Stratification of individuals for PET amyloid positivity and Alzheimer’s Disease risk using polygenic risk score analysis – new opportunities for clinical trial design

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The variaTECT™ array and the Heterogeneity of patient populations and lack of early diagnostic makers have been cited as factors in the last 15 years of clinical trial failures in Alzheimer’s disease (AD) therapeutics. PET amyloid imaging and/or CSF amyloid testing are established techniques in selection of subjects for clinical trials irrespective of the therapy target. The challenge to identify pre-symptomatic individuals who are likely to suffer future cognitive decline is significant.

Using polygenic risk score (PRS) algorithms, it is possible to improve stratification prior to expensive and/or invasive confirmatory tests; particularly important in trials recruiting pre-symptomatic subjects where prevalence of amyloid positivity is low and risk of disease progression highly variable.

PRS algorithms that examine the genetics associated with underlying mechanistic pathways believed to be involved in the development and progression of AD, may also offer opportunities to better understand disease drivers.

A panel of 138,000 SNP variants has been prepared (variaTECT™) in partnership with ThermoFisher Scientific, comprising a comprehensive list of loci associated with pathways relating to AD.

All samples are genotyped on variaTECT™ plates and processed on a GeneTitan™ scanner. The SNPfitR analysis package provides an automated platform using raw genotyping data to produce multi-locus based risk assessments.

The Cardiff PRS approach uses logistic regression analysis utilising AD associated SNPs reported by the ISAG consortium.

The Birmingham variaTECT™ UK, United Kingdom dementia biobank, provides a wealth of data to test the validity of the theoretical knowledge of the pathways involved.

The Cardiff and Birmingham models have been evaluated in various independent datasets.

The SNPR™ analysis package and Cytoxon integrated platform offers fast, accurate, reliable and cost-effective genetic testing solution from whole blood or saliva to assess Alzheimer’s Disease risk progression from MCI to AD.

The Cytoxon Platform

SNPR™ takes processed files from Alexim™ Analysis Suite, utilising the genotyped SNP calls to produce risk estimates based on multiple available PRS algorithms.

Detailed performance parameters are available within the software to facilitate detailed data interrogation.

The Cytoxon Analysis

Polygenic risk score (PRS) analysis tests whether the risk alleles identified in one association study were significantly enriched in the cases relative to the controls in an independent study. The first dataset is used to select the SNPs, the risk score alleles and their genetic effects. The second dataset is used to test whether the polygenic risk scores differ in cases and controls.

Measures of polygenic burden could prove useful in distinguishing patients with Alzheimer’s disease whose disease liability is most likely to carry a large or small polygenic component. It has been shown that PRS has use for calculating the individual level genetic risk profile that can predict disease development (AUC is up to 79% in a clinical AD case/control study and up to 84% in pathologically confirmed case/control study [2]).

To select SNPs and identify risk alleles we used genome wide association data from 17,088 cases and 37,154 controls obtained from the International Genomics of Alzheimer’s Project (IGAP) [3]. This dataset was imputed using the 1000 genomes data (release 2013). In 724 subjects from ADNI [4] four assessments to predict clinical status were made: 1) predicting AD cases vs cognitively normal controls (CN), 2) predicting MCI cases vs CN, 3) predicting progression of amyloid positive MCI cases have subsequently converted to a clinical diagnosis of AD. The performance was measured as AUC.

The genotypic data were used to estimate the success rate of the candidate PRS algorithms. The correlation of the modelled and actual risk was used as the validation parameter. The sensitivity and the specificity of the PRS algorithms were estimated with and without the inclusion of Covariates.

The Birmingham genoTORT™ Algorithm

The molecular pathways disrupted in AD are well documented by several different approaches and many studies. The genome contains molecular functions and interactions with well documented SNPs including the ApoE4.

Molecular network approaches have been successful in several diseases.

Comparison ROC analysis indicates that the genoTORT™ risk score is independent of the ApoE genotype and significantly to AD risk identification.

Conclusion

Cardiff PRS offers high accuracy in predicting clinical AD and MCI and is ApoE4 independent so can be used to predict Alzheimer’s in whole population.

Cardiff PRS can be used to stratify amyloid-positive subjects for risk of clinical relevant AD before randomisation to clinical trials.

The Birmingham genoTORT™ PRS algorithm is ApoE4-independent and can be used to stratify clinical risk of AD, has potential to stratify within an AD population and facilitate pathway-based population segmentation for targeted drug trials.

Integrated Cytoxon platform available on a global basis for clinical sample testing.