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Genetics of multiple sclerosis severity: The importance of statistical power in replication studies

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In a recent study, Campagna et al.[1] revisit the association between MS severity and rs10191329, the first genome-wide significant marker for disease severity[2]. Based on their analysis of 1813 patients[3], they report an inability to replicate our finding.

In this response, we first emphasize, as acknowledged by the authors, that our study included a successful independent replication with 9,805 patients from nine centers[2]. There, as expected, the effect size was modest (β=0.044), smaller than in the discovery (β=0.088) due to the winner's curse, underscoring the challenges of replication. Indeed, Extended Data Figure 3 from our publication[2] illustrates that limited power could misleadingly suggest non-replication if centers were evaluated individually. Nevertheless, all centers were directionally concordant and collectively demonstrated a statistically significant effect. While the utility of genetic evidence in translation is firmly established irrespective of effect size[4], it was never our intention to identify single variants that directly predict clinical outcomes, just as our discoveries of MS genetic risk factors were not expected to provide immediate diagnostic application.

Second, we were intrigued by Campagna et al.'s power estimates, which seemed improbably confident (up to 84.8%) given the modest effect and their small sample size. We recalculated the power based on parameters from our replication cohort: MAF=0.17; β=0.044 for ARMSS and 0.047 for MSSS with unit variance; highest vs. lowest severity quintile OR=1.08 and 1.14, respectively. We estimated their power to detect associations with rs10191329 for binned ARMSS and MSSS at 16.7% and 38.1%, and for median ARMSS and MSSS at 16.1% and 18.8%, respectively (α=0.05). This is further evidenced by considerably wide confidence intervals (e.g., binned ARMSS 0.78–1.38). Notably, all their point estimates are directionally concordant with ours and not statistically different; random-

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effects meta-analysis with our data indeed strengthens the association (ARMSS $P=2.6\times10^{-9}$ from 3.6×10^{-9}, $I^2=0\%$).

Lastly, we contest the assertion that our cross-sectional outcome measure was “less robust”. Many of our cohorts (e.g., EPIC, EIMS/GEMS, CLIMB, etc.) are prospective and deeply phenotyped, and we also confirmed the association with rs10191329 in longitudinal data based on 54,113 visits. Regarding outcome measures, the main difference is that while Jokubaitis et al.[3] used median severity scores (*also cross-sectional*), we selected the most distant scores in time, reasoning that these are the likeliest to capture disability driven by progressive pathology and reflective of patients’ overall outcomes. We contend that our approach proved fruitful, enabling us for instance to demonstrate significant enrichment in CNS tissues after multiple testing correction, in contrast to Jokubaitis et al.[3], who despite claiming similar enrichment, found no such evidence after multiple testing adjustment.

In conclusion, others will assess the effects of rs10191329 within their cohorts and offer additional insights[5]. However, meaningful failure-to-replicate studies should demonstrate higher, not lower, power than the original. Our consortium is firmly committed to collaborative research, encompassing global specialized centers to maximize sample size —whose importance can no longer be debated[6]—and deepen our understanding of MS genetics. We encourage all centers to join in this effort for the benefit of people with MS.

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