ECTRIMS 2024
Copenhagen, Denmark
Annual Congress | 18-20 September 2024
Pre-Day | 17 September 2024
Patient Community Day | 20 September 2024
40TH ANNIVERSARY

Abstract Number: 1170/P128

Genetic-driven impairment of mitochondrial function in primary progressive multiple sclerosis

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Introduction:

Several lines of evidence demonstrate that mitochondrial dysfunction could be one of the driving factors of disease progression in multiple sclerosis (MS). Mitochondria are bacterium-sized organelles involved in several functions within the cell, mainly energy production, as well as apoptosis and calcium homeostasis. They have their own DNA (mtDNA) containing 37 genes codifying for protein involved in the respiratory chain.

Objectives/Aims:

The purpose of this project is to explore the genetic determinants of mitochondrial impairment occurring in primary progressive MS (PPMS).

Methods:

We performed a candidate gene-set enrichment analyses with magma tool, comparing 532 PPMS and 436 benign MS (defined as patients with EDSS<4 after at least 20 years), starting from imputed whole-genome genotyping data (8.5 million SNPs). A total of 166 gene-sets and 1704 nuclear genes covering the main mitochondrial functions were selected: oxidative phosphorylation, mitophagy, transport/movement of mitochondrion, mitochondrial calcium homeostasis, general function of mitochondrion, metabolism, mitochondrion-mediated apoptosis, integrating stress response. Further functional evaluations to confirm the involvement of associated pathways were performed on 20 PPMS and 20 RRMS patient collected peripheral blood mononuclear cells (PBMCs), differentiated and expanded in CD4+ T lymphocytes through a specifically designed protocol. We performed cytofluometric analysis of Tetramethylrhodamine Methyl Ester (TMRM) to measure mitochondrial membrane potential (MMP) and of MitoTracker staining to assess mitochondrial mass.

Results:

Analyses highlighted gene-sets related to fatty acid beta oxidation (p=0.002), mitophagy (p=0.004) and mitochondrial uncoupling (p=0.03) as associated with PPMS. At baseline, no differences were observed in terms of MMP comparing CD4+ enriched T lymphocytes collected from PP and RR patients, while a slight increase in mitochondrial mass was observed in PPMS (Kolmogorov-Smirnov test p<0.0001), coherent with the presumed impairment of mitophagy-related processes.

Conclusion:

Our results suggest the presence of genetic-driven mitochondrial impairment in specific processes in PPMS. Additional functional assessments are ongoing to better support the observed data.

Disclosures:

Massimo Filippi: received compensation for consulting services from Alexion, Almirall, Biogen, Merck, Novartis, Roche, Sanofi, Speaking activities from Bayer, Biogen, Celgene, Chiesi Italia SpA, Eli Lilly, Genzyme, Janssen, Merck-Serono, Neopharmed Gentili, Novartis, Novo Nordisk, Roche, Sanofi, Takeda, and TEVA; Participation in Advisory Boards for Alexion, Biogen, Bristol-Myers Squibb, Merck, Novartis, Roche, Sanofi, Sanofi-Aventis, Sanofi-Genzyme, Takeda; Scientific direction of educational events for Biogen, Merck, Roche, Celgene, Bristol-Myers Squibb, Lilly, Novartis, Sanofi-Genzyme. He receives research support from Biogen Idec, Merck-Serono, Novartis, Roche. Federica Esposito: received consulting and speaking fees from Novartis, Sanofi Genzyme. Melissa Sorosina: nothing to disclose. Daniele De Ritis: nothing to disclose. Ferdinando Clarelli: nothing to disclose. Elisabetta Mascia: nothing to disclose. Michela Crotti: nothing to disclose. Kaalindi Misra: nothing to disclose. Antonino Giordano: nothing to disclose. Sara Scirè: nothing to disclose. Francesca Maltecca: nothing to disclose.