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Type	Oral communication
Session	Biological Networks
Title	Prediction of tissue-specific pathways affected by genomic variants associated with disease activity in Multiple Sclerosis
All Authors	Alice Chiodi(1), Valentina Nale(1), Ferdinando Clarelli(2), Noemi Di Nanni(1), Laura Ferrè(2,3), Elisabetta Mascia(2), Silvia Santoro(2), Matteo Gnocchi(1), Marco Moscatelli(1), Martina Tosi(2), Kaalindi Misra(2), Melissa Sorosina(2), Luciano Milanesi(1), Massimo Filippi(3-5), Federica Esposito(2,3)#, Ettore Mosca(1)#

Affiliation

(1) Institute of biomedical technologies, National Research Council, Segrate (Milan), Italy
(2) Laboratory of Neurological complex disorders, Division of Neurosciences, IRCCS San Raffaele Scientific Institute, Milan, Italy
(3) Neurology, Neurorehabilitation and Neurophysiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy
(4) Neuroimaging Research Unit, Division of Neuroscience, IRCCS San Raffaele Scientific Institute, Milan, Italy
(5) Vita-Salute San Raffaele University, Milan, Italy

Motivation

Multiple Sclerosis (MS) is an autoimmune disease of the Central Nervous System (CNS) characterized by high clinical heterogeneity. MS is the most common cause of acquired neurologic disability in young adults. The pathogenic events of the disease arise from a complex interplay of mechanisms acting at CNS level and peripheral immune cells level. Monitoring the activity of the disease is crucial towards a personalized management of MS patients and approaches based on the analysis of the interactome can prove successful to better elucidate the molecular mechanisms underlying MS disease activity.
According to the omnigenic model, like other complex traits, many genes can affect risk of high disease activity through highly connected molecular networks and while a set of “core genes” have direct effect, many other genes are involved in disease risk by means of tissue-specific interactions with core genes. Here, we analyze tissue-specific molecular interactions to study how the same underlying genetic variants affect the tissues mainly relevant to disease activity in MS. In particular, we compared the molecular networks highly affected by variants (disease modules), pathways and pathway cross-talk (PCT) between different tissues.

Methods

A total of 1174 were included in the study and were classified as EDA (Evidence of Disease Activity) or NEDA (non-evidence of Disease Activity) patients at 4 years of follow-up. The genome-wide association study was performed comparing EDA and NEDA individuals with PLINK, followed by the estimation of gene-wise statistics through VEGAS2v02 tool. The impact of genetic variants throughout molecular networks was quantified using the R package “dmfind” [1], which uses network diffusion to find disease modules. Tissue-specific interactomes at CNS and peripheral level were downloaded from HumanBase [2], using “top edges” network for “brain” and “lymphocyte” interactomes; these networks were filtered to keep only the high confidence interactions. Pathway analysis and PCT was carried out with our R package “Ulisse” [3], which implements enrichment analyses and network-based methods; in particular the PCT was quantified considering the interaction between exclusive pathway genes weighted by their significance. Gene-pathway associations were collected from MSigDB [4]. The statistical significance of the results was assessed by permutation-based approaches. We identified tissue-specific and shared pathways to build networks to identify strictly connected communities and cross-talks differences.

Results

We analysed the list of genes that carry variants associated with MS disease activity (shortly, variant genes) in brain and lymphocyte-specific interactomes. In both tissues, we found networks of variant genes. The networks share common as well as tissue-specific components. We analysed pathways and found that the majority of pathways are shared between the two tissues (shared pathways) while a minor number is tissue-specific. We obtained PCT networks, in which links between pathways indicate interactions between their respective genes. Interestingly, we observed that the PCT networks between shared pathways contain relevant differences between the two tissues. Collectively, our preliminary results highlighted tissue-specific pathways and tissue-specific cross talks within shared pathways, originating from the same underlying genomic variants associated with disease activity in MS. Moreover, our study

underlined the importance of analyzing omics data using tissue-specific models in network analysis.

Info

[1] Bersanelli, M., Mosca, E., Remondini, D., Castellani, G., & Milanesi, L. (2016). Network diffusion-based analysis of high-throughput data for the detection of differentially enriched modules. Scientific reports, 6(1), 1-12.
[2] https://hb.flatironinstitute.org
[3] Chiodi, A., Nale, V. & Mosca E. Ulisse: an R package to go beyond the boundaries of knowledge of molecular pathways. Bioconductor 2021 Conference (Accepted)
[4] http://www.gsea-msigdb.org/gsea/msigdb/index.jsp

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Figure

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Availability -

Corresponding Author

Name, Surname Ettore, Mosca

Email ettore.mosca@itb.cnr.it

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