181	2,022
≤0.100	7.82×10^{-25}	0.193	3,595
≤0.200	6.19×10^{-26}	0.207	6,545
≤0.302	**2.08×10^{-26}**	**0.209**	**9,434**
≤0.500	2.86×10^{-26}	0.207	14,995
≤1.00	7.18×10^{-26}	0.203	28,538

Table 4 – A series of p-value thresholds tested in PRSice.

The table identifies the threshold and the number of SNPs included in the risk scoring model, the P-value, the Nagelkerke's R^2 value corresponding with each threshold increases as the predictive ability of the model at identifying cases and controls increases. A complete list of all p-value thresholds and their corresponding P-values and Nagelkerke's R^2 values is included as Appendix II.

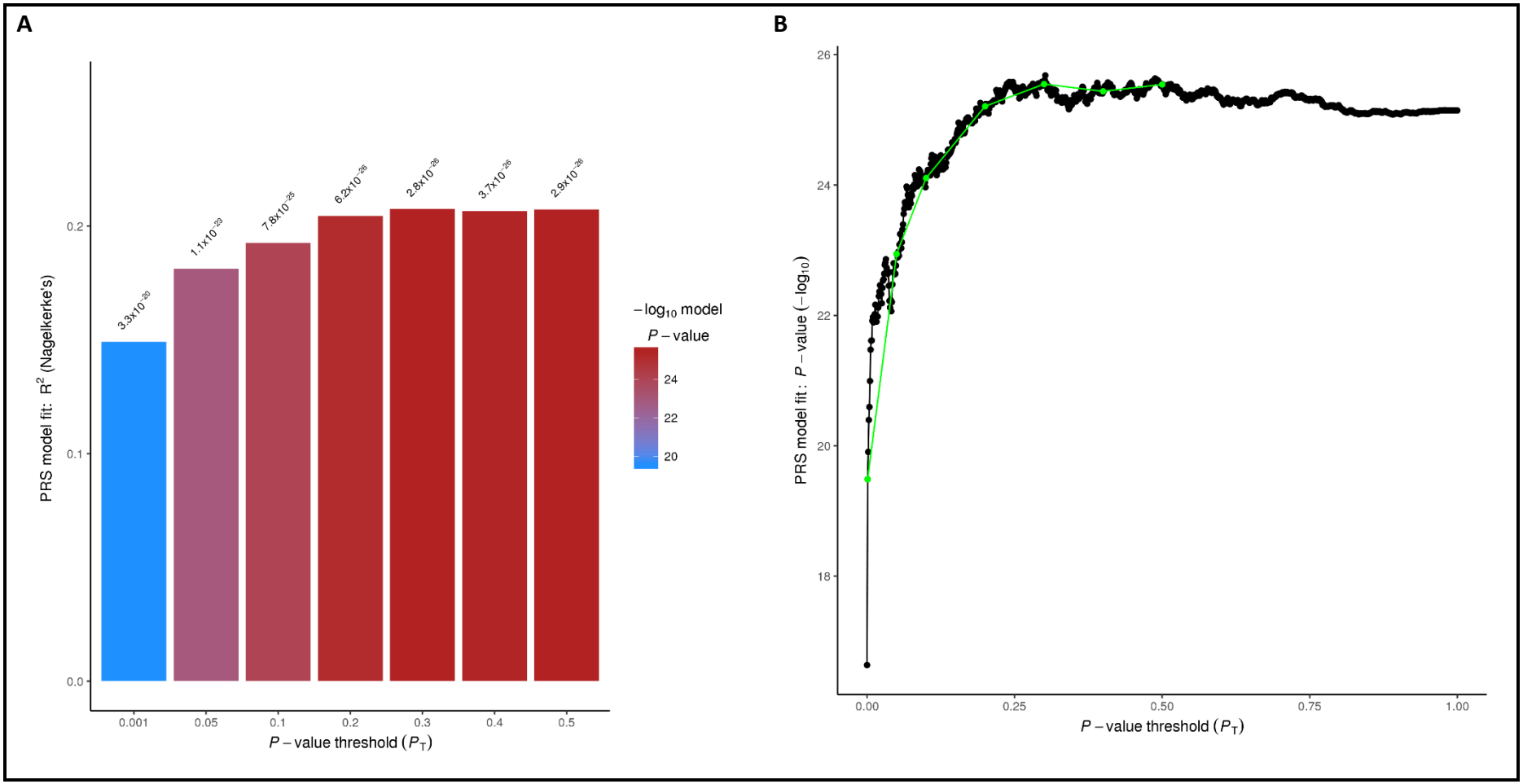


Figure 3 – Output figures produced by PRSice.

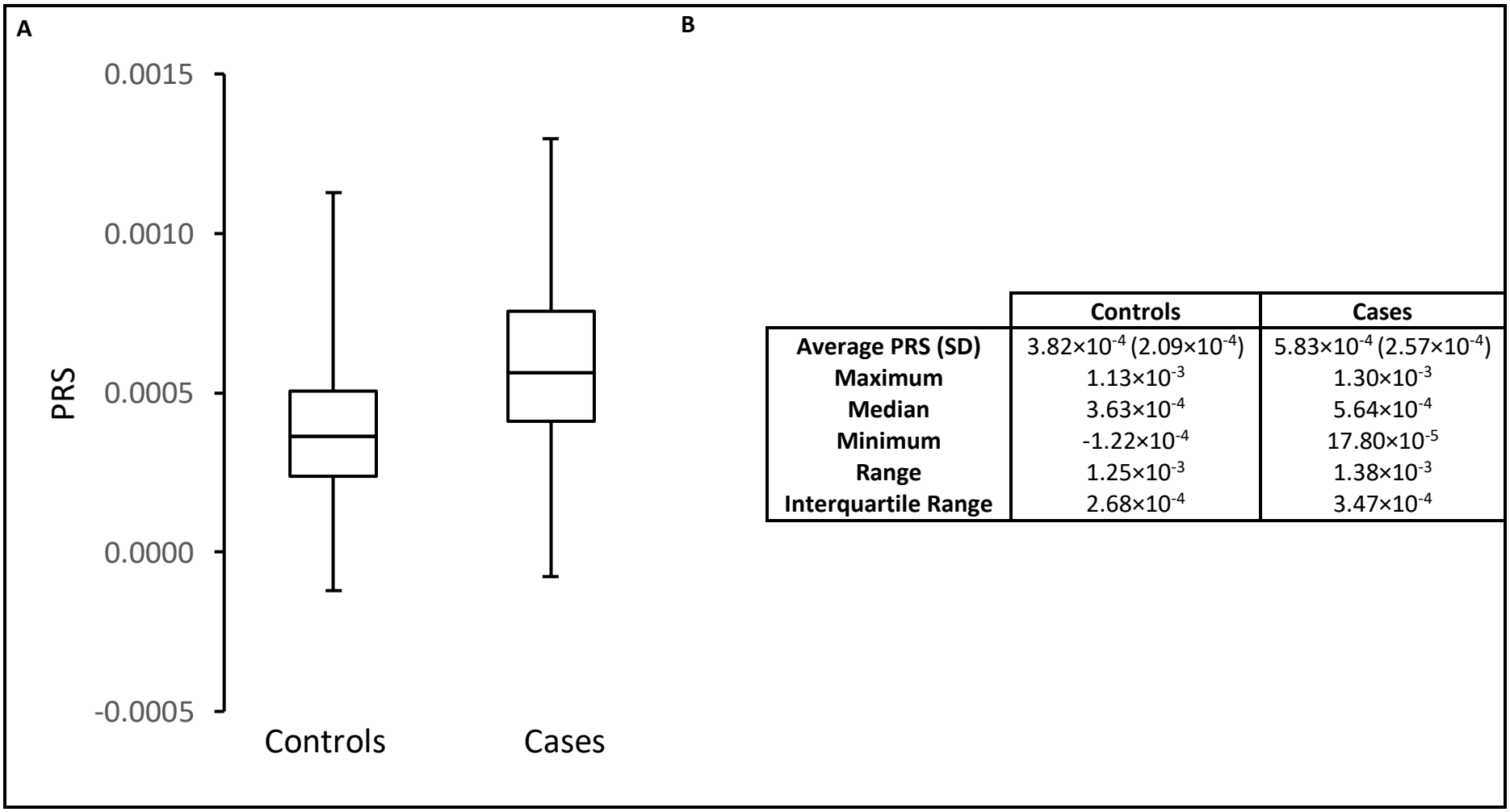
(A) A bar plot comparing Nagelkerke's R2 values with the P-value thresholds tested. The plot describes that a greater predictive model is achieved when more SNPs are included; however, Nagelkerke's R2 value decreases as more SNPs with higher P-values are included, reducing the predictive ability of the model. **(B)** The scatter plot of p-values, irrespective of number of SNPs, in $-\log_{10}$ against the p-value thresholds tested. The lowest p-value, and therefore highest $-\log_{10}$ p-value, is indicative of the greatest predictive ability.

3.2.1 Statistical Analysis

Individual scores at the best-fit P-value threshold were identified and individuals and phenotypes were imported into Excel, the distribution of scores is shown in Figure 4. The distribution of scores are more ranged amongst cases compared to controls. An unpaired t-test identified a significantly greater mean PRS for cases compared to controls with a t-test score of t=12.33 calculating significance as $p<0.0001$. Sensitivity and specificity were calculated in SPSS, the model correctly identified 59.1% of sEOAD cases and 72.9% of controls. The ROC curve produced an AUC value of 72.9%. A Hosmer-Lemeshow P-value was calculated as 0.705 which identifies the model as good. The Nagelkerke's R^2 values were identical between the statistical analysis on SPSS and the result produced in PRSice, which demonstrates the results are reliable.

3.2.2 Decile Scoring

The individual scores ranged from -1.2×10^{-4} to 1.3×10^{-3}, each decile covered a range of around 1.4×10^{-4}. The number of cases and controls in each decile and their average PRS is identified in Table 4 and the percentage of cases and controls within each decile are described in Figure 5. The results show there was a greater proportion of controls in the lower five deciles compared to the upper five deciles, with no controls in the 10th decile. There were five controls present in the 9th decile, which do not typically follow the trend of the data. A PRS score greater than 4.5×10^{-4} suggests a greater chance of being a case than control of sEOAD.



	Controls	Cases
Average PRS (SD)	3.82×10^{-4} (2.09×10^{-4})	5.83×10^{-4} (2.57×10^{-4})
Maximum	1.13×10^{-3}	1.30×10^{-3}
Median	3.63×10^{-4}	5.64×10^{-4}
Minimum	-1.22×10^{-4}	17.80×10^{-5}
Range	1.25×10^{-3}	1.38×10^{-3}
Interquartile Range	2.68×10^{-4}	3.47×10^{-4}

Figure 4 – Distribution of PRS amongst cases and controls.

(A) The box plot shows the distribution of scores for cases and controls, with quartiles and median scores. The box plot identifies a greater range of PRS for cases whilst most controls are more densely populated with a PRS below 5×10^{-4}. **(B)** The table shows there is significant difference ($p<0.0001$) in average PRS in sEOAD cases compared to controls.

Decile	PRS Range	Cases (%)	Average PRS	Controls (%)	Average PRS
1st	$-1.2\times10^{-4} – 2.0\times10^{-5}$	3 (0.7%)	-2.83×10^{-5}	8 (1.8%)	-4.23×10^{-5}
2nd	$2.0\times10^{-5} – 1.6\times10^{-4}$	16 (3.9%)	1.16×10^{-4}	54 (12.4%)	1.00×10^{-4}
3rd	$1.6\times10^{-4} – 3.0\times10^{-4}$	35 (8.6%)	2.54×10^{-4}	102 (23.4%)	2.40×10^{-4}
4th	$3.0\times10^{-4} – 4.5\times10^{-4}$	77 (18.9%)	3.82×10^{-4}	123 (28.2%)	3.74×10^{-4}
5th	$4.5\times10^{-4} – 5.9\times10^{-4}$	84 (20.6%)	5.11×10^{-4}	78 (17.9%)	5.10×10^{-4}
6th	$5.9\times10^{-4} – 7.3\times10^{-4}$	78 (19.1%)	6.53×10^{-4}	45 (10.3%)	6.52×10^{-4}
7th	$7.3\times10^{-4} – 8.7\times10^{-4}$	56 (13.7%)	7.95×10^{-4}	20 (4.6%)	7.88×10^{-4}
8th	$8.7\times10^{-4} – 1.0\times10^{-3}$	38 (9.3%)	9.40×10^{-4}	1 (0.2%)	9.40×10^{-4}
9th	$1.0\times10^{-3} – 1.1\times10^{-3}$	13 (3.2%)	1.06×10^{-3}	5 (1.1%)	1.06×10^{-3}
10th	$1.1\times10^{-4} – 1.3\times10^{-4}$	8 (2.0%)	1.24×10^{-3}		

Table 5 – Number of sEOAD cases and controls at each decile.

The table identifies each decile and the range of scores they cover. The number of cases are given with the proportion of cases within each decile indicated and the average PRS of cases within each decile. The number of controls are also given with the proportion of all controls whose PRS fall within the decile range and the average PRS of controls who fall in each decile.

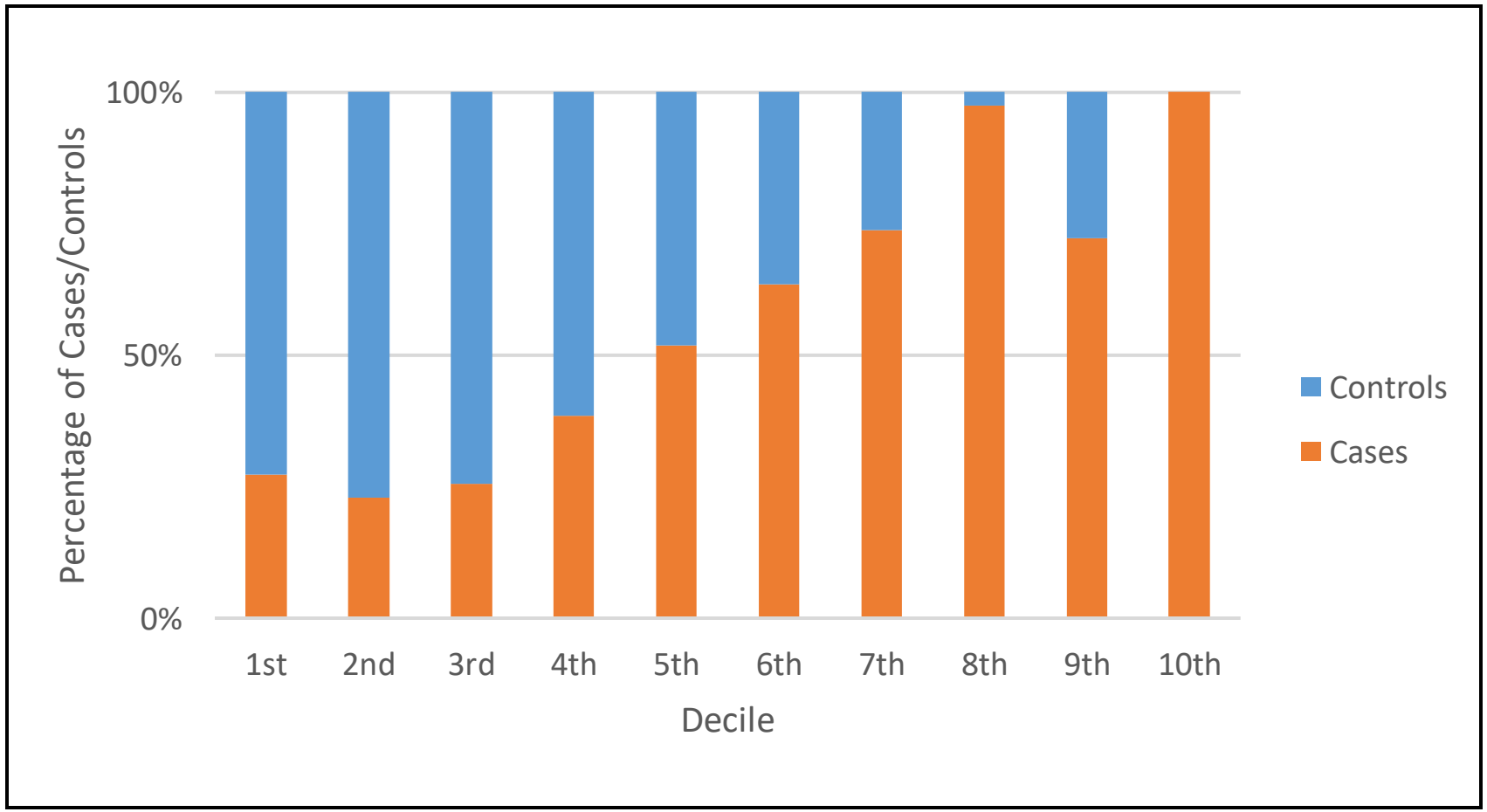


Figure 5 – Percentage of sEOAD cases and controls present at each decile.
The bar plot identifies the proportion of cases (orange) and controls (blue) present at each decile. The trends show an increasing proportion of cases as PRS scores increase and a reduced proportion of controls as PRS scores increase.

3.3 PRS of the *APOE* locus

PRSice was used to calculate PRS for individuals based on the variants present with the *APOE* locus. Between the base dataset and the altered version of the target dataset, with genotypes for 198 SNPs, PRSice found 31 common SNPs. The best-fit P-value threshold was identified as P≤0.001, using 28 SNPs and with a Nagelkerke's R^2 value of 0.124 and a p-value of 2.08×10^{-17}. The sensitivity was identified as 51.7%, lower than the unaltered model. Specificity increases slightly compared to PRS from the NeuroX array to 75.5%. The predictive ability of the model using SNPs within the *APOE* locus was calculated as 65.2%.

3.4 Covariate Analysis

Additional information is generated for individuals in a cohort with sex and *APOE* ε2 and ε4 status being identified; these covariates can affect individuals' risk of AD. Using sex, and the number of ε2 and ε4 alleles, an individual has as a model for predicting cases and controls of AD. An AUC of 71.4% was achieved, with sensitivity and specificity values of 56.9% and 76.8% respectively. Nagelkerke's R^2 and Hosmer-Lemeshow P-value were also calculated as 0.192 and 0.811 respectively, indicating the covariate model to be a viable model with a predictive ability greater than the *APOE* locus model and lower than the PRS model.

Combining these covariates with PRS produces an improved predictive ability of 75.5%. The sensitivity of the model is highest of all models, calculated as 64.5%; however, the specificity is similar to the PRS model, calculated as 73.1% compared to 72.9%. Nagelkerke's R^2 confirms the PRS combined with covariates for sex, ε2 and ε4 is the best model for predicting disease status with a value of 0.252. All models were compared using ROC curves, seen in Figure 6. The results of logistic regression for all models is described in Table 6.

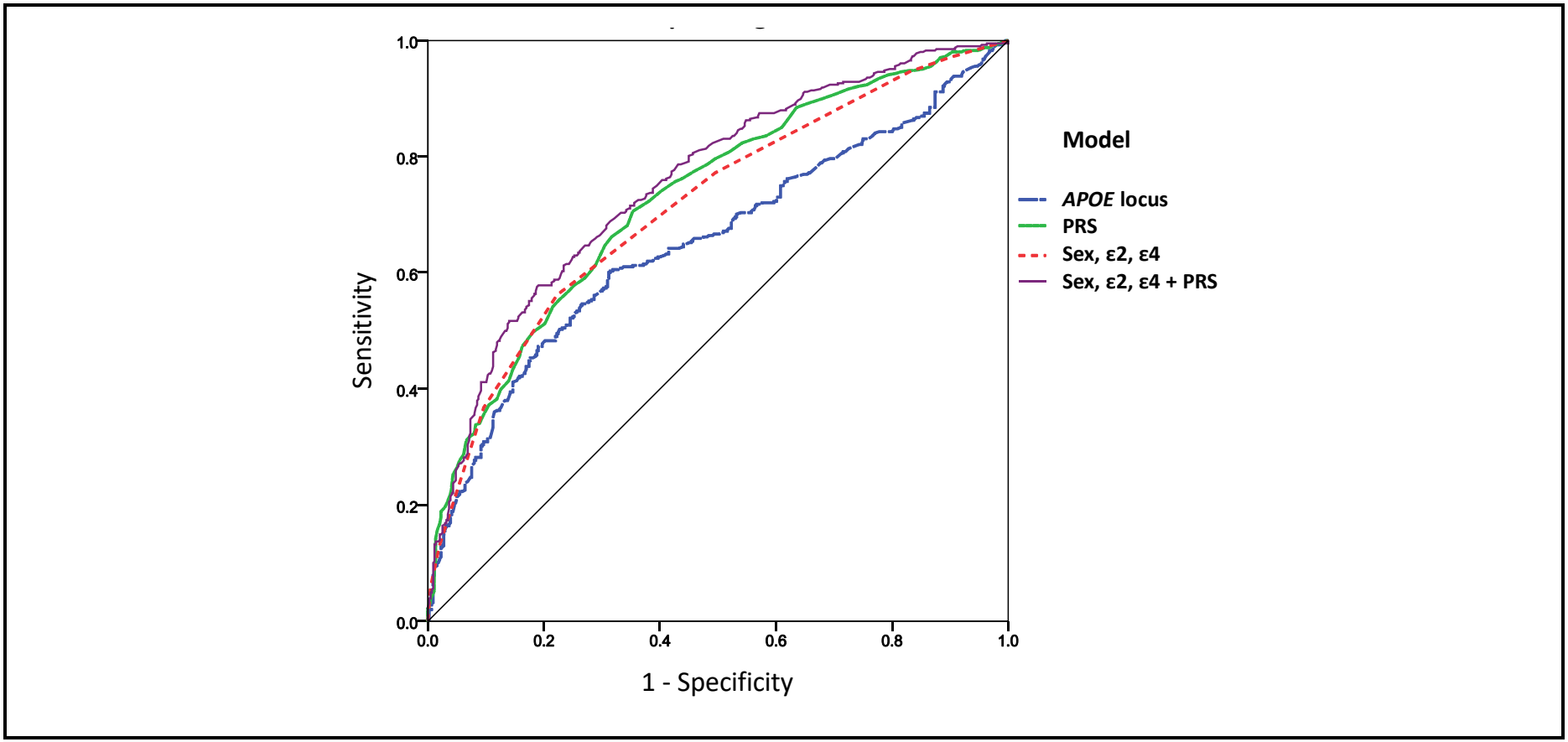


Figure 6 – A Receiver Operating Characteristic curve comparing alternative models for predicting disease status for sEOAD. Various models were produced to identify the predictive ability of determining disease status in a cohort of sEOAD cases and controls genotyped on the NeuroX array. The first model utilises the SNPs common between the base and target datasets within a 500kb region surrounding the *APOE* gene, the second model considers all SNPs common between the base and target dataset at the best fit threshold, the third model predicts disease status from Sex and the number of *APOE* ε2 and ε4 alleles an individual has, and the final model combines the PRS derived from the second model with the covariates of the third model. Area under the receiver operating characteristic curve (AUC) is a scientific value of the predictive ability of a model for identifying disease status.

Model	Sensitivity	Specificity	AUC	Hosmer-Lemeshow P-value	Nagelkerke's R^2 value
***APOE* locus**	0.517	0.755	0.652	0.296	0.124
PRS	0.591	0.729	0.729	0.705	0.209
Sex, ε2, ε4	0.569	0.768	0.714	0.811	0.192
Sex, ε2, ε4 + PRS	0.645	0.731	0.755	0.352	0.252

Table 6 – Results of logistic regression of all models.

Logistic regression was used to calculate sensitivity, specificity, area under the receiver operating characteristic curve (AUC), the Hosmer-Lemeshow p-value and Nagelkerke's R^2 value for all models. The results identify 'Sex, ε2, ε4 + PRS' as the best model with the greatest AUC and Nagelkerke's R^2. Hosmer-Lemeshow p-values indicate none of the models are poor at identifying cases and controls of sEOAD. The best model for correctly identifying cases is 'Sex, ε2, ε4 + PRS', whilst 'Sex, ε2, ε4' is the best model for correctly identifying controls.

4 Discussion

The aim of the study was to generate PRS for a cohort of sEOAD cases and controls genotyped on the NeuroX array based on the effect scores of SNPs implicated in a cohort of LOAD cases and controls. The resulting predictive model could be used to correctly predict risk of developing disease. The hypothesis of the study was that sEOAD cases would have a higher PRS than controls. The results showed significant difference between PRS of sEOAD cases and controls and predictive ability of the model was measured as 72.9%. Logistic regression was used to include covariates for sex and the number of *APOE* ε2 and ε4 alleles, improving predictive ability to 75.5%. The significance of this approach to model risk diseases which have been tested for genome-wide association is the ability to consider more of the identified genetic risk an individual has. The NeuroX, with its custom content, can be used to model risk for individuals for any of the diseases with associated SNPs included on the array.

4.1 Limitations of the NeuroX and IGAP datasets

The NeuroX array was subjected to strict QC, from which many SNPs failed and 115 individuals were removed. This drop-out could be prevented by using higher quality DNA to produce clearer results; improving individual marker assays for better efficiency, or using a cluster file for all markers present on the array. The NeuroX does not have assays for SNPs for all the genes identified in the AD GWAS, some only have a proxy SNP harboured by individuals in similar proportions to the SNP of interest. The SNPs implicated in GWAS have lower risk but are common, the presence of these would give fractional increase in PRS but the accumulation of GWAS implicated risk alleles would increase risk of AD, which would be identified in PRS. The base dataset collated by the IGAP consortium was specific to LOAD; however, after imputation of the dataset to include more SNPs, the dataset has genetic information for over 7 million SNPs. The cohort that make up the genetic information and effect scores are of the same European ancestry as the target dataset, which validates the accuracy of the PRS as effect scores are influenced by allele frequencies in populations depending on their ancestry. Although the base dataset is compiled of SNP statistics from a cohort of LOAD, the pathogenic mechanisms for sporadic AD are not dependent on age at onset (Barber *et al*, 2017).

4.2 Linkage Disequilibrium

GWAS identified chromosomal loci which were affecting risk whilst NGS uses a single SNP for analysis, when using loci, LD needed to be considered. SNPs within an LD block are inherited together and are given the same effect weight as a SNP of phenotypic effect. PRSice would identify both SNPs as independent and give scores based on the effect weight of the SNP, two SNPs from the same LD block would produce a higher PRS based on the phenotypic effect of the index SNP on risk of AD, producing inaccuracies of scores and bias of genetic loci.

Pruning of SNPs on the same chromosome identifies if there is high correlation between the presence of two SNPs on the same chromosome, if so the index SNP is retained and the alternative SNP is pruned out. Clumping mirrors pruning in that the accumulative risk of an LD block is clumped together so that one SNP harbours the genetic risk of the entire LD block.

4.3 Identifying risk using the *APOE* locus

The *APOE* gene is well researched in AD due to the varying effect of each haplotype on risk of AD. An individual harbouring an *APOE* ε4 allele has increased risk of developing AD compared to an ε3ε3 homozygote; harbouring either an ε2ε4 or ε3ε4 phenotype gives a 2.6 and 3.2 times greater risk of developing AD, respectively; ε4ε4 homozygotes have almost 15-fold increased risk of AD (Liu *et al*., 2013). The SNPs which identify which alleles individuals' harbour were included on the NeuroX but one failed QC, so both variants were manually genotyped by TaqMan assay. The results of PRS of the *APOE* locus identifies the significance of the variants within the 500kb region but also identifies genome-wide SNPs which affect risk of AD, as predictive ability increases when using SNPs outside the *APOE* locus. A 500kb region was selected as it accounted for all SNPs which were identified to be in LD with index SNPs within the APOE gene, including SNPs identified in the neighbouring genes.

Escott-Price *et al*. considered an alternative approach regarding the *APOE* region, given that the effect of the region is known and implicated; the study produced an alternative PRS excluding a region of the *APOE* locus, as well as regions of the genetic loci of SNPs identified in GWAS. The resulting model significantly identified disease status, showing the effect of variants across the whole genome affect risk of AD and demonstrating the strength of PRS as a utility.

4.4 Case/Control Overlap

The results from PRSice gave individual scores; although there is a difference between the average score for cases and controls, there was considerable overlap between the two cohorts. In Figure 4 the overlap can be further understood by the majority of controls having a lower PRS with few with high PRS, the interquartile overlap between cases and controls is more discrete. Decile scoring also provides clarity for the trends of the dataset. Figure 5 shows that most controls fall in the lower half and most cases are in the upper half of deciles, there is a gradual increase in proportion of cases compared to controls at higher deciles. This signifies an increase of PRS correlates with an increased risk of AD.

The results identify five controls within the 9th decile, with a high PRS. The high PRS suggests the individuals have SNPs associated with increased risk of AD but may not develop disease. This can be understood as there may be SNPs harboured by these individuals which reduce their risk of AD, which are not characterised in the model and not included in the 28,538 SNPs used by PRSice. These individuals may have also been at risk of developing

LOAD in later life, as their average age at death is below 80; however, controls were selected to be void of dementia. The lack of further clinical data for the controls means symptoms of reduced cognitive ability and pathology are unknown. Cases with low PRS are identified by PRSice, which may suggest risk of AD may be increased by currently unidentified lifestyle and environmental risk factors.

4.5 Risk modelling

The improvement of AUC from 72.9% to 75.5% using covariates of sex and number of *APOE* ε2 and ε4 alleles suggests other covariates can be included to improve predictive ability. Age was disregarded as a covariate for modelling as the controls were not aged matched to samples as the controls are healthy, elderly individuals with no signs of dementia whilst cases had suffered early deaths due to disease. The ages at death in testing for presence of amyloid deposition and tau pathology can provide greater accuracy, as they are identified in CSF before the onset of symptoms (Jack *et al*., 2016). Collecting information on individuals' lifestyle could improve predictive ability as environmental factors can also affect risk of developing AD. Less education in early life; loss of hearing, hypertension, and obesity in midlife; and smoking, depression, physical inactivity, social isolation, and diabetes in later life have all been identified as risk factors for dementia (Livingston *et al*., 2017). Improving genetic risk modelling where predictive ability is much greater would be useful to identify at-risk individuals, for example individuals with mild cognitive impairment (MCI) or stroke sufferers, to predict their risk of AD using PRS.

4.6 Genotyping improvements

The NeuroX array was the first version of a neurological disorder-specific microarray. A new version was released early 2017 containing 486,670 markers, of which 48,153 are known to be involved in AD (Blauwendraat *et al*, 2017). The custom content was increased to include 178,829 markers involved in neurological disorders, which would improve the significance of the array as only 17.3% of the SNPs used to generate PRS at the best fit model were from the custom content of NeuroX. The increase in number of SNPs could provide a greater breadth between scores, whilst also identifying any missing heritability which can reduce the overlap seen between cases and controls. The newly added content includes all GWAS hits recorded in the National Human Genome Research Institute database; several variants recently identified from WGS studies, and all markers previously included on the NeuroX.

4.7 Alternative methods for PRS

Predictive ability can be improved with increased accuracy and depth, when using greater numbers of SNPs in the analysis. Escott-Price *et al*. (2015) has shown greater predictive ability with a cohort of 3,049 LOAD cases and 1,554 controls, the AUC value calculated was 78.2% using sex, age, and the presence of the *APOE* ε2 and ε4 allele. The study produced a more variable set of individual scores with 87,605 SNPs being common between the base

and target dataset, an almost ten-fold increase compared to our study of 408 sEOAD cases with an AUC of 75.5%. A greater number of SNPs common to both datasets was achieved by imputation of the target dataset. Imputation effectively identifies individuals' genotypes for SNPs that have not been genotyped for using LD blocks as references. The imputed SNP may be common to another dataset whereas the index SNP might not be.

Using alternative methods, Escott-Price *et al*. improved predictive ability to 82% by calculating the AUC_{max} from the results of the first study (2017a). The use of post-mortem diagnosed tissue, confirming AD diagnosis, has proven to be most successful at identifying cases and controls from genotype information compared to clinically diagnosed samples as shown in another study (Escott-Price *et al*., 2017b).

Other studies in AD have identified variants of greater effect size to reduce the number of SNPs require to generate risk scores. Desikan *et al*. (2017) produced PRS for a LOAD cohort using genotype information for 31 SNPs including the *APOE* allele SNPs for 6,409 LOAD cases and 9,386 controls. Using tens of SNPs compared to thousands may become more cost-effective with arrays containing fewer markers and a greater number of individual samples, however the diversity in scores gained from results with thousands of SNPs provides better depth and greater predictive ability.

4.8 Future Research

PRS has the potential to predict overall genetic risk of AD, and predictive ability is constantly improving with the inclusion of more risk factors. The generation of PRS through PRSice for at-risk individuals may act as a screening tool for clinical trials of drug therapies. The anti-amyloid drug, Solanezumab, was designed to reduce Aβ levels in the brain. In stage 3 clinical trials the drug passed safety standards but did not have significant effect on individuals with mild dementia compared to the placebo (The Lancet Neurology, 2017). It was suggested the drug could be more effective when given to individuals at an earlier stage of disease progression.

Identifying genetic risk in individuals with MCI using PRS could be useful for predicting likelihood of conversion. If predictive ability between converters and non-converters is significant, action can be taken to reduce the risk of developing AD through lifestyle changes and drug therapy.

The use of PRS in complex disorders provides another use for GWAS results which identify low risk, common variants. The datasets produced and used in meta-analyses can be used as the base dataset. Individuals at risk of certain groups of diseases can be genotyped on a customised array, like the NeuroX and neurodegenerative disorders.

The NeuroX hosts SNPs implicated in many neurological disorders. For example, genotyping PD cases and producing PRS using SNP statistics from the International Parkinson's Disease Genomics Consortium (IPDGC) GWAS could highlight genetic risk factors to further investigate as targets or biomarkers for screening, diagnosis, and treatment. Identifying sub-groups within spectrum disorders could also be accomplished using PRS. Individuals with

Autistic Spectrum Disorders (ASD) could be genotyped on an array with SNPs implicated in disorders within ASD. Using confirmed cases of a single disorder within the spectrum for the base dataset, and identifying which of the disorders ASD cases genotyped on a target dataset are most likely to have.

The clinical information provided for the cohort tested on the NeuroX v2 is more comprehensive to the information provided with the NeuroX cohort. Individuals have been tested to confirm the presence of Aβ-CAA and tau-Braak staging is also indicated. The full clinical diagnoses have been included, therefore further research can be carried out using this information to find trends between PRS and symptoms and severity of disease.

5 Conclusions

The aim of the research was to identify if quantifying polygenic risk can be used to correctly identify sEOAD cases and controls, to produce a model which can be used for early diagnosis, screening, and more specific therapies. The null hypothesis was that there was no significant difference between PRS between sEOAD cases and controls; the alternative hypothesis was that PRS would be higher in sEOAD cases compared to controls. The results found significantly higher PRS in cases, rejecting the null hypothesis. The results mean that the genetic risk of AD is polygenic, and risk of developing AD is affected by variants in genes not involved in amyloid deposition and tau pathology. The full pathology of AD is not known; however, with further research more can be identified and understood. Further advancements in drug therapies using individuals' PRS as a factor for selection for clinical trials, treating the most at risk individuals could help find cures or preventative treatments. Individuals being identified with MCI could also be genotyped and have their genetic risk quantified, improving efficacies of preventative therapies.

References

Barber, I. (2016). 'Investigating the genetics of sporadic early-onset Alzheimer's disease using a customised genotyping chip'. PhD thesis. University of Nottingham. Nottingham.

Barber, I., Braae, A., Clement, N., Patel, T., Guetta-Baranes, T., Brookes, K., Medway, C., Chappell, S., Guerreiro, R., Bras, J., Hernandez, R., Singleton, A., Hardy, J., Mann, D., ARUK Consortium and Morgan, K. (2017). Mutational analysis of sporadic early-onset Alzheimer's disease using the NeuroX array. *Neurobiology of Aging*. 49. 215.e1-215.e8.

Bierer, L. M., Hof, P. R., Purohit, D. P., Carlin, L., Schmeidler, J., Davis, K. L., and Perl, D. P. (1995). Neocortical neurofibrillary tangles correlate with dementia severity in Alzheimer's disease. *Archives of Neurology*. 52 (1). Pages 81-88.

Blauwendraat, C., Faghri, F., Pihlstrom, L., Geiger, J. T., Elbaz, A., Lesage, S., Corvol, J., May, P., Ryten, M., Ferrari, R., Bras, J., Guerreiro, R., Williams, J., Sims, R., Lubbe, S., Hernandez, D. G., Mok, K. Y., Robak, L., Campbell, R. H., Rogaeva, E., Traynor, B. J., Chia, R., Chung, S. J., International Parkinson's Disease Genomics Consortium (IPDGC), COURAGE-PD Consortium, Hardy, J. A., Brice, A., Wood, N. W., Houlden, H., Shulman, J. M., Morris, H. R., Gasser, T., Krüger, R., Heutink, P., Sharma, M., Simón Sánchez, J., Nalls, M. A., Singleton, A. B., Scholz, S. W. (2017). *Neurobiology of Aging*. http://dx.doi.org/10.1016/j.neurobiolaging.2017.05.009

Budson, A. and Kowall, N. (2011). *The Handbook of Alzheimer's Disease and Other Dementias.* Chichester, UK. Wiley-Blackwell. Preface XV-XV.

Bush, W. and Moore, J. (2012). Chapter 11: Genome-Wide Association Studies. *PLoS Computational Biology*. 8(12). Page e1002822.

Desikan, R. S., Fan, C. C., Wang, Y., Schork, A. J., Cabral, H. J., Cupples, L. A., Thompson, W. K., Besser, L., Kukull, W. A., Holland, D., Chen, C., Brewer, J. B., Karow, D. S., Kauppi, K., Witoelar, A., Karch, C. M., Bonham, L. W., Yokoyama, J. S., Rosen, H. J., Miller, B. L., Dillion, W. P., Wilson, D. M., Hess, C. P., Pericak-Vance, M., Haines, J. L., Farrer, L. A., Mayeux, R., Hardy, J., Goate, A. M., Hyman, B. T., Schellenberg, G. D., McEvoy, L. K., Andreassen, O. A., Dale, A. M. (2017). Genetic assessment of age-associated Alzheimer's disease risk: Development and validation of a polygenic hazard score. *PLoS Medicine*. 14(3). Page e1002258.

Duyckaerts, C., Delatour, B., and Potier, M. C. (2009). Classification and basic pathology of Alzheimer disease. *Acta Neuropathologica*. 118. Pages 5-36.

Escott-Price, V., Sims, R., Bannister, C., Harold, D., Vronskaya, M., Majounie, E., Badarinarayan, N., GERAD/PARADES, IGAP consortia, Morgan, K., Passmore, P., Holmes, C., Powell, J., Brayne, C., Gill, M., Mead, S., Goate, A., Cruchaga, C., Lambert, J., van Duijn, C., Maier, W., Ramirez, A., Holmans, P., Jones, L., Hardy, J., Seshadri, S., Schellenberg, G. D., Amouyel and Williams, J. (2015). Common polygenic variation enhances risk prediction for Alzheimer's disease. *Brain*. 138. Pages 3673-3684.

Escott-Price, V., Shoai, M., Pither, R., Williams, J., and Hardy, J. (2017). Polygenic score prediction captures nearly all common genetic risk for Alzheimer's disease. *Neurobiology of Aging*. 49. Pages 214e7-11.

Escott-Price, V., Myers, A. J., Huentelman, M., Hardy, J. (2017b). Polygenic Risk Score Analysis of Pathologically Confirmed Alzheimer's Disease. *Annals of Neurology*. 10.1002/ana.24999

Euesden, J., Lewis, C. and O'Reilly, P. (2014). PRSice: Polygenic Risk Score software. *Bioinformatics*. 31(9). Pages 1466-1468.

Giri, M., Zhang, M. and Lü, Y. (2016). Genes associated with Alzheimer's disease: an overview and current status. *Clinical Interventions of Aging*. 11. Pages 665-681

Guerreiro R., Wojtas A., Bras J., Carrasquillo M., Rogaeva E., Majounie E., Cruchaga C., Sassi, C., Kauwe J.S.K., Younkin S., Hazrati L., Collinge J., Pocock J., Lashley T., Williams J., Amouyel P., Goate A., Rademakers R., Morgan K., Powell J., George-Hislop P., Singleton A., Hardy J., and the Alzheimer Genetic Analysis Group, (2013). TREM2 variants in Alzheimer's disease. *The New England Journal of Medicine*. 368(2). Pages 117-127.

Hodges, J. R. (2006). Alzheimer's centennial legacy: origins, landmarks and the current status of knowledge concerning cognitive aspects. *Brain*. 129 (11). Pages 2811-2822.

IBM Corp. (2013). IBM SPSS Statistics for Windows. Version 22.0. Armonk, NY: IBM Corp.

Illumina. (2012). HumanExome BeadChips. Data Sheet: DNA Analysis.

Jack, C. R. Jr., Bennet, D. A., Blennow, K., Carillo, M. C., Feldman, H. H., Frisoni, G. B., Hampel, H., Jagust, W. J., Johnson, K. A., Knopman, D. S., Petersen, R. C., Scheltens, P., Sperling, R. A., Dubois, B. (2016). A/T/N: An unbiased descriptive classification scheme for Alzheimer's disease biomarkers. *Neurology*. 87 (5). Pages 539-547.

Jonsson T., Stefansson H., Steinberg S., Jonsdottir I., Jonsson P.V., Snaedal J., et al. (2013). Variant of TREM2 associated with the risk of Alzheimer's disease. *The New England Journal of Medicine*. 368(2). Pages 107-116.

Karch, C. M. and Goate, A. M. (2015). Alzheimer's Disease Risk Genes and Mechanisms of Disease Pathogenesis. *Biological Psychiatry*. 77 (1). Pages 43-51.

Karolchik, D., Hinrichs, A. S., Furey, T. S., Roskin, K. M., Sugnet, C. W., Haussler, D. and Kent, W. J. (2004). The USCS Table Browser data retrieval tool. *Nucleic Acids Research*. 32. Pages D493-496.

Kent, W. J., Sugnet, C. W., Furey, T. S., Roskin, K. M., Pringle, T. H., Zahler, A. M. and Haussler, D. The human genome browser at UCSC. (2002). *Genome Research*. 12(6). Pages 996-1006.

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., DeStafano, A. L., Bis, J. C., Beecham, G. W., Grenier-Boley, B., Russo, G., Thorton-Wells, T. A., Jones, N., Smith, A. V., Chouraki, V., Thomas, C., Ikram, M. A., Zelenika, D., Vardarajan, B. N.,

Kamatani, Y., Lin, C. F., Gerrish, A., Schmidt, H., Kunkle, B., Dunstan, M. L., Ruiz, A., Bihoreau, M.T., Choi, S.H., Reitz, C., Pasquier, F., Cruchaga, C., Craig, D., Amin, N., Berr, C., Lopez, O.L., De Jager, P. L., Deramecourt, V., Johnston, J. A., Evans, D., Lovestone, S., Letenneur, L., Morón, F. J., Rubinsztein, D. C., Eiriksdottir, G., Sleegers, K., Goate, A. M., Fiévet, N., Huentelman, M. W., Gill, M., Brown, K., Kamboh, M. I., Keller, L., Barberger-Gateau, P., McGuiness, B., Larson, E. B., Green, R., Myers, A. J., Dufouil, C., Todd, S., Wallon, D., Love, S., Rogaeva, E., Gallacher, J., St George-Hyslop, P., Clarimon, J., Lleo, A., Bayer, A., Tsuang, D. W., Yu, L., Tsolaki, M., Bossù, P., Spalletta, G., Proitsi, P., Collinge, J., Sorbi, S., Sanchez-Garcia, F., Fox, N. C., Hardy, J., Deniz Naranjo, M. C., Bosco, P., Clarke, R., Brayne, C., Galimberti, D., Mancuso, M., Matthews, F.; European Alzheimer's Disease Initiative (EADI); Genetic and Environmental Risk in Alzheimer's Disease; Alzheimer's Disease Genetic Consortium; Cohorts for Heart and Aging Research in Genomic Epidemiology, Moebus, S., Mecocci, P., Del Zompo, M., Maier, W., Hampel, H., Pilotto, A., Bullido, M., Panza, F., Caffarra, P., Nacmias, B., Gilbert, J. R., Mayhaus, M., Lannefelt, L., Hakonarson, H., Pichler, S., Carrasquillo, M. M., Ingelsson, M., Beekly, D., Alvarez, V., Zou, F., Valladares, O., Younkin, S. G., Coto, E., Hamilton-Nelson, K. L., Gu, W., Razquin, C., Pastor, P., Mateo, I., Owen, M. J., Faber, K. M., Jonsson, P. V., Combarros, O., O'Donovan, M. C., Cantwell, L. B., Soininen, H., Blacker, D., Mead, S., Mosley, T. H. Jr., Bennett, D. A., Harris, T. B., Fratiglioni, L., Holmes, C., de Bruijn, R. F., Passmore, P., Montine, T. J., Bettens, K., Rotter, J. I., Brice, A., Morgan, K., Foroud, T. M., Kukull, W. A., Hannequin, D., Powell, J. F., Nalls, M. A., Ritchie, K., Lunetta, K. L., Kauwe, J. S., Boerwinkle, E., Riemenschneider, M., Boada, M., Hiltuenen, M., Martin, E. R., Schmidt, R., Rujescu, D., Wang, L. S., Dartigues, J. F., Mayeux, R., Tzourio, C., Hofman, A., Nöthen, M. M., Graff, C., Psaty, B. M., Jones, L., Haines, J. L., Holmans, P. A., Lathrop, M., Pericak-Vance, M. A., Launer, L. J., Farrer, L. A., van Duijn, C. M., Van Broeckhoven, C., Moskvina, V., Seshadri, S., Williams, J., Schellenberg, G. D. and Amouyel, P. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer’s disease. *Nature Genetics*. 45(12). Pages 1452-1458.

Liu, C., Kanekiyo, T., Xu, H. and Bu, G. (2013). Apolipoprotein E and Alzheimer’s disease: risk, mechanisms, and therapy. *Nature Reviews Neurology*. 9(2). Pages 106-118.

Liu, Y., Nyunoya, T., Leng, S., Belinsky, S. A., Tesfaigzi, Y., Bruse, S. (2013). Softwares and methods for estimating genetic ancestry in human populations. *Human Genomics*. 7(1). Pages 1-7.

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., Samus, Q., Schneider, L. S., Selbaek, G., Teri, L. and Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet*. http://dx.doi.org/10.1016/S0140-6736(17)31363-6

Minati, L., Edginton, T., Grazia Bruzzone, M. and Giaccone, G. (2009). Current concepts in Alzheimer's disease: A multidisciplinary review. *American Journal of Alzheimer's Disease and Other Dementias*. 24 (2). Pages 95-121.

Naj, A. C. and Schellenberg, G. D. (2016). Genomic Variants, Genes, and Pathways of Alzheimer's Disease: An Overview. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*. 174. Pages 5-26.

Nalls, M. A., Bras, J., Hernandez, D. G., Keller, M. F., Majounie, E., Renton, A. E., Saad, M., Jansen, I., Guerreiro, R., Lubbe, S., Plagnol, V., Gibbs, J. R., Schulte, C., Pankratz, N., Sutherland, M., Bertram, L., Lill, C. M., DeStefano, A. L., Faroud, T., Eriksson, N., Tung, J. Y., Edsall, C., Nichols, N., Brooks, J., Arepalli, S., Pilner, H., Letson, C., Heutink, P., Martinez, M., Gasser, T., Traynor, B. J., Wood, N., Hardy, J., Singleton, A. B. (2015). NeuroX, a fast and efficient genotyping platform for investigation of neurodegenerative diseases. *Neurobiology of Aging*. 36(3). Pages 1605e7-12.

Prince, M., Wimo, A., Guerchet, M., Ali, G., Wu, Y., Prina, M. (2015). World Alzheimer's Report 2015. The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International.

Purcell, S. M., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A., Bender, D., Maller, J., Sklar, P., de Bakker, P., Daly, M. and Sham, P. (2007). PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *The American Journal of Human Genetics*. 81(3). Pages 559-575.

R Core Team. (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Thal, D. R., Ghebremedhin, E., Rüb, U., Yamaguchi, H., Del Tredici, K., Braak, H. (2002). The Types of Sporadic Cerebral Amyloid Angiopathy. *Journal of Neuropathology and Experimental Neurology*. 61 (3). Pages 282-293.

The International Schizophrenia Consortium. (2009). Common polygenic variation contributes to risk of schizophrenia that overlaps with bipolar disorder. *Nature*. 460 (7256). Pages 748-752.

The Lancet Neurology. (2017). Solanezumab: too late in mild Alzheimer's disease? *The Lancet Neurology*. 16 (2). Page 97.

Wingo, T. S., Lah, J. J., Levey, A. I. and Cutler, D. J. (2012). Autosomal Recessive Causes Likely in Early-Onset Alzheimer's Disease. *Archives of Neurology*. 69. Page 59.

Appendix I

Individual ID	Phenotype	PRS
OA0521	sEOAD	-0.00012
M357	Control	-0.00008
OA0339	sEOAD	-0.00007
A149-01	sEOAD	-0.00007
OA1043	sEOAD	-0.00005
OA0573	sEOAD	-0.00004
M105	Control	-0.00003
LND-0108	sEOAD	-0.00001
OA1121	sEOAD	0.00001
A134-00	sEOAD	0.00001
M121	Control	0.00002
OA0446	sEOAD	0.00002
OA0960	sEOAD	0.00003
LBB6A	sEOAD	0.00003
DCR00045	sEOAD	0.00003
MRC064	Control	0.00004
OA0901	sEOAD	0.00005
LND-0035	sEOAD	0.00005
OA0639	sEOAD	0.00005
BRI326	Control	0.00005
LND-0155	sEOAD	0.00006
OA0892	sEOAD	0.00006
OA0646	sEOAD	0.00006
LND-0140	sEOAD	0.00007
OA1090	sEOAD	0.00007
A053-11	sEOAD	0.00007
O0119	Control	0.00007
LND-0154	sEOAD	0.00007
O0296	Control	0.00007
OA1041	sEOAD	0.00008
DCR00371	sEOAD	0.00008
DCR00497	sEOAD	0.00008
OA0311	sEOAD	0.00008
OA0673	sEOAD	0.00008
OA0990	sEOAD	0.00009
OA0716	sEOAD	0.00009
A089-89	sEOAD	0.00009
OA0873	sEOAD	0.00009
DCR00772	sEOAD	0.00009
A170-00	sEOAD	0.00009
LND-0113	sEOAD	0.00010
M127	Control	0.00010
OA1081	sEOAD	0.00010
LND-0018	sEOAD	0.00011

OA0888	sEOAD	0.00011
LND-0111	sEOAD	0.00011
OA0351	sEOAD	0.00011
OA0938	sEOAD	0.00011
OA1027	sEOAD	0.00011
OA0510	sEOAD	0.00011
M075	Control	0.00012
DCR00121	sEOAD	0.00012
OA0902	sEOAD	0.00012
M146	Control	0.00012
M224	Control	0.00012
DCR00212	sEOAD	0.00012
OA0441	sEOAD	0.00012
DCR00771	sEOAD	0.00012
DCR00061	sEOAD	0.00013
OA0900	sEOAD	0.00013
M159	Control	0.00013
OA1017	sEOAD	0.00013
OA0517	sEOAD	0.00013
OA0773	sEOAD	0.00014
M253	Control	0.00014
DCR00217	sEOAD	0.00014
M229	Control	0.00014
OA0459	sEOAD	0.00014
M283	Control	0.00014
O0147	Control	0.00015
LND-0092	sEOAD	0.00015
AD208	Control	0.00015
DCR00014	sEOAD	0.00015
A033-96	sEOAD	0.00015
MRC073	Control	0.00015
OA0620	sEOAD	0.00015
M342	Control	0.00016
OA1130	sEOAD	0.00016
LBB117E	sEOAD	0.00016
DCR00161	sEOAD	0.00016
DCR00070	sEOAD	0.00016
A295-93	sEOAD	0.00016
DCR00288	sEOAD	0.00016
MRC065	Control	0.00016
OA0866	sEOAD	0.00017
DCR00712	sEOAD	0.00017
DCR00246	sEOAD	0.00017
OA0697	sEOAD	0.00017
M713	Control	0.00017
OA0726	sEOAD	0.00017
OA0795	sEOAD	0.00017

DCR00013	sEOAD	0.00017
A077-00	sEOAD	0.00018
OA0736	sEOAD	0.00018
OA0354	sEOAD	0.00018
OA0367	sEOAD	0.00019
A097-89	sEOAD	0.00019
OA0932	sEOAD	0.00019
M072	Control	0.00019
OA1158	sEOAD	0.00019
OA1006	sEOAD	0.00019
LND-0164	sEOAD	0.00019
LND-0104	sEOAD	0.00019
DCR00614	sEOAD	0.00020
DCR00508	sEOAD	0.00020
M049	Control	0.00020
OA0604	sEOAD	0.00020
OA0897	sEOAD	0.00021
O0509	Control	0.00021
OA1194	sEOAD	0.00021
A135-93	sEOAD	0.00021
DCR00009	sEOAD	0.00021
OA0784	sEOAD	0.00021
DCR00332	sEOAD	0.00021
OA0708	sEOAD	0.00022
OA0714	sEOAD	0.00022
M058	Control	0.00022
LND-0156	sEOAD	0.00022
OA0806	sEOAD	0.00022
MRC007	Control	0.00022
A346-95	sEOAD	0.00022
LND-0081	sEOAD	0.00022
DCR00559	sEOAD	0.00022
O0656	Control	0.00022
DCR00261	sEOAD	0.00022
OA1059	sEOAD	0.00023
DCR00223	sEOAD	0.00023
M689	Control	0.00023
O0710	Control	0.00023
DCR00163	sEOAD	0.00023
O0335	Control	0.00023
A389-94	sEOAD	0.00023
M053	Control	0.00023
DCR00420	sEOAD	0.00023
DCR00505	sEOAD	0.00023
DCR00287	sEOAD	0.00023
OA0520	sEOAD	0.00023
DCR00238	sEOAD	0.00024

OA1116	sEOAD	0.00024
A133-95	sEOAD	0.00024
DCR00517	sEOAD	0.00024
M739	Control	0.00024
DCR00077	sEOAD	0.00024
DCR00157	sEOAD	0.00024
M010	Control	0.00025
DCR00074	sEOAD	0.00025
OA0541	sEOAD	0.00025
DCR00170	sEOAD	0.00025
OA0429	sEOAD	0.00025
OA0515	sEOAD	0.00025
A098-89	sEOAD	0.00025
OA0567	sEOAD	0.00025
M194	Control	0.00025
DCR00445	sEOAD	0.00025
OA0917	sEOAD	0.00026
LND-0110	sEOAD	0.00026
OA1171	sEOAD	0.00026
LND-0160	sEOAD	0.00026
DCR00187	sEOAD	0.00026
DCR00096	sEOAD	0.00026
OA0396	sEOAD	0.00026
OA0650	sEOAD	0.00026
M365	Control	0.00026
M057	Control	0.00026
M728	Control	0.00026
M239	Control	0.00027
OA0734	sEOAD	0.00027
OA1009	sEOAD	0.00027
M262	Control	0.00027
DCR00234	sEOAD	0.00027
OA0474	sEOAD	0.00027
OA0717	sEOAD	0.00027
OA0973	sEOAD	0.00027
LND-0127	sEOAD	0.00027
M164	Control	0.00027
OA0559	sEOAD	0.00027
A038-95	sEOAD	0.00027
DCR00408	sEOAD	0.00027
OA0362	sEOAD	0.00027
AD221	Control	0.00027
OA0315	sEOAD	0.00027
M026	Control	0.00028
DCR00134	sEOAD	0.00028
LND-0106	sEOAD	0.00028
M741	Control	0.00028

LND-0138	sEOAD	0.00028
OA0966	sEOAD	0.00028
OA1028	sEOAD	0.00028
A185-04	sEOAD	0.00028
LND-0075	sEOAD	0.00028
LND-0021	sEOAD	0.00028
M697	Control	0.00028
A011-06	sEOAD	0.00028
DCR00191	sEOAD	0.00028
DCR00774	sEOAD	0.00029
BRI541	Control	0.00029
M074	Control	0.00029
LBB44E	sEOAD	0.00029
DCR00364	sEOAD	0.00029
A096-89	sEOAD	0.00029
OA0934	sEOAD	0.00029
MRC067	Control	0.00029
OA0316	sEOAD	0.00029
DCR00239	sEOAD	0.00029
A266-93	sEOAD	0.00029
DCR00499	sEOAD	0.00029
M613	Control	0.00030
OA0908	sEOAD	0.00030
M267	Control	0.00030
A195-96	sEOAD	0.00030
M743	Control	0.00030
OA0939	sEOAD	0.00030
OA0263	sEOAD	0.00030
M326	Control	0.00030
M810	Control	0.00030
O0636	Control	0.00030
M331	Control	0.00030
DCR00460	sEOAD	0.00030
DCR00622	sEOAD	0.00030
M718	Control	0.00030
LND-0152	sEOAD	0.00030
M695	Control	0.00030
MRC011	Control	0.00031
DCR00262	sEOAD	0.00031
M807	Control	0.00031
DCR00095	sEOAD	0.00031
M750	Control	0.00031
M001	Control	0.00031
O0297	Control	0.00031
OA0494	sEOAD	0.00031
OA0690	sEOAD	0.00031
A031-96	sEOAD	0.00032

BRI592	Control	0.00032
OA0880	sEOAD	0.00032
OA0965	sEOAD	0.00032
M873	Control	0.00032
OA1054	sEOAD	0.00032
LND-0117	sEOAD	0.00032
OA1013	sEOAD	0.00032
DCR00116	sEOAD	0.00032
M291	Control	0.00032
A278-96	sEOAD	0.00032
A134-95	sEOAD	0.00032
OA1106	sEOAD	0.00032
DCR00740	sEOAD	0.00032
M690	Control	0.00032
M726	Control	0.00032
LND-0029	sEOAD	0.00032
M021	Control	0.00032
A264-94	sEOAD	0.00033
DCR00337	sEOAD	0.00033
LND-0048	sEOAD	0.00033
A127-11	sEOAD	0.00033
DCR00215	sEOAD	0.00033
DCR00069	sEOAD	0.00033
OA0730	sEOAD	0.00033
M621	Control	0.00033
DCR00220	sEOAD	0.00033
M380	Control	0.00033
OA0513	sEOAD	0.00033
DCR00592	sEOAD	0.00034
LND-0136	sEOAD	0.00034
M432	Control	0.00034
LND-0103	sEOAD	0.00034
DCR00547	sEOAD	0.00034
A074-89	sEOAD	0.00034
M255	Control	0.00034
M877	Control	0.00034
DCR00403	sEOAD	0.00034
OA1021	sEOAD	0.00034
LND-0143	sEOAD	0.00034
OA0772	sEOAD	0.00034
DCR00352	sEOAD	0.00035
DCR00347	sEOAD	0.00035
M133	Control	0.00035
OA0961	sEOAD	0.00035
M278	Control	0.00035
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DCR00091	sEOAD	0.00035

MRC017	Control	0.00035
M005	Control	0.00035
OA1104	sEOAD	0.00035
LND-0034	sEOAD	0.00035
OA0882	sEOAD	0.00035
DCR00256	sEOAD	0.00035
OA0947	sEOAD	0.00035
MRC069	Control	0.00035
M134	Control	0.00036
DCR00556	sEOAD	0.00036
OA0741	sEOAD	0.00036
OA0360	sEOAD	0.00036
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OA1022	sEOAD	0.00036
M308	Control	0.00036
DCR00136	sEOAD	0.00036
DCR00050	sEOAD	0.00036
DCR00219	sEOAD	0.00036
OA0997	sEOAD	0.00036
M183	Control	0.00036
M003	Control	0.00036
M703	Control	0.00036
LND-0170	sEOAD	0.00036
DCR00094	sEOAD	0.00036
M686	Control	0.00037
DCR00295	sEOAD	0.00037
M154	Control	0.00037
OA0352	sEOAD	0.00037
OA0988	sEOAD	0.00037
OA1155	sEOAD	0.00037
OA0580	sEOAD	0.00037
AD217	Control	0.00037
DCR00242	sEOAD	0.00037
M254	Control	0.00037
M198	Control	0.00038
DCR00286	sEOAD	0.00038
DCR00221	sEOAD	0.00038
OA0359	sEOAD	0.00038
LBB125E	sEOAD	0.00038
LND-0070	sEOAD	0.00038
MRC055	Control	0.00038
OA0585	sEOAD	0.00038
DCR00017	sEOAD	0.00038
M457	Control	0.00038
LBB124E	sEOAD	0.00038
OA0922	sEOAD	0.00038
M126	Control	0.00038

M214	Control	0.00038
A189-94	sEOAD	0.00038
M143	Control	0.00039
OA0702	sEOAD	0.00039
A223-96	sEOAD	0.00039
OA0884	sEOAD	0.00039
O0325	Control	0.00039
DCR00210	sEOAD	0.00039
OA1019	sEOAD	0.00039
DCR00346	sEOAD	0.00039
M627	Control	0.00039
OA1149	sEOAD	0.00039
OA0653	sEOAD	0.00039
M050	Control	0.00039
M757	Control	0.00039
DCR00274	sEOAD	0.00039
M546	Control	0.00040
OA0326	sEOAD	0.00040
OA0683	sEOAD	0.00040
DCR00320	sEOAD	0.00040
DCR00090	sEOAD	0.00040
M682	Control	0.00040
OA0788	sEOAD	0.00040
M193	Control	0.00041
A094-95	sEOAD	0.00041
DCR00075	sEOAD	0.00041
LND-0019	sEOAD	0.00041
DCR00015	sEOAD	0.00041
M749	Control	0.00041
DCR00237	sEOAD	0.00041
M237	Control	0.00041
M077	Control	0.00041
LBB126E	sEOAD	0.00041
DCR00083	sEOAD	0.00041
M351	Control	0.00041
LND-0107	sEOAD	0.00041
M722	Control	0.00041
M691	Control	0.00041
OA0139	sEOAD	0.00041
OA0181	sEOAD	0.00041
OA0468	sEOAD	0.00041
BRI780	Control	0.00042
M210	Control	0.00042
M136	Control	0.00042
M218	Control	0.00042
MRC047	Control	0.00042
OA0864	sEOAD	0.00042

DCR00205	sEOAD	0.00042
DCR00147	sEOAD	0.00042
DCR00176	sEOAD	0.00042
OA0427	sEOAD	0.00042
A067-89	sEOAD	0.00042
OA0756	sEOAD	0.00042
M269	Control	0.00042
OA0626	sEOAD	0.00042
M707	Control	0.00042
LBB4A	sEOAD	0.00042
A093-96	sEOAD	0.00043
OA0895	sEOAD	0.00043
DCR00005	sEOAD	0.00043
DCR00434	sEOAD	0.00043
LBB62A	sEOAD	0.00043
BRI764	Control	0.00043
DCR00520	sEOAD	0.00043
DCR00051	sEOAD	0.00043
BRI687	Control	0.00043
M168	Control	0.00043
M152	Control	0.00043
OA1039	sEOAD	0.00043
M117	Control	0.00043
M390	Control	0.00043
OA0666	sEOAD	0.00043
M700	Control	0.00043
OA1064	sEOAD	0.00043
DCR00072	sEOAD	0.00043
DCR00169	sEOAD	0.00043
M090	Control	0.00044
M256	Control	0.00044
M320	Control	0.00044
M178	Control	0.00044
M717	Control	0.00044
DCR00748	sEOAD	0.00044
DCR00053	sEOAD	0.00044
M228	Control	0.00044
M870	Control	0.00044
M135	Control	0.00044
OA0533	sEOAD	0.00044
M338	Control	0.00044
O0334	Control	0.00044
DCR00164	sEOAD	0.00044
M306	Control	0.00045
OA1060	sEOAD	0.00045
MRC026	Control	0.00045
M158	Control	0.00045

M217	Control	0.00045
OA1024	sEOAD	0.00045
OA0858	sEOAD	0.00045
M046	Control	0.00045
LND-0053	sEOAD	0.00045
DCR00318	sEOAD	0.00045
BRI726	Control	0.00045
OA0414	sEOAD	0.00045
BRI778	Control	0.00045
DCR00299	sEOAD	0.00045
LND-0026	sEOAD	0.00045
OA0484	sEOAD	0.00045
M275	Control	0.00045
OA0696	sEOAD	0.00045
LND-0112	sEOAD	0.00045
OA1000	sEOAD	0.00045
M309	Control	0.00046
M149	Control	0.00046
LND-0082	sEOAD	0.00046
DCR00523	sEOAD	0.00046
BRI404	Control	0.00046
DCR00073	sEOAD	0.00046
OA0753	sEOAD	0.00046
M709	Control	0.00046
OA0740	sEOAD	0.00046
M208	Control	0.00046
BRI713	Control	0.00046
DCR00047	sEOAD	0.00047
OA1015	sEOAD	0.00047
M336	Control	0.00047
M369	Control	0.00047
M714	Control	0.00047
DCR00713	sEOAD	0.00047
M215	Control	0.00047
M742	Control	0.00047
O0340	Control	0.00047
A136-10	sEOAD	0.00047
M880	Control	0.00047
MRC024	Control	0.00047
A359-08	sEOAD	0.00047
M611	Control	0.00047
M706	Control	0.00047
LND-0151	sEOAD	0.00048
M346	Control	0.00048
M207	Control	0.00048
DCR00549	sEOAD	0.00048
M302	Control	0.00048

M705	Control	0.00048
LND-0088	sEOAD	0.00049
OA0651	sEOAD	0.00049
M699	Control	0.00049
M039	Control	0.00049
M017	Control	0.00049
O0354	Control	0.00049
OA0467	sEOAD	0.00049
OA0524	sEOAD	0.00049
DCR00380	sEOAD	0.00049
DCR00747	sEOAD	0.00049
DCR00060	sEOAD	0.00049
M350	Control	0.00049
OA0440	sEOAD	0.00049
M111	Control	0.00049
M211	Control	0.00049
M740	Control	0.00049
MRC048	Control	0.00049
M200	Control	0.00050
M823	Control	0.00050
OA0358	sEOAD	0.00050
M820	Control	0.00050
LND-0077	sEOAD	0.00050
DCR00087	sEOAD	0.00050
M748	Control	0.00050
OA0748	sEOAD	0.00050
OA0863	sEOAD	0.00050
OA0789	sEOAD	0.00050
A167-98	sEOAD	0.00050
DCR00226	sEOAD	0.00050
M257	Control	0.00050
OA0767	sEOAD	0.00051
OA0151	sEOAD	0.00051
M259	Control	0.00051
OA0942	sEOAD	0.00051
M142	Control	0.00051
M079	Control	0.00051
M056	Control	0.00051
OA1254	sEOAD	0.00051
LND-0051	sEOAD	0.00052
M375	Control	0.00052
OA0671	sEOAD	0.00052
OA1126	sEOAD	0.00052
M096	Control	0.00052
M296	Control	0.00052
M162	Control	0.00052
M151	Control	0.00052

OA0603	sEOAD	0.00052
DCR00054	sEOAD	0.00052
OA0743	sEOAD	0.00052
O0617	Control	0.00052
DCR00470	sEOAD	0.00052
LND-0079	sEOAD	0.00053
DCR00413	sEOAD	0.00053
M876	Control	0.00053
M187	Control	0.00053
M615	Control	0.00053
M354	Control	0.00053
OA0454	sEOAD	0.00053
DCR00565	sEOAD	0.00053
LND-0089	sEOAD	0.00053
M279	Control	0.00053
M330	Control	0.00054
M701	Control	0.00054
M715	Control	0.00054
M287	Control	0.00054
LND-0144	sEOAD	0.00054
M216	Control	0.00054
OA0838	sEOAD	0.00054
OA1175	sEOAD	0.00054
M384	Control	0.00054
M219	Control	0.00055
M297	Control	0.00055
M735	Control	0.00055
DCR00076	sEOAD	0.00055
M059	Control	0.00055
M818	Control	0.00055
OA0647	sEOAD	0.00055
M381	Control	0.00055
DCR00058	sEOAD	0.00055
OA0236	sEOAD	0.00056
LND-0147	sEOAD	0.00056
M165	Control	0.00056
DCR00269	sEOAD	0.00056
DCR00292	sEOAD	0.00056
DCR00209	sEOAD	0.00056
M304	Control	0.00056
OA0549	sEOAD	0.00056
OA0823	sEOAD	0.00056
M047	Control	0.00056
M155	Control	0.00056
MRC028	Control	0.00056
LND-0044	sEOAD	0.00056
O0663	Control	0.00056

OA0648	sEOAD	0.00056
OA1004	sEOAD	0.00057
M114	Control	0.00057
OA0763	sEOAD	0.00057
M260	Control	0.00057
DCR00137	sEOAD	0.00057
M041	Control	0.00057
LND-0066	sEOAD	0.00057
M872	Control	0.00057
M031	Control	0.00057
M107	Control	0.00058
MRC053	Control	0.00058
M692	Control	0.00058
OA0539	sEOAD	0.00058
M246	Control	0.00058
OA1169	sEOAD	0.00058
OA0506	sEOAD	0.00058
M738	Control	0.00058
LND-0049	sEOAD	0.00058
MRC013	Control	0.00059
M280	Control	0.00059
OA0719	sEOAD	0.00059
M729	Control	0.00059
OA0890	sEOAD	0.00059
O0033	Control	0.00059
M340	Control	0.00059
M051	Control	0.00059
M518	Control	0.00059
O0703	Control	0.00060
A140-93	sEOAD	0.00060
M144	Control	0.00060
DCR00018	sEOAD	0.00060
BRI752	Control	0.00060
M130	Control	0.00060
LND-0013	sEOAD	0.00060
OA0877	sEOAD	0.00060
M038	Control	0.00060
BRI690	Control	0.00060
M235	Control	0.00060
M327	Control	0.00060
M745	Control	0.00060
LBB114E	sEOAD	0.00060
OA0590	sEOAD	0.00061
M547	Control	0.00061
M387	Control	0.00061
M221	Control	0.00061
M813	Control	0.00061

OA0634	sEOAD	0.00061
BRI435	Control	0.00061
LND-0087	sEOAD	0.00061
MRC023	Control	0.00061
M746	Control	0.00061
O0059	Control	0.00061
A206-90	sEOAD	0.00062
OA0318	sEOAD	0.00062
M013	Control	0.00062
M189	Control	0.00062
M816	Control	0.00063
OA0486	sEOAD	0.00063
OA0632	sEOAD	0.00063
DCR00458	sEOAD	0.00063
M261	Control	0.00063
M236	Control	0.00063
OA0476	sEOAD	0.00063
M206	Control	0.00063
M285	Control	0.00064
M317	Control	0.00064
M355	Control	0.00064
OA0903	sEOAD	0.00064
LND-0010	sEOAD	0.00064
LND-0011	sEOAD	0.00064
O0107	Control	0.00064
M875	Control	0.00064
M753	Control	0.00064
M808	Control	0.00064
DCR00278	sEOAD	0.00065
BRI051	Control	0.00065
M815	Control	0.00065
LND-0157	sEOAD	0.00065
A081-89	sEOAD	0.00065
OA0185	sEOAD	0.00065
OA0770	sEOAD	0.00065
M150	Control	0.00065
M756	Control	0.00065
OA0636	sEOAD	0.00065
OA0623	sEOAD	0.00066
A034-96	sEOAD	0.00066
LND-0059	sEOAD	0.00066
M619	Control	0.00066
M418	Control	0.00066
O0483	Control	0.00066
A220-93	sEOAD	0.00066
MRC039	Control	0.00066
M277	Control	0.00066

M305	Control	0.00066
M175	Control	0.00066
DCR00012	sEOAD	0.00067
M115	Control	0.00067
OA0511	sEOAD	0.00067
M755	Control	0.00067
M720	Control	0.00067
M754	Control	0.00067
DCR00716	sEOAD	0.00067
M073	Control	0.00067
M881	Control	0.00067
M203	Control	0.00068
DCR00144	sEOAD	0.00068
OA1152	sEOAD	0.00068
OA1047	sEOAD	0.00068
M076	Control	0.00069
O0332	Control	0.00069
M313	Control	0.00069
DCR00750	sEOAD	0.00069
M618	Control	0.00069
M386	Control	0.00069
M685	Control	0.00069
OA0470	sEOAD	0.00070
OA0971	sEOAD	0.00070
DCR00489	sEOAD	0.00070
M223	Control	0.00070
OA0872	sEOAD	0.00070
M270	Control	0.00070
M400	Control	0.00070
OA0508	sEOAD	0.00071
M213	Control	0.00071
M339	Control	0.00071
OA0800	sEOAD	0.00071
OA0382	sEOAD	0.00072
M172	Control	0.00072
M334	Control	0.00072
DCR00048	sEOAD	0.00072
M040	Control	0.00072
MRC030	Control	0.00072
MRC033	Control	0.00072
M080	Control	0.00072
M300	Control	0.00072
M879	Control	0.00072
M129	Control	0.00072
M616	Control	0.00072
M732	Control	0.00073
O0521	Control	0.00073

DCR00114	sEOAD	0.00073
M125	Control	0.00073
LND-0071	sEOAD	0.00073
DCR00178	sEOAD	0.00073
M378	Control	0.00073
O0254	Control	0.00074
M288	Control	0.00074
DCR00162	sEOAD	0.00074
M688	Control	0.00074
O0108	Control	0.00074
DCR00432	sEOAD	0.00074
M170	Control	0.00074
OA0607	sEOAD	0.00075
M736	Control	0.00075
M871	Control	0.00075
OA1058	sEOAD	0.00075
M252	Control	0.00075
M725	Control	0.00075
OA0656	sEOAD	0.00075
M358	Control	0.00075
M325	Control	0.00076
A088-93	sEOAD	0.00076
O0091	Control	0.00076
M645	Control	0.00076
M684	Control	0.00076
M702	Control	0.00076
M620	Control	0.00076
M719	Control	0.00076
M266	Control	0.00076
M687	Control	0.00077
M186	Control	0.00077
M811	Control	0.00078
M091	Control	0.00078
M063	Control	0.00078
M347	Control	0.00078
OA0171	sEOAD	0.00078
O0016	Control	0.00079
M385	Control	0.00079
OA0669	sEOAD	0.00079
BRI491	Control	0.00079
M544	Control	0.00079
M202	Control	0.00079
OA0940	sEOAD	0.00079
DCR00501	sEOAD	0.00080
A094-93	sEOAD	0.00080
M683	Control	0.00080
M088	Control	0.00080

M197	Control	0.00080
M348	Control	0.00080
A063-95	sEOAD	0.00081
M008	Control	0.00081
M102	Control	0.00081
OA0206	sEOAD	0.00081
A101-89	sEOAD	0.00082
M294	Control	0.00082
M314	Control	0.00083
M625	Control	0.00083
M116	Control	0.00083
AD143	Control	0.00083
M696	Control	0.00084
M185	Control	0.00084
M759	Control	0.00084
M721	Control	0.00084
O0066	Control	0.00084
OA0379	sEOAD	0.00084
OA0444	sEOAD	0.00085
M024	Control	0.00085
M182	Control	0.00085
OA0619	sEOAD	0.00086
BRI601	Control	0.00086
M415	Control	0.00086
O0133	Control	0.00086
BRI580	Control	0.00087
DCR00459	sEOAD	0.00087
BRI239	Control	0.00087
BRI698	Control	0.00087
M461	Control	0.00087
M693	Control	0.00087
BRI681	Control	0.00088
M382	Control	0.00088
M708	Control	0.00088
M045	Control	0.00088
M232	Control	0.00088
M238	Control	0.00088
M878	Control	0.00090
O0176	Control	0.00090
M809	Control	0.00090
M711	Control	0.00090
M120	Control	0.00091
M744	Control	0.00091
M370	Control	0.00092
M391	Control	0.00093
M226	Control	0.00093
M249	Control	0.00093

M394	Control	0.00094
M245	Control	0.00094
OA0779	sEOAD	0.00094
BRI426	Control	0.00094
M177	Control	0.00095
M086	Control	0.00095
M710	Control	0.00095
M328	Control	0.00096
M822	Control	0.00097
M694	Control	0.00097
AD211	Control	0.00097
M145	Control	0.00098
M112	Control	0.00098
O0342	Control	0.00099
M712	Control	0.00099
M251	Control	0.00099
M163	Control	0.00100
M374	Control	0.00100
MRC016	Control	0.00100
M025	Control	0.00101
M124	Control	0.00101
M731	Control	0.00101
O0179	Control	0.00102
LND-0124	sEOAD	0.00102
M264	Control	0.00103
M341	Control	0.00104
M036	Control	0.00104
DCR00225	sEOAD	0.00104
DCR00112	sEOAD	0.00104
M167	Control	0.00104
M506	Control	0.00104
M070	Control	0.00105
M376	Control	0.00105
M062	Control	0.00106
DCR00056	sEOAD	0.00106
M019	Control	0.00107
M396	Control	0.00108
M727	Control	0.00113
DCR00341	sEOAD	0.00113
M292	Control	0.00115
M397	Control	0.00116
M414	Control	0.00121
M004	Control	0.00122
O0549	Control	0.00122
M067	Control	0.00125
M061	Control	0.00126
M099	Control	0.00128

M263	Control	0.00130

Appendix II

Threshold	P-value	Nagelkerke's R^2	SNPs
0	2.30875E-17	0.124147381	0
0.001	3.25753E-20	0.149185607	141
0.002	1.23981E-20	0.153655633	203
0.003	4.01186E-21	0.158070306	263
0.004	2.53749E-21	0.159829276	314
0.005	1.01472E-21	0.163211971	355
0.006	3.35161E-22	0.16774405	402
0.007	2.44055E-22	0.168868183	431
0.008	2.41958E-22	0.168789974	462
0.009	1.20832E-22	0.171723034	505
0.01	1.06153E-22	0.172213361	546
0.011	1.28021E-22	0.171590836	576
0.012	1.0674E-22	0.172341961	618
0.013	9.57719E-23	0.172852529	662
0.014	6.86054E-23	0.174231318	694
0.015	1.03716E-22	0.17268725	725
0.016	1.24712E-22	0.172170405	767
0.017	1.0591E-22	0.172793066	808
0.018	1.0411E-22	0.173043894	845
0.019	7.57014E-23	0.174330608	891
0.02	5.06491E-23	0.175816626	930
0.021	4.31374E-23	0.176198516	975
0.022	3.4429E-23	0.177145668	1012
0.023	3.53911E-23	0.177011176	1055
0.024	4.68661E-23	0.176009747	1091
0.025	6.51098E-23	0.174866015	1124
0.026	3.78013E-23	0.177150273	1165
0.027	2.92117E-23	0.178098334	1203
0.028	2.7977E-23	0.178131428	1241
0.029	2.29571E-23	0.178880492	1276
0.03	1.67473E-23	0.17996014	1307
0.031	1.54899E-23	0.180238653	1346
0.032	1.37464E-23	0.181006316	1385
0.033	1.84978E-23	0.179769085	1423
0.034	2.22003E-23	0.178907347	1458
0.035	2.30241E-23	0.178603923	1497
0.036	2.12395E-23	0.178953522	1530
0.037	3.50256E-23	0.176690331	1565
0.038	5.97422E-23	0.174731847	1610
0.039	7.56866E-23	0.173653478	1643
0.04	5.78104E-23	0.174619011	1682
0.041	8.61979E-23	0.17291145	1710
0.042	6.22619E-23	0.174299992	1755
0.043	3.34548E-23	0.176941273	1790

0.044	2.16645E-23	0.178724395	1816
0.045	1.58534E-23	0.179955928	1851
0.046	2.19419E-23	0.17847605	1883
0.047	2.34216E-23	0.178317068	1914
0.048	2.296E-23	0.178488157	1953
0.049	1.71533E-23	0.179545072	1983
0.05	1.14308E-23	0.181193661	2022
0.051	1.1735E-23	0.181262568	2060
0.052	1.28861E-23	0.180841765	2090
0.053	1.05651E-23	0.181639393	2117
0.054	1.21364E-23	0.181047397	2147
0.055	8.1907E-24	0.182393453	2185
0.056	5.64424E-24	0.183836	2215
0.057	7.77569E-24	0.182555493	2250
0.058	9.29939E-24	0.18177412	2276
0.059	7.51769E-24	0.182450562	2310
0.06	4.80987E-24	0.18433319	2342
0.061	4.0117E-24	0.185063308	2374
0.062	2.76838E-24	0.186597673	2412
0.063	2.32132E-24	0.187430537	2445
0.064	1.83979E-24	0.188444444	2472
0.065	2.07334E-24	0.187876188	2513
0.066	2.09345E-24	0.187924785	2538
0.067	1.05636E-24	0.190697086	2576
0.068	1.12784E-24	0.190393623	2610
0.069	1.41717E-24	0.189441111	2653
0.07	1.73809E-24	0.188848804	2690
0.071	2.19787E-24	0.187841001	2717
0.072	1.67865E-24	0.188912906	2749
0.073	1.70983E-24	0.188804918	2768
0.074	1.91591E-24	0.188210391	2801
0.075	1.35305E-24	0.189644886	2832
0.076	1.46072E-24	0.189402881	2859
0.077	1.06161E-24	0.190723258	2890
0.078	1.13438E-24	0.190431398	2927
0.079	1.1446E-24	0.190399925	2956
0.08	9.80233E-25	0.190965009	2999
0.081	7.04497E-25	0.192383304	3021
0.082	7.47991E-25	0.192146333	3056
0.083	8.32615E-25	0.191762546	3083
0.084	8.79118E-25	0.191486038	3109
0.085	1.04496E-24	0.190879559	3135
0.086	8.28597E-25	0.191801386	3164
0.087	9.94212E-25	0.191286519	3194
0.088	5.77505E-25	0.193652668	3230
0.089	6.93931E-25	0.193055837	3274
0.09	6.17015E-25	0.19345941	3299

0.091	6.93605E-25	0.193094497	3321
0.092	7.58696E-25	0.192680918	3347
0.093	7.24874E-25	0.192752454	3382
0.094	8.78963E-25	0.19200621	3412
0.095	8.3038E-25	0.192364398	3445
0.096	7.83176E-25	0.192661384	3477
0.097	9.89583E-25	0.191718372	3501
0.098	9.15166E-25	0.192024183	3534
0.099	1.08062E-24	0.19132141	3563
0.1	7.82259E-25	0.192651	3595
0.101	7.409E-25	0.192930687	3631
0.102	6.65047E-25	0.19326173	3660
0.103	5.85985E-25	0.193847557	3684
0.104	5.93592E-25	0.193844181	3712
0.105	5.97799E-25	0.193928326	3749
0.106	6.3368E-25	0.193643562	3782
0.107	7.12565E-25	0.193160097	3805
0.108	4.77943E-25	0.194978356	3835
0.109	3.88449E-25	0.195884739	3866
0.11	3.46034E-25	0.196430333	3901
0.111	4.9515E-25	0.195003574	3933
0.112	6.35671E-25	0.194048909	3960
0.113	4.56137E-25	0.195285094	4001
0.114	4.17642E-25	0.195758052	4032
0.115	3.66162E-25	0.196223802	4073
0.116	5.02512E-25	0.194982572	4101
0.117	5.84792E-25	0.194710013	4135
0.118	7.06693E-25	0.193923889	4166
0.119	6.34042E-25	0.194219163	4200
0.12	5.19963E-25	0.195085966	4224
0.121	5.56867E-25	0.194771528	4263
0.122	4.34996E-25	0.195895303	4301
0.123	3.96931E-25	0.196268228	4333
0.124	4.44274E-25	0.195780468	4363
0.125	3.506E-25	0.196796397	4390
0.126	3.88821E-25	0.196554932	4422
0.127	5.76697E-25	0.19490981	4454
0.128	5.27232E-25	0.195339946	4487
0.129	5.73344E-25	0.194919908	4516
0.13	5.50247E-25	0.195098903	4548
0.131	4.54235E-25	0.196028407	4577
0.132	4.84245E-25	0.195628716	4604
0.133	5.33477E-25	0.195199772	4634
0.134	4.55386E-25	0.195860624	4655
0.135	3.52101E-25	0.196980045	4689
0.136	3.67712E-25	0.196737527	4717
0.137	2.91031E-25	0.197797487	4749

0.138	2.84359E-25	0.19793964	4773
0.139	3.41003E-25	0.197192492	4794
0.14	2.9879E-25	0.197890764	4826
0.141	3.22153E-25	0.197798905	4856
0.142	3.02179E-25	0.198085878	4881
0.143	2.8638E-25	0.198328088	4909
0.144	2.22525E-25	0.19951119	4937
0.145	2.56686E-25	0.198827778	4969
0.146	2.27744E-25	0.199408109	5007
0.147	2.26777E-25	0.199538426	5035
0.148	2.16565E-25	0.199692272	5060
0.149	1.96253E-25	0.200198211	5086
0.15	2.24504E-25	0.19973148	5118
0.151	2.00275E-25	0.200057956	5160
0.152	1.6609E-25	0.201002509	5185
0.153	1.52775E-25	0.201362179	5214
0.154	1.41246E-25	0.201637062	5244
0.155	1.10497E-25	0.202502443	5268
0.156	1.36236E-25	0.201588864	5295
0.157	1.18332E-25	0.20215214	5333
0.158	1.6625E-25	0.200649503	5369
0.159	1.67815E-25	0.200567422	5398
0.16	1.44109E-25	0.201196716	5430
0.161	1.21799E-25	0.201823307	5458
0.162	1.32965E-25	0.201393518	5477
0.163	1.4859E-25	0.200960491	5507
0.164	1.12474E-25	0.202098526	5541
0.165	1.60587E-25	0.200483755	5578
0.166	1.46839E-25	0.200847123	5597
0.167	1.08555E-25	0.20221195	5623
0.168	9.74648E-26	0.202615175	5646
0.169	9.4762E-26	0.20274161	5676
0.17	9.5874E-26	0.202796101	5702
0.171	9.14888E-26	0.202905892	5728
0.172	9.57692E-26	0.202832404	5753
0.173	1.03611E-25	0.202414081	5788
0.174	1.03463E-25	0.202311484	5817
0.175	1.10047E-25	0.202059013	5855
0.176	1.10907E-25	0.201963764	5878
0.177	1.10899E-25	0.202057034	5901
0.178	1.13227E-25	0.201942722	5932
0.179	1.02707E-25	0.202412361	5967
0.18	1.02345E-25	0.202431648	5984
0.181	1.0517E-25	0.202252794	6008
0.182	1.03035E-25	0.202361034	6029
0.183	1.03194E-25	0.202295129	6065
0.184	8.45396E-26	0.203103142	6086

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0.186	7.52499E-26	0.203509124	6149
0.187	7.58718E-26	0.203561617	6190
0.188	8.21554E-26	0.203284257	6209
0.189	8.5836E-26	0.203098796	6229
0.19	8.18056E-26	0.203348786	6262
0.191	6.60194E-26	0.204296032	6294
0.192	5.50418E-26	0.205069342	6321
0.193	6.28212E-26	0.204538819	6351
0.194	7.06294E-26	0.204045546	6369
0.195	6.97446E-26	0.204013368	6403
0.196	7.33798E-26	0.203723277	6426
0.197	7.63767E-26	0.203521148	6452
0.198	7.29508E-26	0.203701692	6485
0.199	7.45401E-26	0.203684689	6512
0.2	6.18917E-26	0.204442101	6545
0.201	5.69335E-26	0.204804305	6575
0.202	5.72978E-26	0.204797026	6606
0.203	6.52829E-26	0.204206668	6632
0.204	7.55505E-26	0.203604224	6663
0.205	7.89932E-26	0.203220904	6695
0.206	7.9986E-26	0.203125432	6732
0.207	6.74737E-26	0.20389748	6763
0.208	5.65735E-26	0.204699993	6782
0.209	5.62011E-26	0.204648686	6819
0.21	5.60579E-26	0.204568276	6845
0.211	5.9078E-26	0.204316953	6866
0.212	5.8378E-26	0.204397549	6900
0.213	5.26882E-26	0.204914352	6929
0.214	5.35334E-26	0.204774033	6956
0.215	5.00973E-26	0.205115488	6994
0.216	5.13533E-26	0.205079105	7026
0.217	5.04795E-26	0.205252219	7067
0.218	5.31468E-26	0.205024931	7096
0.219	3.49324E-26	0.2068092	7122
0.22	3.7539E-26	0.206546568	7156
0.221	3.85784E-26	0.20644121	7183
0.222	4.31457E-26	0.206020196	7214
0.223	3.98621E-26	0.206338802	7244
0.224	3.52637E-26	0.206921643	7277
0.225	3.79613E-26	0.206673687	7303
0.226	3.67939E-26	0.206690145	7333
0.227	4.23008E-26	0.206082284	7359
0.228	5.03382E-26	0.205307603	7387
0.229	5.22002E-26	0.205159159	7410
0.23	4.17184E-26	0.206023434	7437
0.231	3.9916E-26	0.206288614	7458

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0.234	3.48554E-26	0.206969738	7554
0.235	3.09966E-26	0.207457581	7581
0.236	3.16128E-26	0.207471162	7605
0.237	2.80742E-26	0.207956794	7640
0.238	2.74797E-26	0.207966126	7665
0.239	2.9527E-26	0.207772265	7688
0.24	3.02575E-26	0.207683398	7716
0.241	2.61842E-26	0.208245715	7745
0.242	2.80418E-26	0.207885189	7769
0.243	2.67269E-26	0.20815457	7798
0.244	2.85922E-26	0.207821509	7825
0.245	2.90767E-26	0.20769607	7848
0.246	3.16258E-26	0.207237402	7875
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0.249	3.15205E-26	0.20735438	7959
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0.267	3.84897E-26	0.206581058	8452
0.268	4.24422E-26	0.206106887	8477
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0.271	3.60379E-26	0.206914526	8574
0.272	3.43976E-26	0.207155157	8596
0.273	3.815E-26	0.206715148	8624
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0.276	3.19847E-26	0.207487394	8712
0.277	3.07751E-26	0.207715167	8748
0.278	3.06831E-26	0.207733393	8770

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0.397	3.74585E-26	0.206597293	12144
0.398	3.68797E-26	0.206700097	12174
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0.418	3.69316E-26	0.206333916	12723
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0.441	3.70651E-26	0.206230321	13362
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0.463	3.94755E-26	0.205888164	14006
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0.466	3.76593E-26	0.206154043	14066

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0.469	3.76072E-26	0.206155746	14159
0.47	3.50778E-26	0.206448173	14184
0.471	3.45183E-26	0.206463098	14215
0.472	3.01125E-26	0.207087482	14245
0.473	2.74132E-26	0.207531297	14276
0.474	2.97177E-26	0.207177245	14300
0.475	2.97805E-26	0.207192273	14326
0.476	3.09805E-26	0.207047845	14355
0.477	3.20992E-26	0.206911781	14380
0.478	3.09924E-26	0.207011979	14419
0.479	2.95201E-26	0.207217371	14433
0.48	2.92187E-26	0.207210575	14465
0.481	2.8159E-26	0.207358242	14490
0.482	2.77396E-26	0.207402072	14522
0.483	2.57003E-26	0.207674325	14542
0.484	2.56095E-26	0.207671986	14566
0.485	2.58226E-26	0.207649877	14592
0.486	2.4985E-26	0.20780546	14609
0.487	2.39683E-26	0.208000313	14642
0.488	2.31748E-26	0.208155598	14668
0.489	2.40683E-26	0.207961611	14698
0.49	2.37925E-26	0.208030533	14724
0.491	2.42675E-26	0.207903504	14753
0.492	2.56519E-26	0.207610657	14787
0.493	2.48018E-26	0.207779607	14804
0.494	2.57548E-26	0.207641025	14836
0.495	2.74175E-26	0.207436405	14861
0.496	2.78924E-26	0.207402171	14895
0.497	2.75475E-26	0.207413993	14923
0.498	3.01575E-26	0.207039119	14955
0.499	2.97331E-26	0.207101351	14976
0.5	2.86493E-26	0.207244936	14995
0.501	2.86162E-26	0.207240951	15030
0.502	2.9272E-26	0.20715303	15056
0.503	3.40482E-26	0.206402394	15082
0.504	3.53861E-26	0.206220083	15109
0.505	3.59283E-26	0.206111477	15135
0.506	4.05007E-26	0.205600981	15163
0.507	3.3283E-26	0.206511129	15191
0.508	3.63212E-26	0.206135668	15224
0.509	3.17842E-26	0.206723548	15250
0.51	2.90262E-26	0.207096643	15281
0.511	2.86288E-26	0.207169048	15304
0.512	3.15215E-26	0.206805111	15337
0.513	2.99389E-26	0.206989376	15361

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0.515	2.84439E-26	0.207137981	15422
0.516	2.9949E-26	0.20694257	15449
0.517	3.27506E-26	0.206594611	15473
0.518	3.3557E-26	0.206517336	15505
0.519	3.17473E-26	0.206718471	15531
0.52	3.25879E-26	0.206594659	15557
0.521	3.43105E-26	0.206356918	15591
0.522	3.32341E-26	0.206498772	15619
0.523	3.09488E-26	0.206784968	15642
0.524	3.23137E-26	0.206632724	15670
0.525	3.10089E-26	0.206772693	15697
0.526	3.55703E-26	0.206205803	15724
0.527	3.73848E-26	0.206024918	15761
0.528	3.87577E-26	0.205824172	15791
0.529	3.76923E-26	0.205945716	15819
0.53	3.48789E-26	0.206355825	15852
0.531	3.77615E-26	0.206031573	15884
0.532	3.94819E-26	0.205838562	15915
0.533	3.93297E-26	0.205882108	15935
0.534	4.12929E-26	0.205653771	15956
0.535	4.56548E-26	0.205217489	15982
0.536	4.49991E-26	0.205262536	16002
0.537	4.1883E-26	0.205571608	16027
0.538	4.06146E-26	0.205760176	16055
0.539	4.16479E-26	0.205633388	16077
0.54	4.36546E-26	0.205397873	16103
0.541	5.03536E-26	0.204761914	16126
0.542	4.54528E-26	0.205144967	16162
0.543	4.69864E-26	0.204967765	16196
0.544	4.51345E-26	0.205149032	16217
0.545	4.23728E-26	0.20547641	16244
0.546	4.27246E-26	0.205442142	16267
0.547	4.10122E-26	0.205546665	16293
0.548	4.18155E-26	0.205479948	16315
0.549	4.27962E-26	0.205370132	16342
0.55	4.83527E-26	0.204840804	16372
0.551	4.81641E-26	0.204858876	16394
0.552	4.75837E-26	0.204934703	16424
0.553	4.3998E-26	0.205303782	16447
0.554	4.13642E-26	0.205549863	16477
0.555	4.14014E-26	0.205587548	16508
0.556	4.13845E-26	0.205572168	16535
0.557	4.36893E-26	0.205325025	16558
0.558	4.20851E-26	0.205494363	16584
0.559	4.01333E-26	0.205651355	16620
0.56	3.83421E-26	0.205814057	16649

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0.562	3.97679E-26	0.205551592	16698
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0.564	4.21204E-26	0.205295393	16754
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0.566	3.56115E-26	0.206098285	16815
0.567	3.84362E-26	0.205760952	16842
0.568	3.82813E-26	0.205772364	16869
0.569	3.58946E-26	0.206077646	16907
0.57	3.66937E-26	0.205911633	16932
0.571	3.80019E-26	0.205761579	16955
0.572	3.88764E-26	0.205663523	16986
0.573	3.93351E-26	0.205645295	17017
0.574	4.04021E-26	0.205538989	17043
0.575	3.92218E-26	0.205690532	17070
0.576	3.76422E-26	0.205876388	17100
0.577	3.30473E-26	0.206477778	17131
0.578	3.39245E-26	0.206360062	17157
0.579	3.50187E-26	0.206241932	17187
0.58	3.44156E-26	0.206308651	17210
0.581	3.50926E-26	0.206207414	17234
0.582	3.53848E-26	0.206180769	17258
0.583	3.68214E-26	0.20593922	17288
0.584	3.86377E-26	0.205739479	17315
0.585	3.71209E-26	0.205938504	17343
0.586	3.45017E-26	0.206184566	17377
0.587	3.42754E-26	0.206201478	17402
0.588	3.62562E-26	0.205959429	17426
0.589	3.53124E-26	0.206104958	17454
0.59	3.60919E-26	0.206016294	17479
0.591	3.86505E-26	0.205711707	17496
0.592	4.13009E-26	0.205406617	17522
0.593	4.37478E-26	0.205197032	17551
0.594	4.38574E-26	0.205201341	17583
0.595	4.55996E-26	0.205015474	17601
0.596	4.35907E-26	0.205218822	17626
0.597	4.51785E-26	0.205017423	17654
0.598	4.49882E-26	0.20502527	17676
0.599	4.58017E-26	0.204980512	17709
0.6	4.7837E-26	0.204806773	17731
0.601	5.08033E-26	0.204509425	17758
0.602	4.97785E-26	0.204604611	17785
0.603	5.51357E-26	0.2041383	17815
0.604	5.82547E-26	0.203880461	17839
0.605	5.52691E-26	0.204095962	17865
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0.607	5.63049E-26	0.204002247	17916

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0.614	5.52572E-26	0.203981121	18122
0.615	5.75388E-26	0.203803938	18149
0.616	5.41143E-26	0.204127867	18183
0.617	5.07392E-26	0.20439408	18209
0.618	5.26759E-26	0.204236903	18242
0.619	5.04008E-26	0.204477453	18271
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0.621	4.94558E-26	0.204562796	18321
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0.624	5.30106E-26	0.204215398	18393
0.625	5.43532E-26	0.204102644	18420
0.626	5.14046E-26	0.204349129	18449
0.627	5.21371E-26	0.204325197	18474
0.628	4.95991E-26	0.204570723	18499
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0.63	5.06975E-26	0.20446282	18546
0.631	5.62299E-26	0.204010518	18568
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0.642	4.76809E-26	0.204757776	18881
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0.654	5.15984E-26	0.204331939	19195

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0.663	5.924E-26	0.203713457	19431
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0.694	4.11022E-26	0.205193208	20279
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0.794	6.37208E-26	0.203488955	22959
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0.809	7.50333E-26	0.202891319	23354
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0.821	7.13911E-26	0.203101291	23710
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0.823	7.62802E-26	0.202839842	23764
0.824	7.49141E-26	0.202899534	23796
0.825	7.59894E-26	0.202825963	23822
0.826	7.70952E-26	0.202776831	23855
0.827	7.97461E-26	0.202615784	23876
0.828	7.91277E-26	0.20264642	23901
0.829	7.93396E-26	0.202629639	23925
0.83	7.92069E-26	0.202635843	23959
0.831	7.84618E-26	0.202664502	23994
0.832	8.11253E-26	0.202520023	24014
0.833	8.2282E-26	0.202437049	24039
0.834	8.18099E-26	0.202462828	24065
0.835	7.97099E-26	0.202558813	24090
0.836	7.92549E-26	0.202598533	24116
0.837	8.05141E-26	0.202534961	24138
0.838	8.03806E-26	0.202539711	24171
0.839	7.9327E-26	0.202597505	24198
0.84	7.93183E-26	0.202588814	24223
0.841	7.92459E-26	0.202598483	24250
0.842	8.04544E-26	0.202536805	24287

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0.847	8.11055E-26	0.202520171	24421
0.848	8.1294E-26	0.202510432	24450
0.849	8.12588E-26	0.202512147	24473
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0.852	7.93226E-26	0.202604748	24553
0.853	7.80894E-26	0.202664924	24582
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0.855	7.63007E-26	0.202757251	24627
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0.886	7.95152E-26	0.20253529	25456
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0.889	8.17232E-26	0.202419867	25531

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