2325 COGNITIVE PROCESSING SPEED PREDICTS DISEASE PROGRESSION IN SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS: POST HOC ANALYSIS FROM THE EXPAND STUDY

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Objective Assess the predictive value of cognitive processing speed (CPS), using the Symbol Digit Modalities Test (SDMT) score, on disability progression in secondary progressive multiple sclerosis (SPMS).

Methods SPMS patients from the Phase 3 EXPAND study (core part [CP] and core+extension part [CP+EP]) were categorized into quartiles of baseline SDMT score (worst-WQ [Q1], intermediate [Q2-Q3], and best-BQ [Q4] quartile). The predictive value of baseline SDMT quartiles for time-to-wheelchair (T2W; i.e., Expanded Disability Status Scale [EDSS] score $\geq$7) sustained until end of follow-up, or 6-month confirmed disability progression (6mCDP) by EDSS, were assessed at the end of the CP (up to 37-months) and CP+EP (up to 5-years) by Cox regression (adjusted for treatment, age, gender, baseline EDSS, baseline SDMT quartile, and treatment-by-baseline SDMT quartile interaction).

Results Analyses included 1628/1651 patients (98.6%) randomized in EXPAND (baseline SDMT: WQ, n=435; intermediate, n=808; BQ, n=385). Risk of T2W (WQ vs BQ) was higher in the CP ($HR_{WQ/BQ}$=1.31, 95% CI:0.72–2.38; p=0.37) and increased with long-term follow-up ($HR_{WQ/BQ}$=1.81; 1.17–2.78; p=0.01). Baseline SDMT was not predictive of 6mCDP. The predictive value of baseline SDMT for T2W in the CP was weaker with siponimod (n=1088; $HR_{WQ/BQ}$=1.12, 0.55–2.29; p=0.75) vs placebo (n=540; $HR_{WQ/BQ}$=1.86, 0.73–4.78; p=0.19), possibly due to siponimod preventing relatively more T2W events in the WQ.

Conclusions The results support the predictive value of CPS for long-term (up to 5-years) physical disability progression in SPMS and highlight relevance of monitoring CPS in daily practice to help identify patients at risk of progressing

2326 DIFFERENTIAL METHYLATION MEDIATES SIGNIFICANT PROPORTIONS OF ENVIRONMENTAL AND LIFESTYLE FACTORS' ASSOCIATIONS WITH MS RISK: RESULTS FROM THE AUSIMMUNE CASE-CONTROL STUDY

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Background The mechanisms by which modifiable environmental and lifestyle factors, including Epstein-Barr virus (EBV) exposure, sun exposure/vitamin D, and smoking exert their effects on multiple sclerosis (MS) risk are unclear. Here, we explored the extent to which differential DNA methylation mediated the associations of previously reported environmental/lifestyle risk factors for first clinical demyelination (FCD).

Methods The Ausimmune case-control study was a multicentre study comprising 282 people recruited soon after an FCD referral and 576 matched-controls. Smoking status, glandular fever history, and recent summer and winter sun exposure were queried. Serum samples were analysed for 25-hydroxyvitmain D (25(OH)D) and anti-EBV serology. Whole-blood EWAS measures were measured using Illumina EPIC BeadChip Array. FCD-associated methylation points (CpG, n=2,432) were inputs to weighted gene-correlation network analysis and 10 CpG clusters were identified. Mediation by dimension-reduced CpG cluster scores was assessed using the MedFlex package in R.

Results Of the 10 CpG clusters, eight were significant mediators of environmental/lifestyle risk factors, indirect effects ranging between 19–34% of EBV, 15–40% of sun exposure, 17–49% of 25(OH)D, and 15–30% of smoking, with some factors acting through common CpG clusters. CpG clusters aligned with pathways involved in signal transduction and transcription regulation, and T-cell activation/proliferation.

Discussion These results demonstrate for the first time that roughly one-third of the associations seen for EBV exposure, sun exposure, 25(OH)D, and smoking are explicable by differential methylation of loci involved in immune cell regulation, providing biologically plausible mechanisms by which these factors can affect MS risk, and suggesting potential points of intervention.