UNIVERSITÀ DI PARMA

THE COMPLEX RELATIONSHIP BETWEEN CHOLESTEROL AND NEURODEGENERATIVE DISEASES: FOCUS ON HDL AND MULTIPLE SCLEROSIS

Relator:
Marcella Palumbo

ALIFAR
DIPARTIMENTO DI ECCELLENZA
MUR 2023-2027
UNIVERSITÀ DI PARMA

GIORNATA DEL CENTRO E. GROSSI PAOLETTI 2024
28 giugno 2024

CENTRO ENRICA GROSSI PAOLETTI

Disclosure

UNIVERSITÀ DI PARMA

DECLARES that he/she **has not had any** relationship, including financial relationships, with entities with commercial interests in the health care field during the past two years.

Neurodegenerative diseases, Multiple Sclerosis and cerebral cholesterol homeostasis

UNIVERSITÀ DI PARMA

Relationship between **cholesterol regulators' genes** and **neurodegenerative diseases**

Dysregulated cholesterol homeostasis in central nervous system leads to neurodegeneration

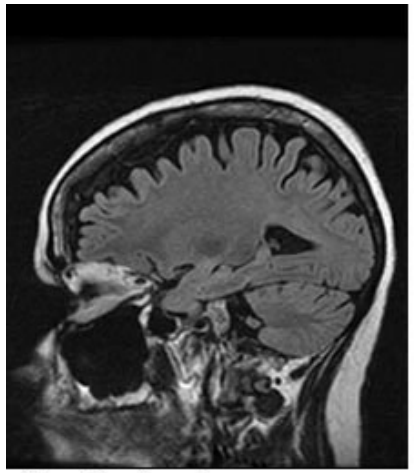
162 lipid-related SNPs found in Multiple Sclerosis

APOE	rs7412	19	LDL	A/G	-0.139	3×10^{-40}
PCSK9	rs11591147	1	LDL	A/C	-0.121	1×10^{-8}
LIPC	rs261334	15	HDL	G/C	0.031	6×10^{-7}
SNPC2	rs116635738	19	HDL, LDL	A/G	-0.057; 0.060	3×10^{-7}, 5×10^{-7}

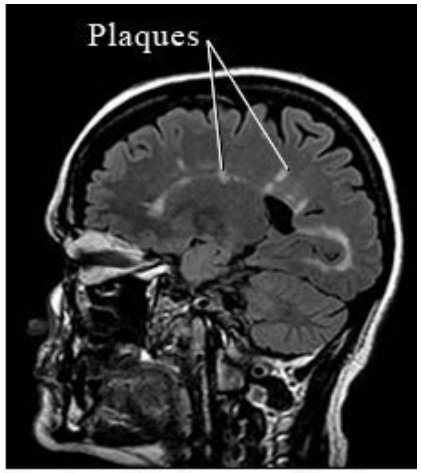
Yan Zhang, 2019, J Neurol Neurosurg Psychiatry

Saher, G. et al., *Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids* . 2015:.

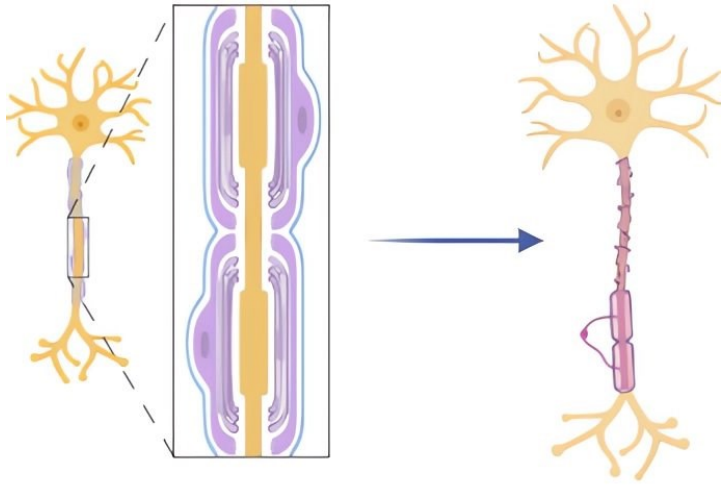
Multiple sclerosis (MS)



Healthy brain



Brain with damage (lesions or plaques) caused by MS



Selective demyelination of central nervous system (CNS) neuron axons.

Heterogeneous disease of complex aetiology.

Multiple risk factors
- -chronic neuroinflammation
- -alterated lipid profile

Diagnosis→clinical history, neurologic examination, magnetic resonance imaging, blood and cerebrospinal fluid (CSF) test,
Routine CSF examination for MS diagnosis:
-Oligoclonal bands (OCB) status
-IgG index
-albumin ratio

No cure

MS and HDL-C lipid profile

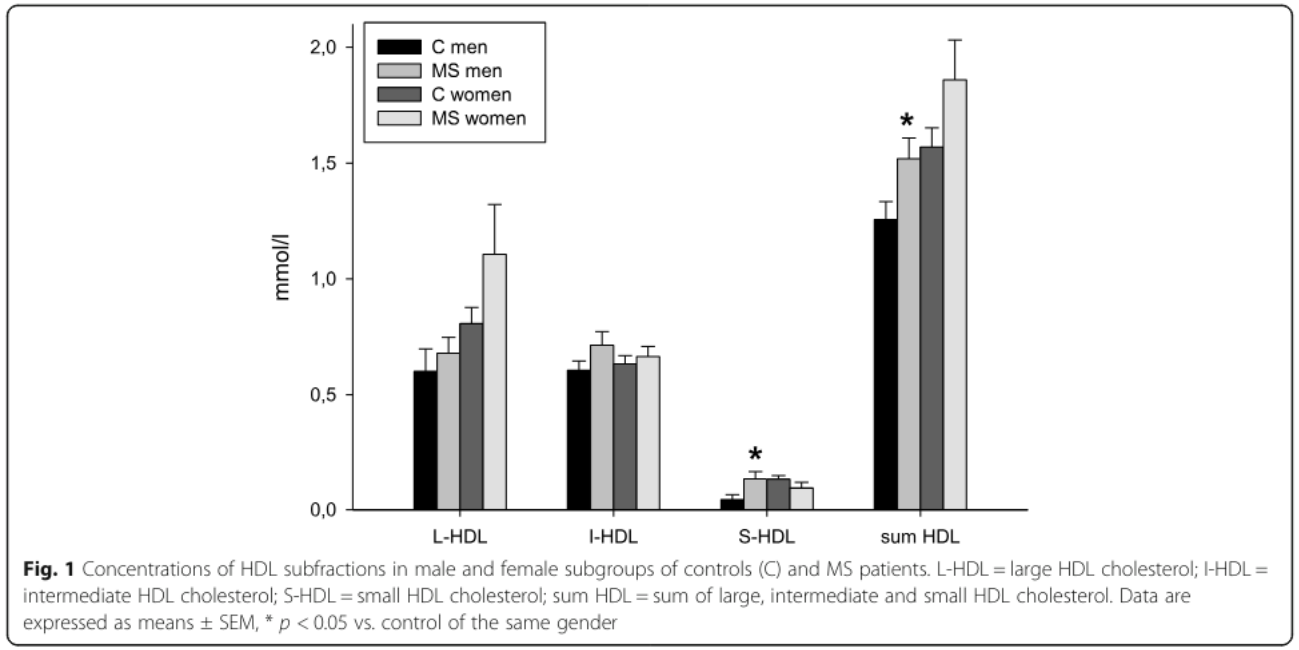
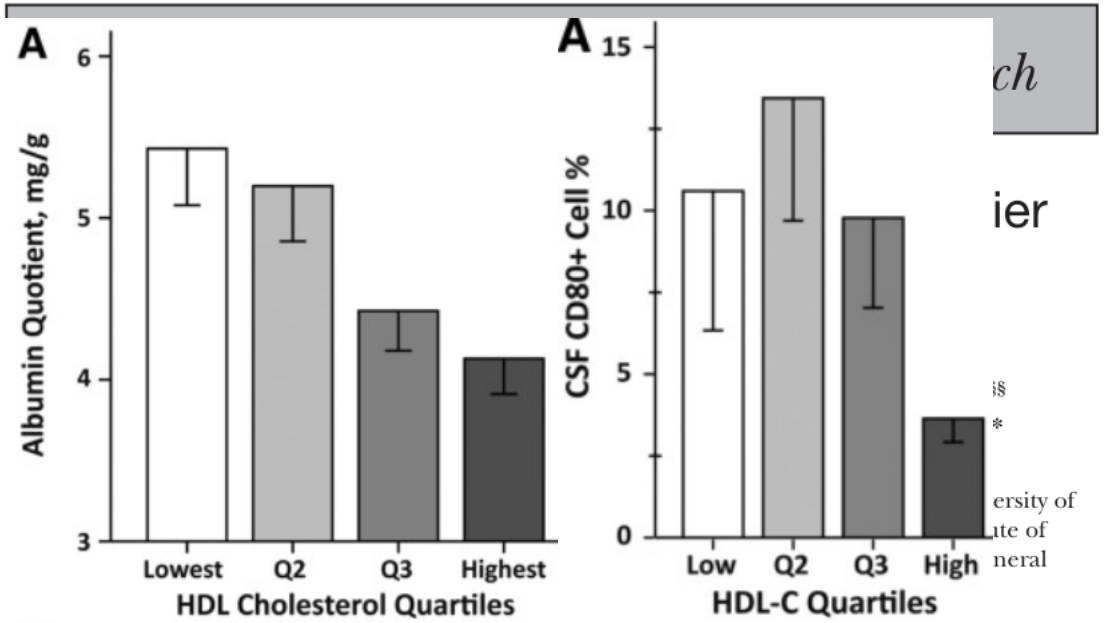


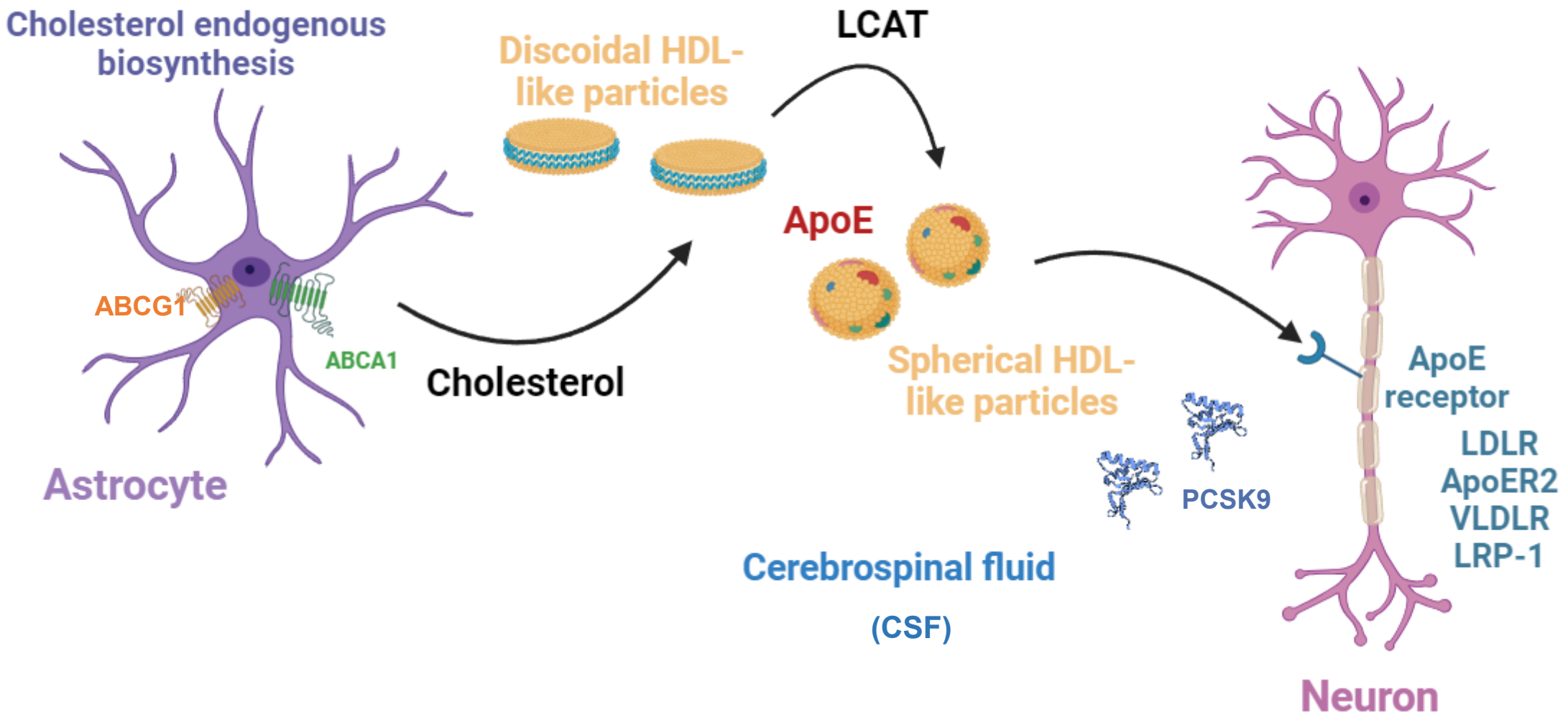
Fig. 1 Concentrations of HDL subfractions in male and female subgroups of controls (C) and MS patients. L-HDL = large HDL cholesterol; I-HDL = intermediate HDL cholesterol; S-HDL = small HDL cholesterol; sum HDL = sum of large, intermediate and small HDL cholesterol. Data are expressed as means ± SEM, * $p < 0.05$ vs. control of the same gender

Balazs Lorincz, Autoimmun Rev. 2022

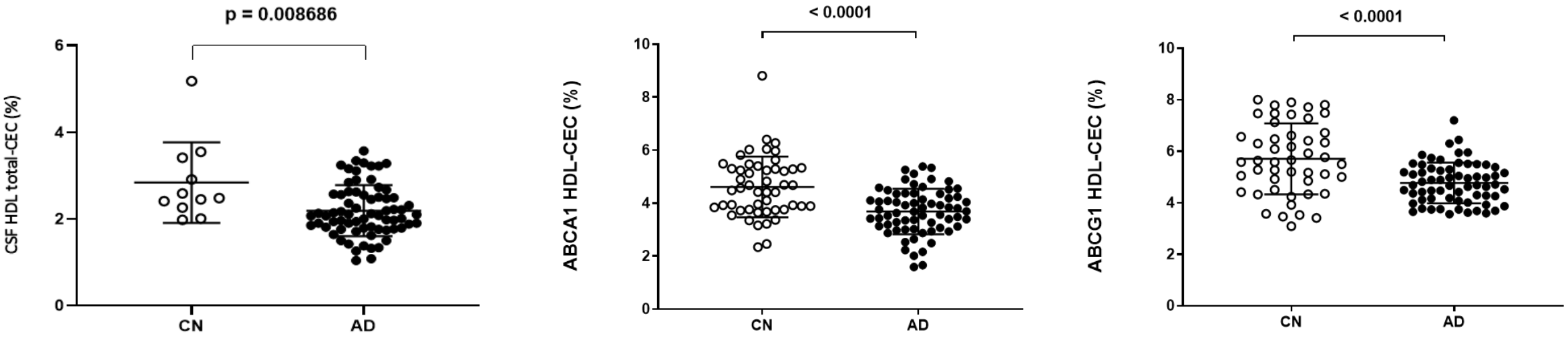
Protecti
injury in



CEREBRAL CHOLESTEROL TRANSPORT



Cerebral cholesterol homeostasis and neurodegeneration: evidence in humans



○: *Cognitively Normal subjects;* ●: *Alzheimer's Disease subjects*

M Turri, **M Palumbo**, F Bernini, F Zimetti, L Calabresi; Alzheimers Res Ther. 2023 May 20;15(1):95. doi: 10.1186/s13195-023-01241-6.

Aims of the study

Identify possible disturbances of lipoprotein function in Multiple Sclerosis, by **measuring:**

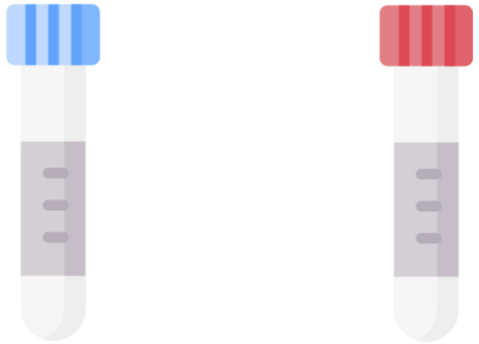
-Cerebrospinal fluid (CSF) HDL cholesterol efflux capacity (CSF HDL-CEC)

-Serum HDL cholesterol efflux capacity (serum HDL-CEC)

MS Subjects

- N 25 relapsing-remitting or progressive, mainly primary, MS (according to McDonald criteria 2017)

- N 13 age- and sex-comparable controls (CTRL) subjects undergoing a lumbar puncture, diagnosed with non-inflammatory and non-degenerative diseases, mostly headache

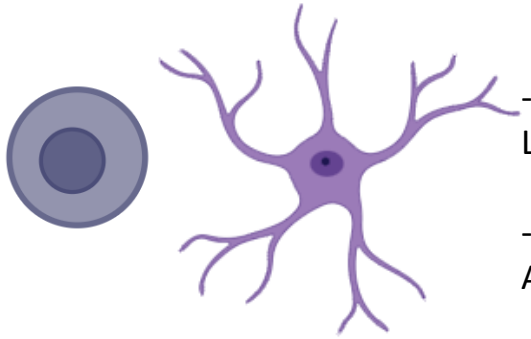


13
CTRL

25
MS

Patients were recruited by Prof Granella research gruop from Parma University Hospital. Project approved by the Ethics Committee 17/10/2023

Materials and Methods

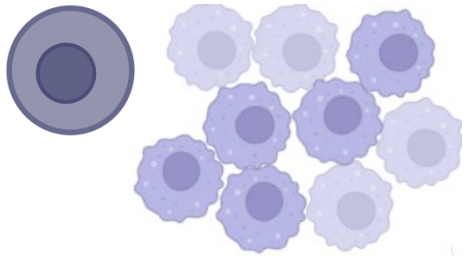


Cerebral Nervous System cell models

CSF HDL-CEC

- U373 treated with LXR/RXR agonists

-CHO transfected with ABCG1 gene



Peripheral cell/ macrophage models

Serum HDL-CEC

-J774 treated with cAMP

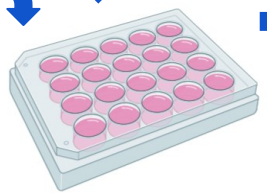
-CHO transfected with ABCG1 gene

Cells plated

Labelled with 3H-Cholesterol

Equilibration/ Transporter upregulation

Incubation with internal controls and HDL from CSF and serum of subjects included in the study

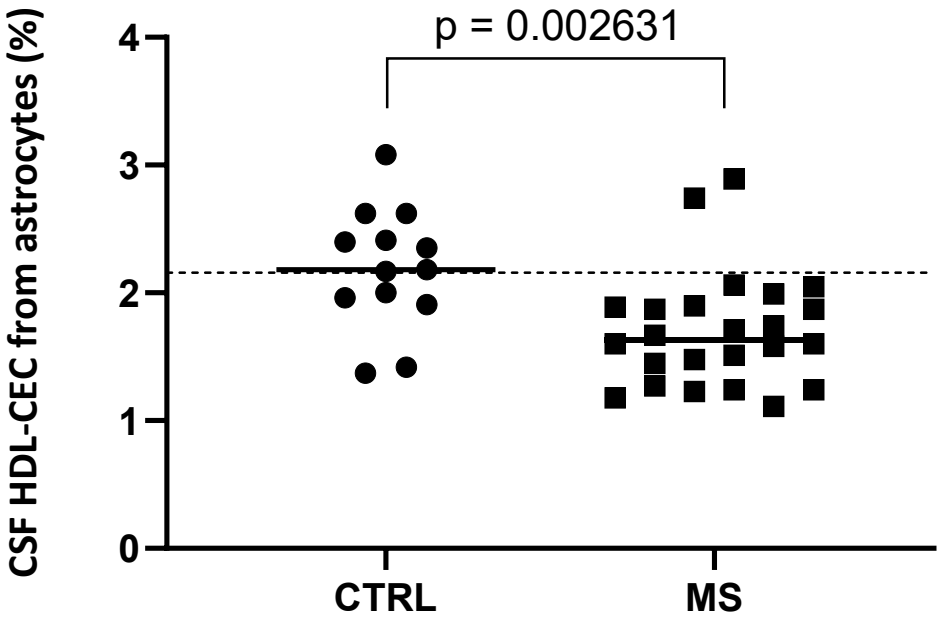


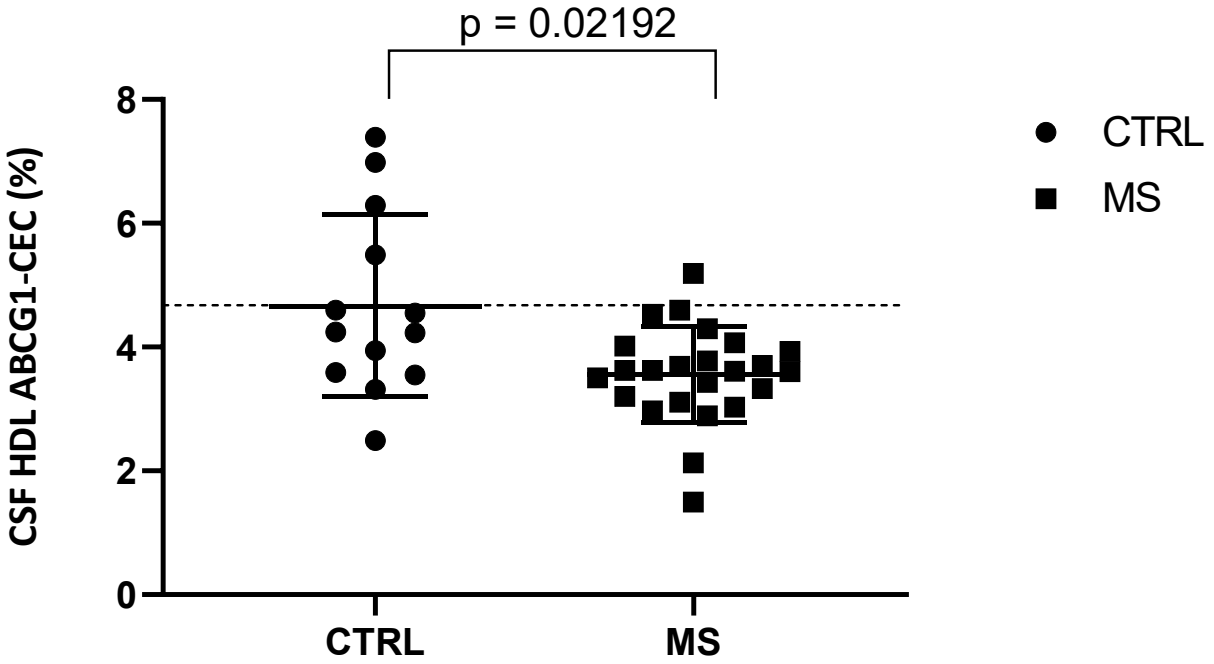
Cholesterol efflux quantification by liquid scintillation counting (%)

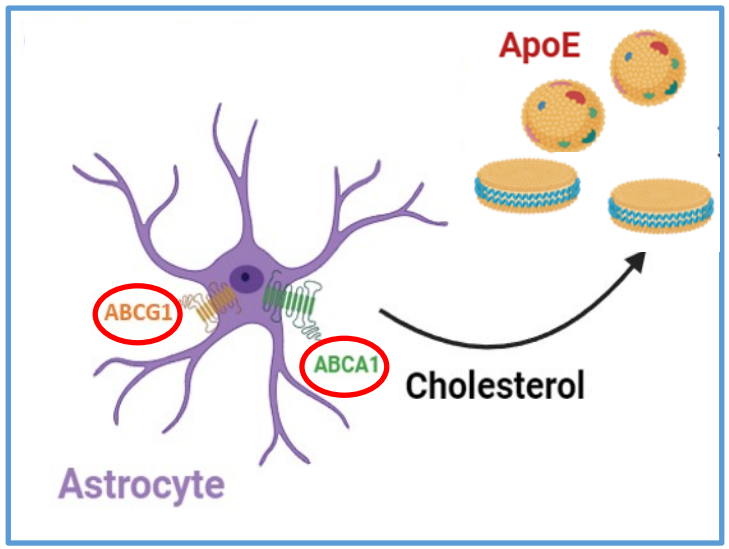
Clinical demographics data

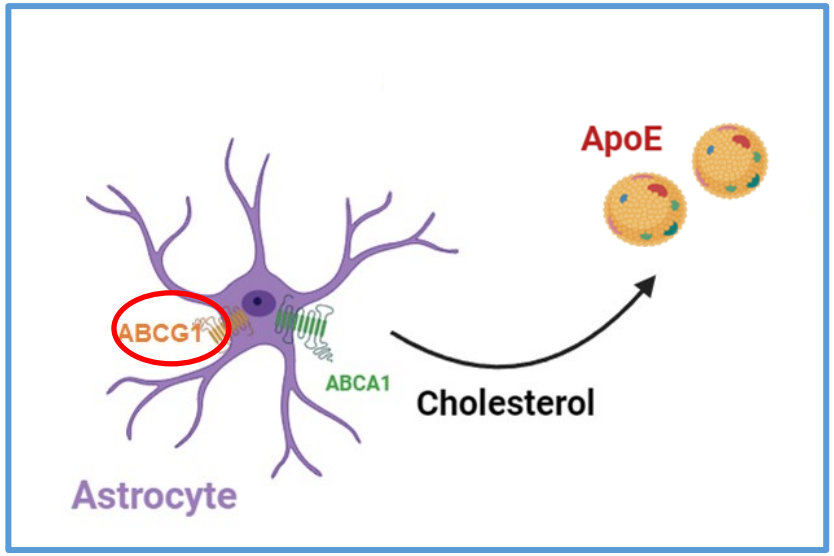
Patients' characteristics	CTRL N = 13	MS N = 25	P value
Age - years	43 ± 14.76	38 ± 12.26	0.2787
Male - n (%)	5 (38.46)	9 (36)	>0,9999
Clinical data			
EDSS – (0 - 10)	-	2.00 (1.50 – 3.00)	-
RM9			
0 (0≤9 lesions) – n (%)	1 (7.7)	10 (40)	0,0597
1 (>9 lesions) – n (%)	1 (7.7)	14 (56)	**0,0050**
OCB positive – n (%)	1 (9.1)	20 (80)	**<0,0001**
Lipid profile—mg/dL			
Total Cholesterol	208.1 ± 39.68	184.7 ± 45.14	0.1644
HDL Cholesterol	53.44 ± 9.59	61.33 ± 14.67	0.1462
LDL Cholesterol	143.89 ± 31.72	116.57 ± 34.17	**0.0469**
Triglyceride	138.5 (107.0 - 203.8)	72.5 (54.6- 101.8)	**0.0010**
Disease Modifying therapy (DMT) – n (%)			
Treated – n (%)	0 (100)	21 (84)	**<0,0001**

MS CSF HDL Cholesterol efflux capacity (CSF HDL-CEC)

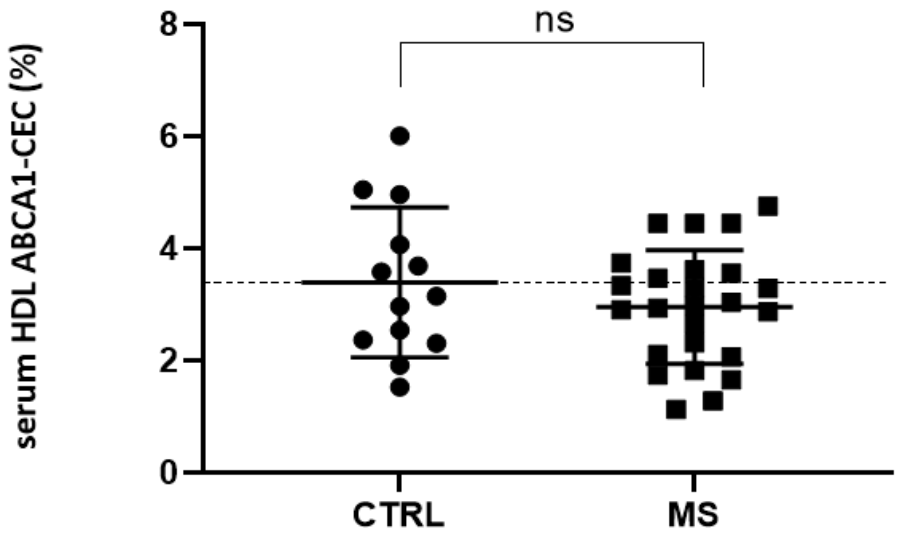


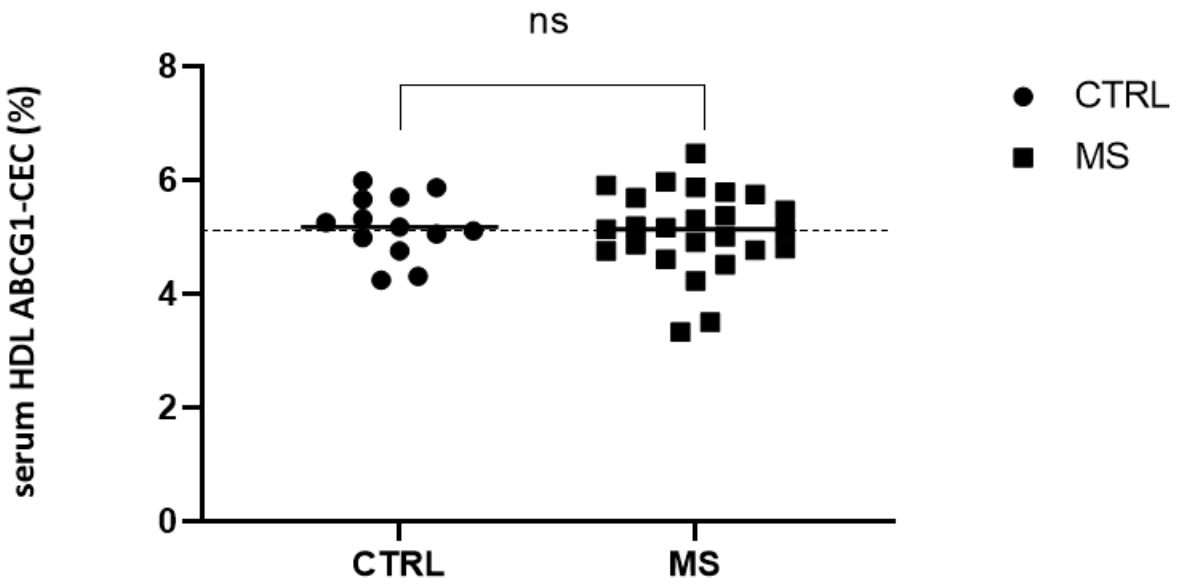


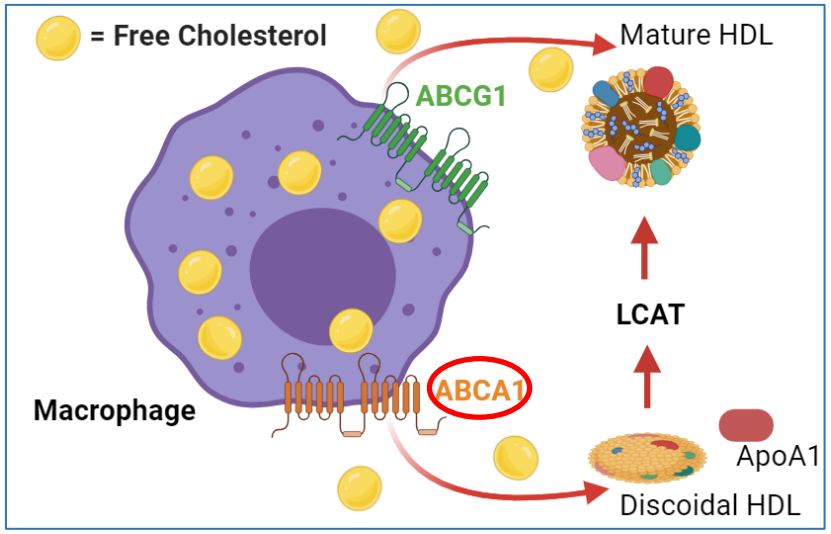


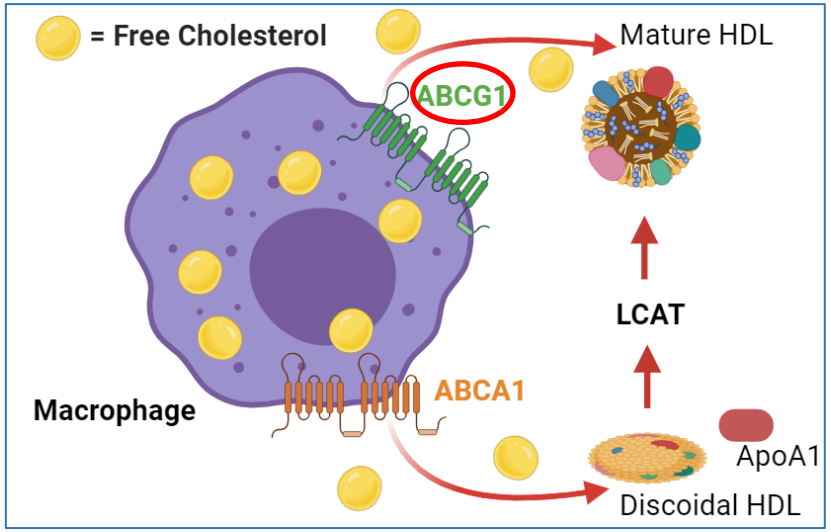


MS serum HDL Cholesterol efflux capacity (serum HDL-CEC)

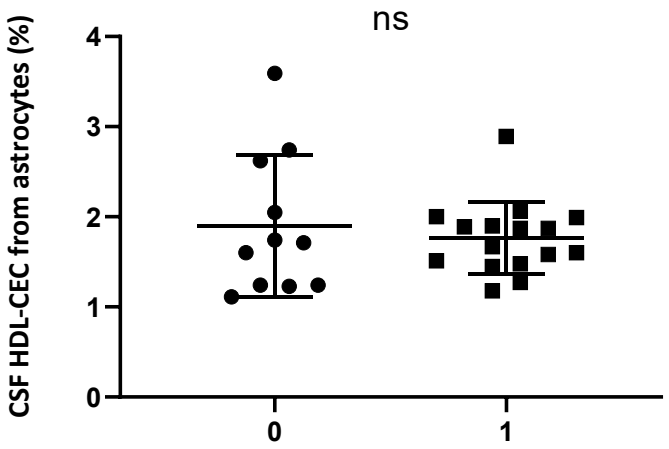


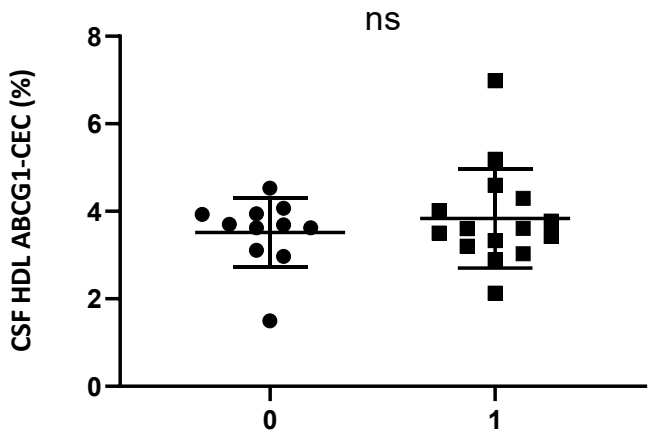






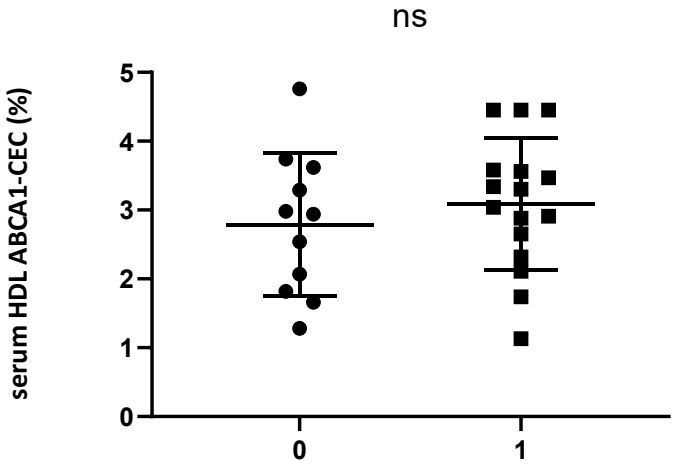
Serum CSF HDL Cholesterol efflux capacity (CSF/serum HDL-CEC) after stratification for disease severity: RM9 (all subjects)

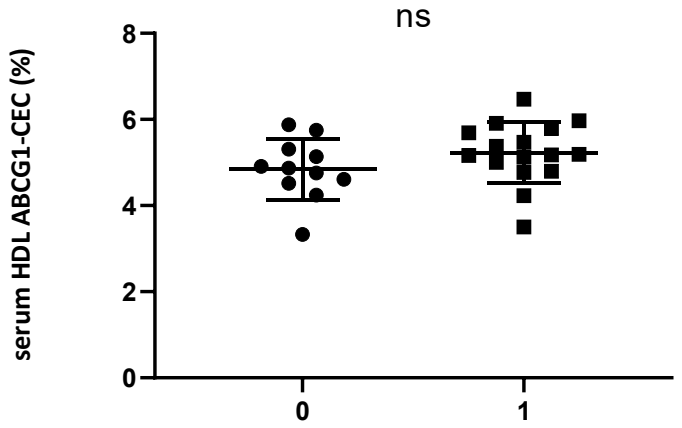




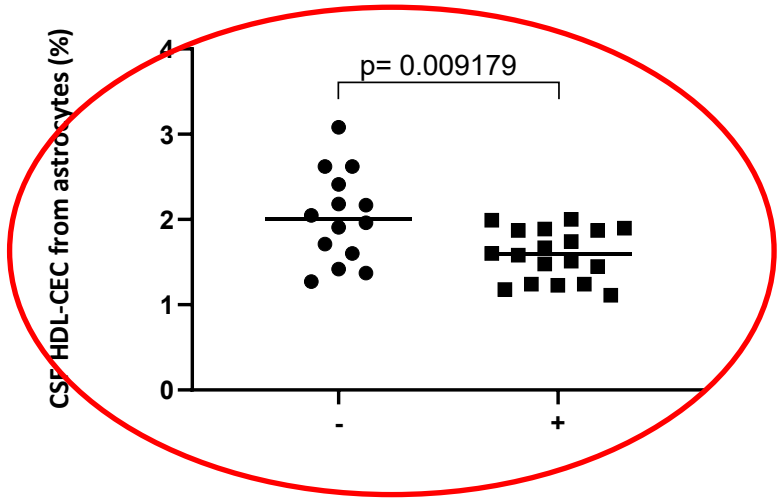
● 0 ≤ 9 RM lesions
■ 1 > 9 lesions

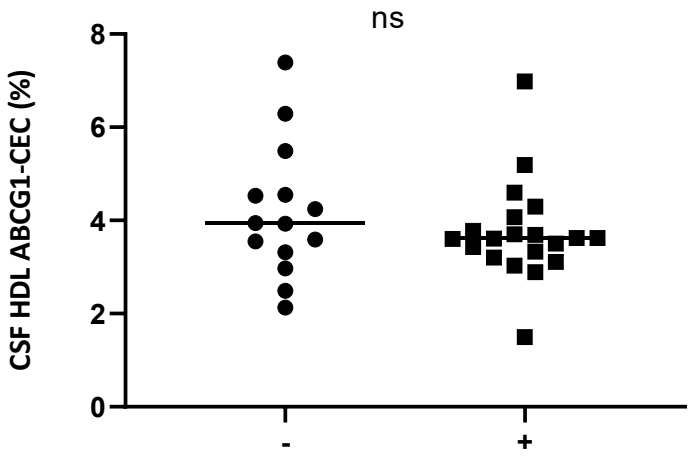
0 = CTRL 1/11; MS 10/11
1 = CTRL 1/; MS 15/16





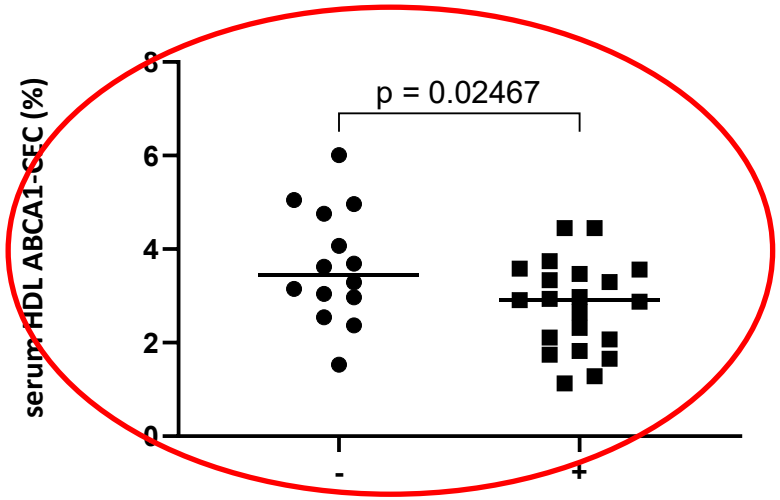
Serum CSF HDL Cholesterol efflux capacity (CSF/serum HDL-CEC) after stratification for OCB positivity (all subjects)

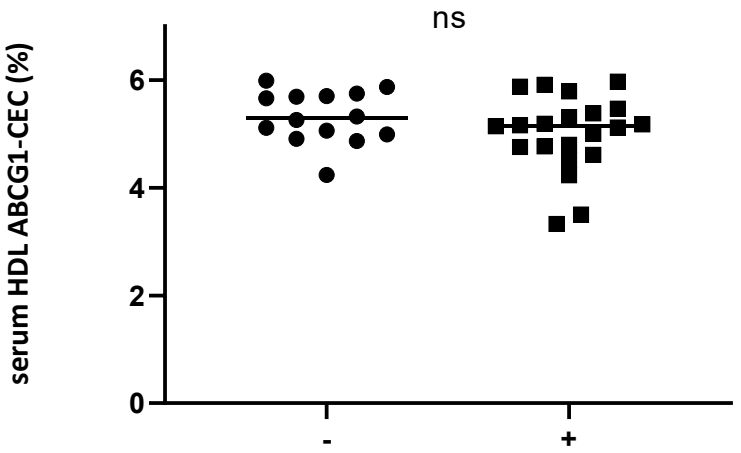




- OCB negativity ⩽1
+ OCB positivity ⩾2

- = CTRL 10/14; MS 4/14
+ = CTRL 1/21; MS 20/21





MS preliminary findings

UNIVERSITÀ DI PARMA

CTRL Vs MS

CSF HDL-CEC from astrocytes and mediated by ABCG1 were lower in MS compared to controls;

OCB - Vs OCB +

CSF HDL-CEC from astrocytes was lower in subjects OCB positive;

Serum HDL-CEC mediated by the transporters ABCA1 was lower in subjects OCB positive.

1. These results suggest that MS is associated with a defect in CSF HDL capacity to promote the first step of the cerebral cholesterol transport

2. The observation that also Serum HDL-CEC mediated by ABCA1 is lower in subjects OCB positive may put the premises to study Serum HDL CEC as a potential biomarker of the disease

ACKNOWLEDGEMENTS

ALIFAR
DIPARTIMENTO
DI ECCELLENZA
MUR 2023-2027
UNIVERSITÀ DI PARMA

F. Bernini
F. Zimetti
M. P. Adorni
N. Ronda
I. Zanotti
F. Potì
B. Papotti
M. Ugolotti
B. Mattina
M. Scauso

UNIVERSITÀ
DI PARMA

F. Granella
group