PLATFORM PRESENTATIONS

GRAND PLENARY ABSTRACTS

GP.1

The genetic basis of multiple sclerosis severity

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Background: The mechanisms underlying the severity and wide heterogeneity of multiple sclerosis (MS) remain poorly understood. A persistent challenge has been determining whether genetic variation influences these traits. Methods: In 12,584 people with MS (pwMS), we estimated the proportion of age-related MS severity score variance attributable to additive genetic variation (SNP-heritability). Then, we interrogated for enrichment in hundreds of tissues and cell types using gene expression annotations. We performed a genome-wide association study (GWAS) using 7.8 million variants and attempted replication in an independent cohort of 9,805 pwMS. A subset of 8,325 pwMS was examined longitudinally over 54,113 visits. Results: We observed a 10% SNP-heritability for MS severity. In contrast to MS susceptibility, robust tissue-level enrichment was apparent in the brain and cervical spinal cord, but not in immune cells. We identified a novel MS severity locus ($p<5x10^{-8}$) and confirmed this in the replicate population. The lead variant was associated with higher hazards of 6-month confirmed disability worsening (p=0.008) and faster EDSS worsening (p=0.002). Time to walking aid (EDSS 6.0) was 3.2 years earlier in homozygous risk carriers. Conclusions: This study identifies the first genetic modifier of MS progression, establishes the genetic contributions to its heterogeneity and describes a distinct genetic architecture from susceptibility.

GP.2

Deep learning prediction of response to disease modifying therapy in primary progressive multiple sclerosis

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Background: Only one disease modifying therapy (DMT), ocrelizumab, was found to slow disability progression in primary progressive multiple sclerosis (PPMS). Modeling the conditional average treatment effect (CATE) using deep learning could identify individuals more responsive to DMTs, allowing for predictive enrichment to increase the power of future clinical trials. Methods: Baseline clinical and MRI data were acquired as part of three placebo-controlled randomized clinical trials: ORATORIO (ocrelizumab), OLYMPUS (rituximab) and ARPEGGIO (laquinimod). Data from ORATORIO and OLYMPUS was separated into a training (70%) and testing (30%) set, while ARPEGGIO served as additional validation. An ensemble of multitask multilayer perceptrons was trained to predict the rate of disability progression on both treatment and placebo to estimate CATE. Results: The model could separate individuals based on their predicted treatment effect. The top 25% of individuals predicted to respond most have a larger effect size (HR 0.442, p=0.0497) than the entire group (HR 0.787, p=0.292). The model could also identify responders to laquinimod. A simulated study where the 50% most responsive individuals are randomized would require 6-times less participants to detect a significant effect. Conclusions: Individuals with PPMS who respond favourably to DMTs can be identified using deep learning based on their baseline clinical and imaging characteristics.

GP.3

Measurement of decremental response is repeatable in amyotrophic lateral sclerosis

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Background: Neuromuscular junction transmission impairment has been described in amyotrophic lateral sclerosis (ALS). The degree of repetitive nerve stimulation (RNS) decrement may correlate with disease activity if measurement is repeatable. We determined test-retest correlation of decremental response in patients with ALS. Methods: RNS (3 Hz) was assessed by blinded technician and clinician on median - abductor pollicis brevis (median-APB), ulnar - adductor digiti minimi (ulnar-ADM), and/or accessory - trapezius (accessory-TRAP) nerve-muscle pairs during two evaluations. Repeatability was assessed by measuring the strength of test-retest correlation using the Pearson correlation coefficient (r). Results: 24 patients were included. Decrement was measured for 16 patients on median-APB, 22 on ulnar-ADM, and 24 on accessory-TRAP. Repeated measures of decrement demonstrated strong test-retest correlation for median-APB ($r = 0.82$, $p < 0.001$) and accessory-TRAP ($r = 0.87$, $p < 0.001$). Correlation was poor in ulnar-ADM ($r = -0.01$, $p = 0.949$). Correlation was superior in median-APB muscles with higher Medical Research Council (MRC) grade strength (MRC $\geq$ 4, r = 0.89, $p = 0.001$ vs MRC < 4, r = 0.73, $p = 0.062$). Conclusions: Decremental response in patients with ALS has strong test-retest correlation in median-APB and accessory-TRAP, but not in ulnar-ADM.