Tanasescu Radu (Orcid ID: 0000-0003-2282-1793)

Title:

To predict or not to predict: multiple sclerosis and B cell subset-specific genetic risk scores

Authors:

Radu Tanasescu[1,2,*], Andrew Chan[3]

[1]-Academic Clinical Neurology, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

[2]-Department of Neurology, Nottingham University Hospitals National Health Service Trust, Queen's medical Centre, Nottingham, UK

[3]-Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

*Corresponding author:

Dr Radu Tanasescu

Department of Neurology, D floor, West block, Nottingham University Hospitals National Health Service Trust, Queen's Medical Centre, NG7 2UH, Nottingham, UK

radu.tanasescu@nottingham.ac.uk

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Even in families with a high prevalence of MS, we are as yet unable to predict the development of MS with adequate accuracy, at the individual level. Despite major progress in the understanding of genetic risk factors for MS, blending this information into predictive scoring systems has yet been unsatisfactory. The genetic component of MS susceptibility involves a large number of individually small effects spread across more than two hundred thirty genetic loci. This genomic map of MS links specific peripheral immune cells and microglia to the susceptibility of developing the disease[1]. In this issue of European Journal of Neurology, de Mol et al. report associations between B-cell-associated MS risk variants and circulating naive and memory B cells in six-year-old children from the general population, who are participants in the Generation R Study, a large population birth cohort in the Netherlands[2]. A number of 26 naive B-cell MS risk variants are reported to be connected with higher numbers of memory B cells in the blood, independently of the presence of EBV (capsid antigen in the blood) or of HLA-DRB1*15:01 (both of which are risk factors for developing MS). The authors suggest that the MS-risk SNPs in naive B cells bear a specific impact on B-cell memory early in life, and thus can possibly contribute to the development of B cell subsets involved in the pathophysiology of MS. Thus, the current work is an important attempt to link genetic changes to immune-function.

Whilst this work does show that the genetic susceptibility factors of MS correlate with the composition of the B-cell compartment early in life even of healthy children, it also highlights some current limitations and unmet needs in improving MS prediction. As the authors note, the main limitation pertains to its interpretability. How these findings are to be translated in the 'true risk' of developing MS is unclear. The subjects are 6yo children, whose immune biology is an ongoing transformative process and it is unclear how many of these children will develop MS; notwithstanding the predictive value of the polygenic risk scores, the development of MS is multifactorial. Moreover, it is not clear how the findings of this study would apply to populations with non-European ancestry. The MS genetic risk score used is based on MS-GWAS in people of European ancestry. Studies on non-European MS cohorts show that the genetic basis of MS is not identical for people with African or Hispanic ancestry [3-5].

The aim of studies on factors of risk to develop MS should be providing data that can contribute in identifying potential candidates for MS prevention trials (such as, possibly, EBV vaccination [6]). Thorough characterisation of populations at risk is required. The authors of the current report have also performed studies of association of MS polygenic risk scores (PRS) with T cell phenotypes in a group from the same population study[7]. They found that PRSs for MS are associated with T cell numbers in the peripheral blood from 6yo children, with a higher genetic MS-risk associated with an increased CD4+/CD8+ ratio. Interestingly, in the current observation the association of the B cell risk variants with a higher numbers of memory B cells was independent of the CD4+/CD8+ ratio. As the authors note, the independent effects of genetic MS-risk on B and T cells in children could suggest that risk variants have an impact on both compartments already early in life, thus possibly affecting their interaction and contributing to the development of MS. Unfortunately, the lack of information of overlap of the groups in the studies published separately precludes further integrative understanding of independent or joint effects of impact of the genetic MS risk genetic score on B and T cells compartments.

Further prospective follow-up work on the study population is required to demonstrate the validity of findings of de Mol et al. and their impact on the risk of developing MS, and ensure its applicability across different ancestry populations. Nevertheless, if confirmed, this is could be another stepping-stone on the path of selecting individuals at risk for MS who could benefit from earliest preventive

interventions. The rapid therapeutic progress in this field of neurology may also alleviate some of the ethical concerns associated with prediction of disease.

References:

[1]. International Multiple Sclerosis Genetics C. Multiple sclerosis genomic map implicates peripheral immune cells and microglia in susceptibility. *Science*. 2019 **365**.
[2]. Kooijman MN, Kruithof CJ, van Duijn CM*, et al.* The Generation R Study: design and cohort update 2017. *Eur J Epidemiol*. 2016 **31:** 1243-1264.
[3]. Chi C, Shao X, Rhead B*, et al.* Admixture mapping reveals evidence of differential multiple sclerosis risk by genetic ancestry. *PLoS Genet*. 2019 **15:** e1007808.
[4]. Isobe N, Madireddy L, Khankhanian P*, et al.* An ImmunoChip study of multiple sclerosis risk in African Americans. *Brain*. 2015 **138:** 1518-1530.
[5]. Beecham AH, Amezcua L, Chinea A*, et al.* The genetic diversity of multiple sclerosis risk among Hispanic and African American populations living in the United States. *Mult Scler*. 2020 **26:** 1329-1339.
[6]. Maple PA, Ascherio A, Cohen JI*, et al.* The Potential for EBV Vaccines to Prevent Multiple Sclerosis. *Front Neurol*. 2022 **13:** 887794.
[7]. de Mol CL, Looman KIM, van Luijn MM*, et al.* T cell composition and polygenic multiple sclerosis risk: A population-based study in children. *Eur J Neurol*. 2021 **28:** 3731-3741.

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