Design of an Alzheimer's Disease Specific SNP Array for Driving Polygenic Risk Scoring Algorithms

Richard Pither PhD[2] ; Ganna Leonenko[1]; Rebecca Sims[1]; Eftychia Bellou PhD[1];Paula Daunt PhD[2]; Greg Davidson PhD[2]; Alex Gibson PhD[2]; Olusegun Oshota PhD[2]; Maryam Shoai PhD[3]; Zsuzsanna Nagy[4] and John Hardy, PhD, DSc[3]; Julie Williams PhD[1,5]; Valentina Escott-Price, PhD[1,5]

[1]Cardiff University, Cardiff, United Kingdom, [2]Cytox Ltd, UK, Oxford, United Kingdom, [3]UCL Institute of Neurology, London, United Kingdom, [4]University of Birmingham, United Kingdom, [5]Dementia Research Institute, Cardiff, United Kingdom

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Key Conclusions

- The *varia*TECTII™ array is believed to be the most comprehensive SNP array suitable for understanding the genetic profile of individuals and specifically their risk of future onset of Alzheimer's Disease. It allows for genotyping of DNA extracted from either whole blood or saliva and will provide all the full spectrum of genetic information from an ApoE genotype to the ability to derive multiple polygenic risk scores from several algorithms.

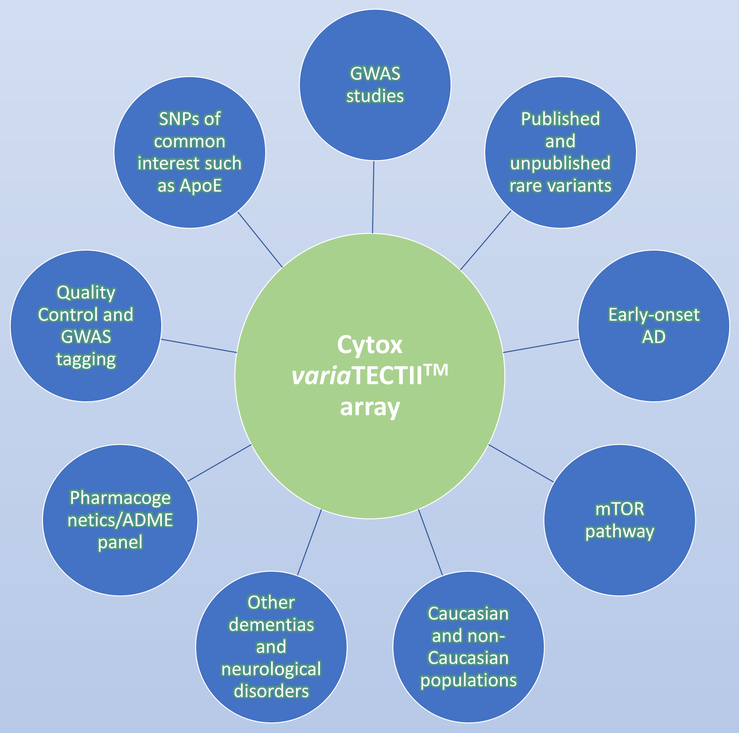
Background

- Stratification and subsequent selection of suitable subjects for clinical trials remains a challenge for Alzheimer's Disease studies and though more tests are becoming available many of them are not feasible for large scale use. Over recent years genetics, beyond ApoE genotyping, has emerged as a potential useful tool for assessing risk of disease and as such is now being considered as part of trial participant screening. In addition to the identification of further risk associated variants, polygenic risk scores have been developed by a number of groups to improve upon the assessment of underlying genetic risk for onset of Alzheimer's Disease. Current methods for collecting genetic data through whole genome sequencing or commercially available SNP arrays are not necessarily optimal for capturing all the relevant genetic information ideally required.

- Cytox has been working in partnership with leading academic teams in Cardiff University, The University of Birmingham and UCL to implement different PRS algorithms into our SNPfitR™ software to validate the performance of these PRS algorithms and to facilitate global access to these tools by drug developers and researchers on a global basis. In addition, we have designed a SNP array in conjunction with Thermo Fisher Scientific that will not only allow generation of genotyping data to drive these PRS algorithms, but also report specifically on key variants in Alzheimer's Disease and other dementias.

Objective and Methods

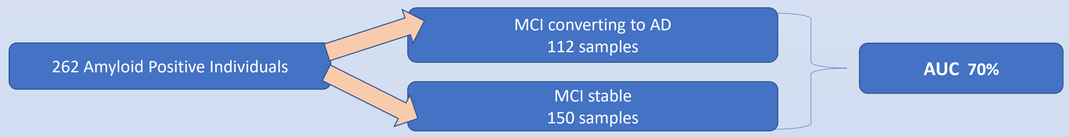
- To design, build and test a high-density SNP array to provide optimal coverage for Alzheimer's Disease (and other dementias) genetic profiling, specifically to be able to run multiple PRS algorithms from a single genotyping platform.
- Cytox, working in partnership with Thermo Fisher Scientific, has developed a next generation dementia specific SNP genotyping array from which multiple PRS algorithms can be run
- Named *varia*TECTII™ (Affymetrix Axiom™) plates are processed on an Affymetrix GeneTitan® scanner. The content of the array was designed to include approximately 800,000 probes that represent the following segments



- Observed technical performance metrics show >99% sample pass rate, >99% average SNP call rate and >99% SNP call concordance in reproducibility studies from blood samples
- Equivalence was observed in studies comparing DNA extracted from blood and saliva from the same donor. SNP call concordance was >99%

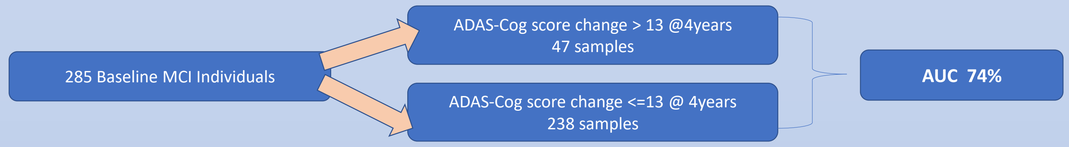
Results

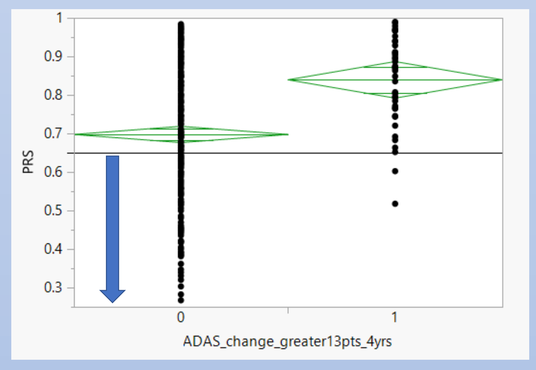
- It has previously been shown that PRS has utility for calculating an individual level genetic risk profile that can predict disease development (AUC is up to 78.2% in a clinical AD case/control study and up to 84% in pathologically confirmed case/control study [1])
- In ADNI [2] an AUC of 82% was observed in a clinical AD case/control study and 70% in prediction of clinical conversion of amyloid positive MCI cases [3]

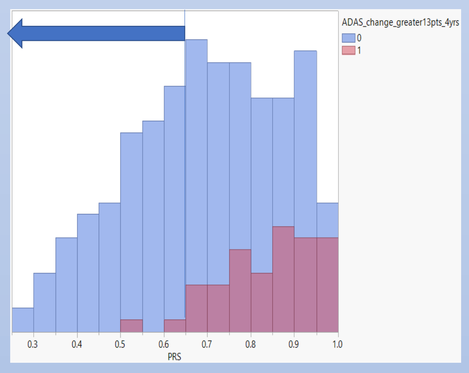


- An analysis of the magnitude of cognitive decline* observed within the baseline MCI population in ADNI indicates that the PRS could have utility in identifying those subjects least likely to experience cognitive decline due to AD over a fixed time period (4 years in this study). In this analysis, subjects with PRS <0.65 could potentially be excluded from a clinical trial population as having low likelihood of significant cognitive decline during the time course of a therapeutic trial.

*Cognitive decline is as measured using ADAS-Cog.[4]



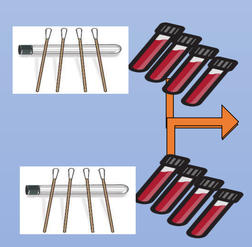




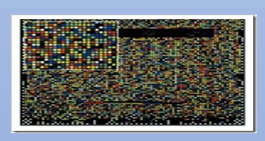
[1] Escott-Price et al (2017) *Annals of Neurology* 82(2):311-314
[2] http://adni.loni.usc.edu/
[3] Pither et al (2018) AAIC poster: Stratification of individuals for PET amyloid positivity and Alzheimer's Disease risk using polygenic risk score analysis – new opportunities for clinical trial design
[4] Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984;141:1356–1364

The Cytox Platform

The SNPFitR™ analysis package and Cytox integrated platform offers fast, accurate, reliable and cost-effective genetic testing solution from whole blood or saliva to assess Alzheimer's Disease risk



Input from extracted DNA, blood or saliva



Custom Cytox variaTECTII™ array

Genotyping on Applied Biosystems GeneTitan™ MC Instruments. Genotypes from Next-Gen Sequencing also accepted

SNPfitR™ pipelines for automated analysis

Output reports with polygenic risk score & ApoE status