Table 3
Associations Between Risk Factors and Cogstate Composite Scores

	DET + IDN (n=1,580) (psychomotor speed, attention)		OCL + ONB (n=1,505) (learning, working memory)		Overall Cognition (n=1,469)	
	β	p	β	p	β	p
Age (years)	-0.03 (-0.04, -0.02)	<0.001	-0.04 (-0.04, -0.03)	<0.001	-0.03 (-0.04, -0.03)	<0.001
Smoking						
Never (ref.)	-	-	-	-	-	-
Former/Current	-0.04 (-0.13,0.06)	0.47	0.10(0.02,0.18)	0.02	0.04 (-0.03,0.12)	0.26
Body mass index						
<22 kg/m^2	-0.01 (-0.18,0.16)	0.88	-0.08 (-0.23,0.06)	0.27	-0.04 (-0.17,0.09)	0.57
22-24.9 kg/m^2 (ref.)	-	-	-	-	-	-
25-29.9 kg/m^2	0.02 (-0.09,0.12)	0.74	0.00 (-0.09,0.09)	0.94	0.01 (-0.07,0.09)	0.82
30+ kg/m^2	0.10 (-0.05,0.25)	0.18	0.03 (-0.10,0.16)	0.61	0.06 (-0.06,0.17)	0.34
Physical activity, MET-hr/wk						
First quartile (ref.)	-	-	-	-	-	-
Second quartile	0.04 (-0.04,0.17)	0.50	0.03 (-0.08,0.14)	0.57	0.01 (-0.09,0.11)	0.83
Third quartile	0.01 (-0.12,0.14)	0.86	0.00 (-0.11,0.11)	0.99	-0.02 (-0.12,0.08)	0.70
Fourth quartile	0.08 (-0.05,0.21)	0.25	0.01 (-0.11,0.12)	0.89	0.00 (-0.10,0.11)	0.95
Alcohol, drinks/day						
None (ref.)	-	-	-	-	-	-
1-2	0.09 (-0.01,0.19)	0.06	0.03 (-0.05,0.11)	0.45	0.05 (-0.03,0.12)	0.21
>2	-0.03 (-0.16,0.11)	0.67	-0.02 (-0.13,0.10)	0.77	-0.03 (-0.13,0.07)	0.56
Nut intake, times/day						
First quartile (ref.)	-	-	-	-	-	-
Second quartile	0.10 (-0.02,0.23)	0.10	0.11 (0.01,0.22)	0.04	0.11 (0.02,0.21)	0.02
Third quartile	0.15 (0.01,0.28)	0.03	0.16 (0.05,0.25)	0.005	0.18 (0.07,0.28)	0.001
Fourth quartile	0.08 (-0.06,0.21)	0.26	0.07 (-0.04,0.19)	0.21	0.09 (-0.01,0.20)	0.09
Diabetes	-0.18 (-0.34, -0.02)	0.03	0.09 (-0.04,0.23)	0.18	-0.05 (-0.18, 0.07)	0.42
Hypertension	-0.07 (-0.16,0.02)	0.12	-0.08 (-0.16,-0.01)	0.03	-0.08 (-0.15, -0.01)	0.03
Myocardial infarction	0.10 (-0.08,0.27)	0.26	0.02 (-0.13,0.16)	0.80	0.05 (-0.09,0.18)	0.48

Notes: Higher scores indicate better performance. All variables were placed into the same model

on all cognitive outcomes ($p < 0.001$). A history of hypertension was significantly associated with worse performance on overall cognition (mean difference=-0.08 standard units [95% CI -0.15, -0.01]) and higher nut consumption was also significantly associated with better performance (Q3 vs. Q1: 0.11 [0.02, 0.21]; Q2 vs. Q1: 0.18 [0.07, 0.28]). When using covariates measured at mid-life, increased physical activity was also significantly associated with better performance on learning and working memory (Q3 vs. Q1: 0.14 [0.04, 0.24]). **Conclusions:** Participation in self-administered computerized cognitive testing in older men was low. However, few differences existed between responders and non-responders. The battery showed significant associations with several risk factors known to be associated with cognitive function. Future epidemiologic studies of cognitive aging may benefit from the numerous advantages of self-administered computerized testing.

TUESDAY, JULY 21, 2015
ORAL SESSIONS
O3-13
GENETICS: ROLE OF RARE AND LOW FREQUENCY VARIANTS IN ALZHEIMER'S DISEASE

O3-13-01 WHOLE GENOME SEQUENCING OF LATE-ONSET ALZHEIMER'S DISEASE PATIENTS FROM GENETIC ISOLATE

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Background: Alzheimer's disease (AD) is a common heritable neurodegenerative disorder. However, aside from ApoEe4, the genetic factors contributing to common late-onset AD remain to be elucidated. In addition to known single genetic risk factor (ApoEe4 allele) and highly penetrant missense-mutations in APP and PSEN1/PSEN2 genes, many other genetic variations with incomplete penetrance may potentially be risk factors for AD. The role of such rare variations in AD would be difficult or impossible to identify by GWAS using a standard population case-control design. Thus, we employed the direct whole-genome sequencing of AD patients from a genetically isolated population from the southwestern area of The Netherlands. **Methods:** We have performed a whole-genome sequencing of pairs of distantly-related late-onset AD patients from extra-large pedigree branches from genetically isolated Dutch population, described previously (Liu et al, Am J Hum Genet,2007). The genome sequencing data were combined

with the previously reported data of genetic linkage analysis in these pedigrees, which identified a set of AD susceptibility chromosomal loci, including 1q25, 1q21, 11q24 and 3q23 loci. **Results:** We selected rare single nucleotide variations (SNV) and insertion deletion (indel) mutations shared between at least two AD patients in each pedigree branch. We searched only for the rare variations with MAF<0.05 that potentially affect protein structure. We filtered out potential sequencing errors and also removed the SNV/indels found in "controls," including genomes of centenarians with no AD symptoms (Illumina sequencing data). The deleterious effects were verified by computational programs. In the primary analysis, we selected the genes with SNVs/indels located on 1q25, 1q21, 11q24 and 3q23 loci. In a broader whole-genome scanning, we listed all the rare variations that had an effect on protein structure and which are shared between at least two affected, distantly-related individuals. **Conclusions:** The data suggested that not a single, but many genetic variations may be involved in risk and modulation of AD pathway, even in a genetic isolate with common genetic founders. A set of candidate genes bearing rare variations in AD patients which are involved in Abeta/tau–metabolism and regulation and in neurodegeneration-related biological processes were revealed and their role will be discussed.

O3-13-02 WHOLE-EXOME SEQUENCING IN EARLY-ONSET ALZHEIMER DISEASE CASES IDENTIFIES NOVEL CANDIDATE GENES

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Background: Mutations in *APP*, *PSEN1* and *PSEN2* lead to early-onset Alzheimer disease (EOAD). These mutations account for ~11% of EOAD overall, leaving the majority of genetic risk for the most severe form of Alzheimer disease unexplained. **Methods:** We performed Whole-Exome Sequencing (WES) in 50 Caucasian EOAD cases previously screened negative for *APP*, *PSEN1*, and *PSEN2* to search for rare variants contributing to risk for EOAD. Variant filtering for functional, damaging rare variants (MAF<0.1%) was performed. Genes with shared (2+ cases with the same variant), damaging variants were examined for interactions with known EOAD genes (*APP, PSEN1, PSEN2, SORL1, GRN*, *MAPT*) and *APOE* using STRINGdb. **Results:** 176 genes had rare functional variants shared in two or more cases. 46 of these genes were prioritized for their damaging potential, defined by their shared rare variants having a Combined Annotation Dependent Depletion (CADD) score in the top 10% of all variants. Gene network analysis of these 46 genes with known EOAD genes and *APOE* identified five top candidate genes: *HSPG2* (interacts with *GRN*, *APOE*, and *APP*), *CLSTN1* (interacts with *PSEN1* and *APP*), *DOCK3* (interacts with *PSEN1* and *PSEN2*), and the *APOE* interactors *SAR1B* and *STAT1*. 5 cases have a variant in *HSPG2*, a gene potentially involved in amyloidogenesis and tau aggregation in AD, while 4 cases have a variant in *DOCK3*, a gene expressed exclusively in the central nervous system and associated with neurofibrillary tangles in AD brains. **Conclusions:** WES of EOAD cases identified several genes with potential roles in AD pathogenesis.

O3-13-03 MASSIVE PARALLEL GENE PANEL SEQUENCING IN A BELGIAN FTLD COHORT OF CAUSAL GENES ASSOCIATED WITH DIVERSE NEURODEGENERATIVE BRAIN DISEASES

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Background: Due to the increasing number of genes associated with neurodegenerative brain diseases (NBDs) like Alzheimer disease (AD), frontotemporal lobar degeneration (FTLD) and related neurodegenerative diseases, and taken the significant overlap in clinical phenotype between these diseases, there is a growing need for high-throughput genetic profiling assays. **Methods:** We designed a diagnostic gene panel for amplicon-based re-sequencing of all coding exons of 14 Mendelian genes linked to NBDs. The assay uses high-level multiplex PCR amplification followed by sequencing on an Illumina MiSeq. **Results:** In 527 FTLD patients from Belgium, we identified 146 rare protein-modifying variants. These included 55 variants that were definitely or probably pathogenic (38GRN LOF, 4MAPT, 7VCP, 1FUS, 2TARDBP, 1CHMP2B, 2PSEN1) and 5 possibly pathogenic (2VCP, 2FUS, 1PSEN1). Together with the C9orf72 repeat expansions, these mutations explained 43% of familial FTLD patients and up to 62% of pathology confirmed patients in our cohort. In one probable FTLD patient of 55 years, we observed a C9orf72 repeat expansion together with a novel VCP p.Ile189Val mutation. Other interesting observations were a.o. the presence of 8 novel APP non-synonymous mutations of which the pathological nature is uncertain. Nonetheless, we identified the APP p.Glu599Lys mutation in 2 probable FTLD patients and one patient diagnosed with probable AD or probable DLB, and all 3 patients shared a common haplotype. In addition, in MAPT non-synonymous mutations outside exon 1 and exon 9-13 were found in multiple FTLD patients, Val244Gly (N=4) and Ser427Phe (N= 5). These findings are interesting since they cross borders between different clinical diagnostic disease categories. However, further studies are needed to see whether these genetic variations contribute to the clinical and/or neuropathological presentations of the carriers or might have disease modifying effects. **Conclusions:** The NBD gene panel is a high throughput and cost effective molecular diagnostic tool that offers a more complete genetic read out than classic Sanger sequencing-based gene by gene testing. Moreover it allows the systematic evaluation of the prevalence and relevance of double and cross-phenotype mutations. At this moment, exome sequencing cannot yet offer the same amount of coverage and fidelity for targeted gene screening.

O3-13-04 GENOME-WIDE RARE VARIANT ANALYSIS IDENTIFIES CANDIDATE GENES SIGNIFICANTLY ASSOCIATED WITH COMPOSITE SCORES FOR MEMORY

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