8° Giornata dello specializzando in Neurologia

CAN WE USE GENETICS TO DISCRIMINATE BETWEEN MULTIPLE SCLEROSIS AND ADULT-ONSET POST-INFECTIOUS NEUROLOGICAL SYNDROMES?

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Background.I

- PINS: a heterogeneous spectrum of disorders affecting CNS, PNS or both.
- Triggered by an infectious event or a vaccination
- ADEM: classical vs atypical presentations

Background.II

- Pathogenesis: environmental and genetic factors
- Few studies have dealt with genetic susceptibility in PINS, mostly based on pediatric cohorts presenting with a classical phenotype
- Large scale multi-site GWAS led to the identification of 200 autosomal non-MHC common variants and 32 signals in HLA regions associated with MS

We propose a method which calculates the burden of genetic variants, called weighted genetic risk score (wGRS), which sums up the number of risk alleles and their relative risk carried by each individual

Aim of the study

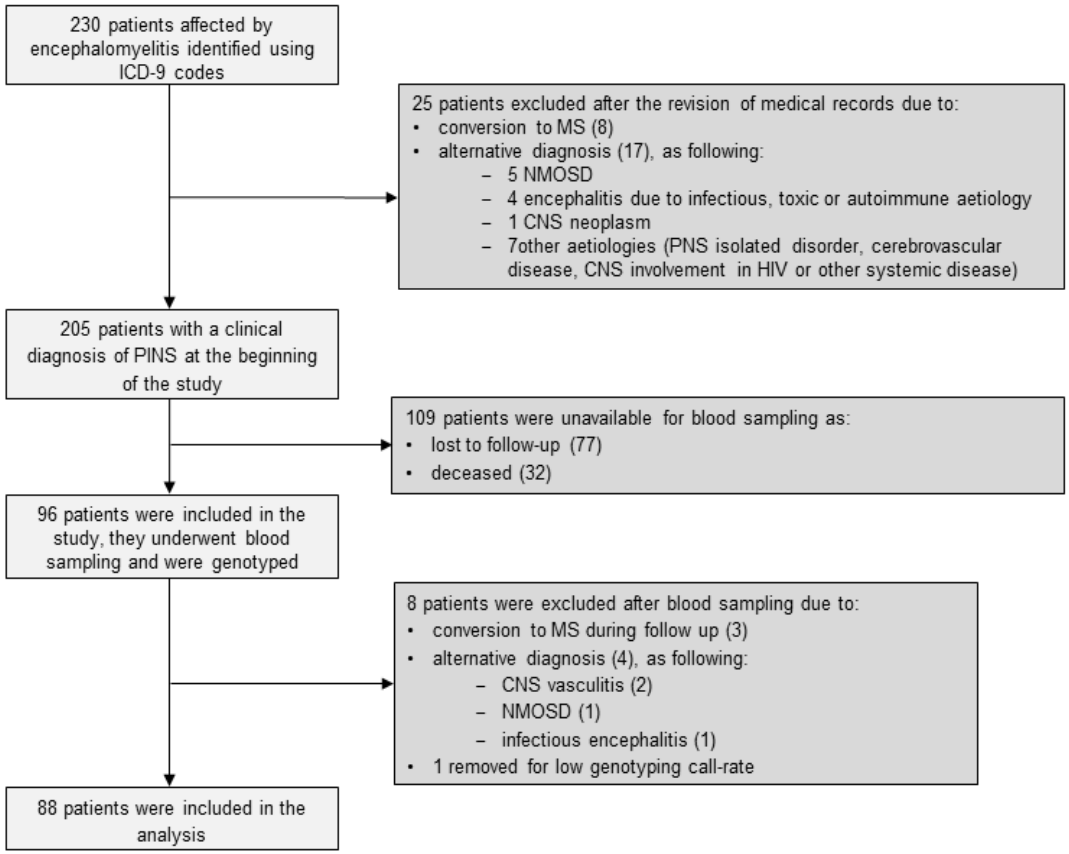
1. To better describe the clinical and paraclinical features of a cohort of adult PINS patients

2. To determine whether PINS and MS share a common genetic burden

Patients and methods - I

Fig 1. Flowchart of PINS cohort.

Legend. ICD-9: International Classification of Diseases; MS: multiple sclerosis; NMOSD: Neuromyelitis Optica spectrum disorders; CNS= central nervous system; PNS= peripheral nervous system; PINS= post-infectious neurological syndromes



Patients and methods - II

- DNA extraction (Flexigene DNA kit 250, QIAGEN GmbH)
- Genotyping (Illumina BeadChip Human OmniExpress-24)
- Quality control and Imputation (Reference Panels : 1000 Genomes Phase 3 and T1DGCHLA)
- Separate calculation of non-HLA loci genetic risk burden (wGRS) and HLA-related (HLAGB).
- Due to unbalanced sample size, consistency of results was evaluated by random sub-sampling 1000 times without replacements a comparable number of BOMS and HC cohorts down to PINS cohort's sample size (n=88)

Results – I

Table 2. Demographic and disease features of PINS, BOMS and HC cohorts

	PINS	BOMS	HC
Gender, M:F	1 : 1.4	1 : 2.1	1 : 0.49
Age, mean years ± SD	56.9 ± 16.2	39 ± 10.2	45 ± 12.9
Age at onset, mean years ± SD	50.1 ± 15.4	29 ± 9.1	-
Disease duration, mean years ± SD	7.2 ± 4.6	11 ± 9.1	-

Results – II

Table 1. Clinical and paraclinical features in the cohort of 88 PINS patients included in the analyses.

Prodromal event	
Infection	59/88 (68%)
Vaccination	4/88 (5%)
Clinical manifestations	
Myelopathy	72/88 (81%)
Encephalopathy	21/88 (24%)
Meningismus	9/88 (10%)
Seizures	3/88 (3%)
Focal deficits	2/88(2%)
Optic neuritis	10/88 (12%)
Brainstem/cerebellar dysfunction	13/88 (15%)
Cranial nerve palsies	8/88 (9%)
PNS involvement *	28/68 (41%)
Pattern of PNS involvement	
Axonal	11/28 (39%)
Demyelinating	16/28 (57%)
Mixed	1/28 (4%)
CSF analysis	
Elevated protein levels	56/80 (70%)
Pleocytosis	32/80 (40%)
CSF-specific oligoclonal bands	16/76 (21%)

Lesion distribution on MRI	
Periventricular or subcortical white matter	27/87 (31%)
Corpus callosum	3/87 (3%)
Basal ganglia	6/87 (7%)
Brainstem/cerebellum	27/87 (31%)
Spinal cord	67/87 (77%)
Steroid administration	78/88(89%)
Response to steroids **	
Good	52/78 (67%)
Poor	25/78 (23%)
Intravenous immunoglobulin administration	16/88 (18%)
mRS at peak	
0-2	30/88 (34%)
>2	58/88 /66%)
mRS at discharge	
0-2	60/88 (68%)
>2	28/88(32%)
Disease course	
Monophasic	59/88 (67%)
Relapsing	16/88 (18%)
Chronic progressive	13/88 (15%)

Legend. CSF= cerebrospinal fluid; MRI=magnetic resonance imaging; mRS=modified Rankin Score; PNS=peripheral nervous system.

* disclosed or confirmed by electroneurography

** defined by a decrease of at least one point on the modified Rankin Score

Results – III

Fig 2a. wGRS score in the three cohorts

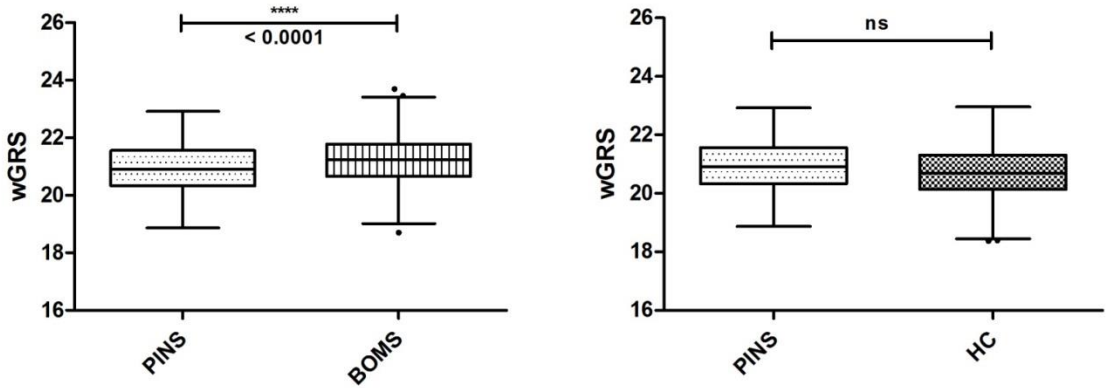
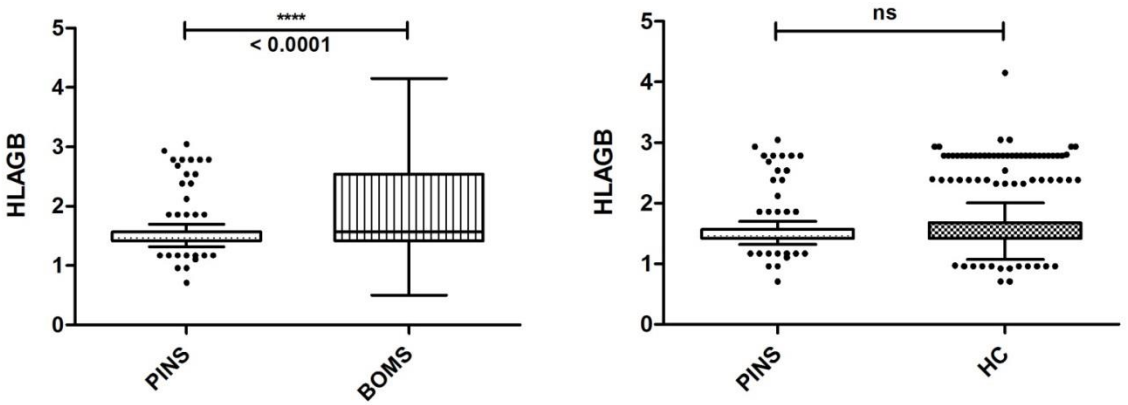
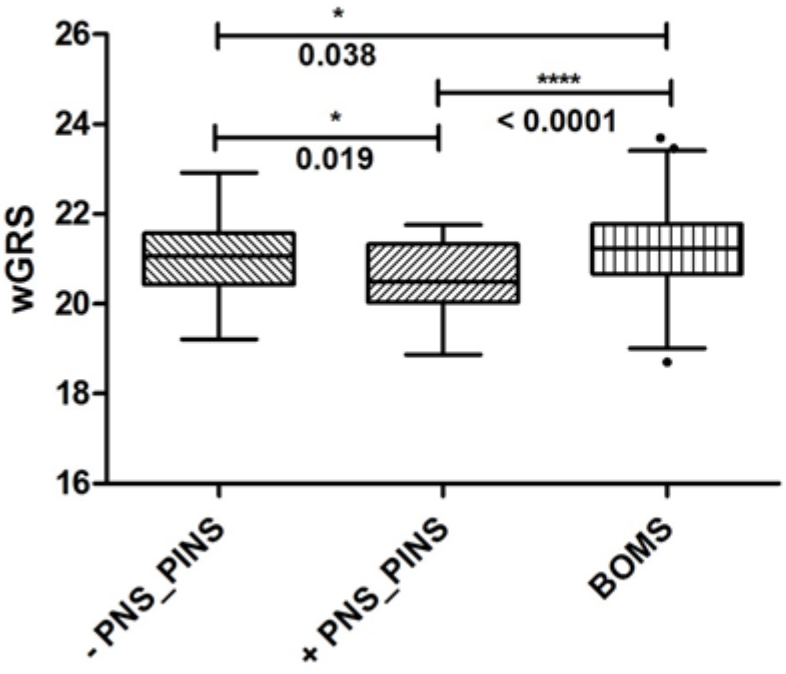


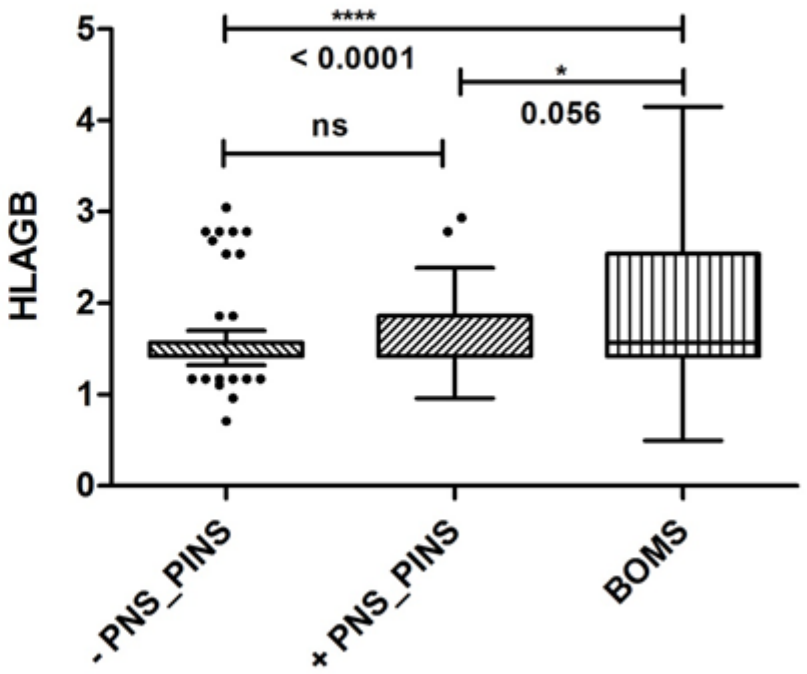
Fig 2b. HLAGB score in the three cohorts



Results – IV

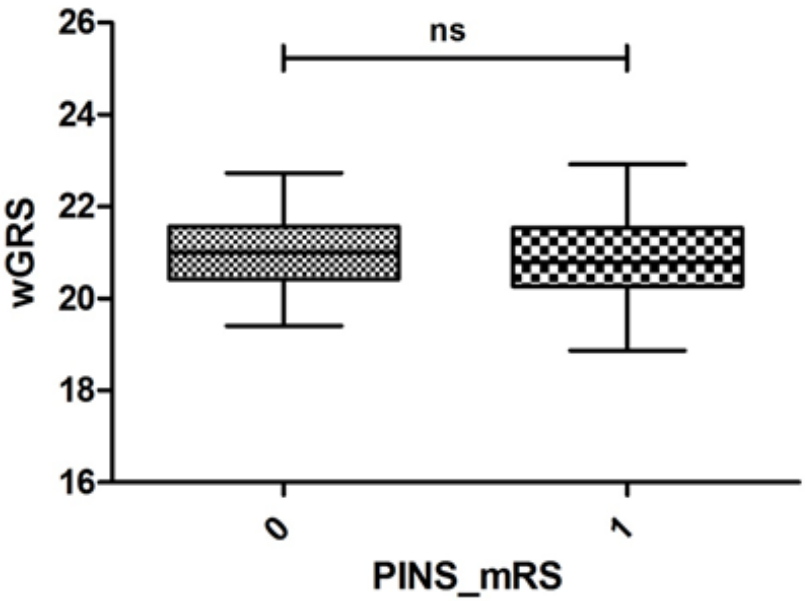
Fig 3. wGRS and HLAGB scores in PINS with and without PNS involvment

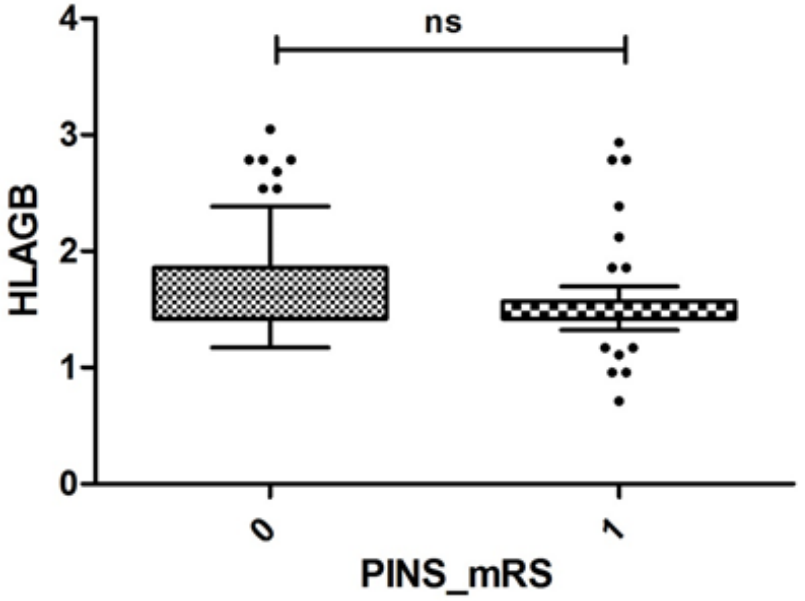




Results – V

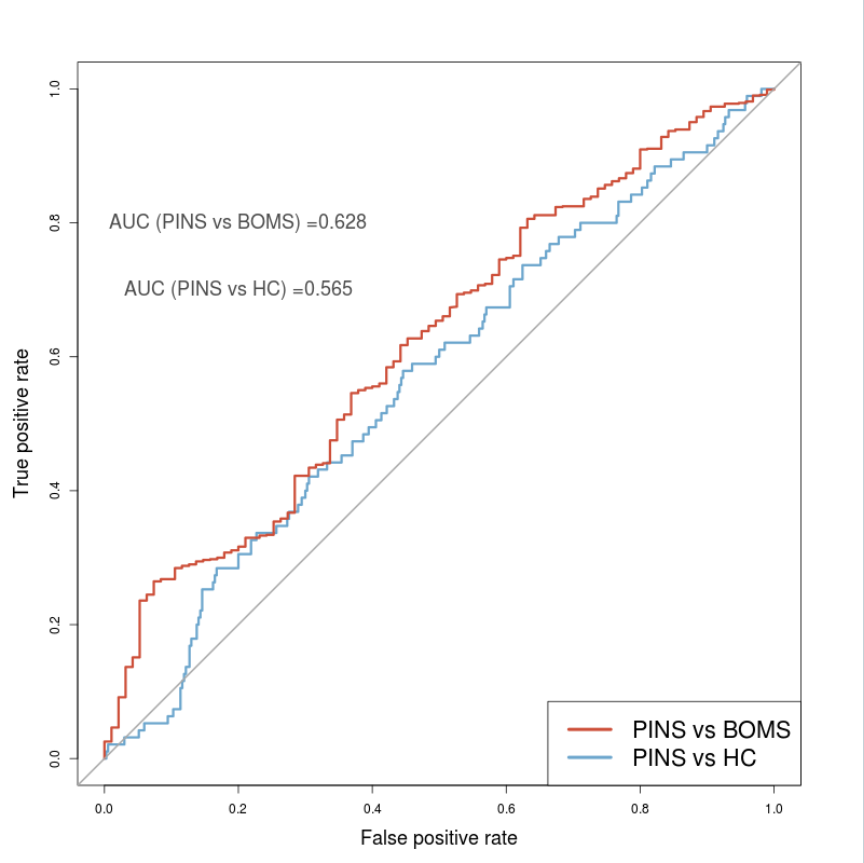
Fig 4. wGRS and HLAGB scores at final rankin in PINS patients



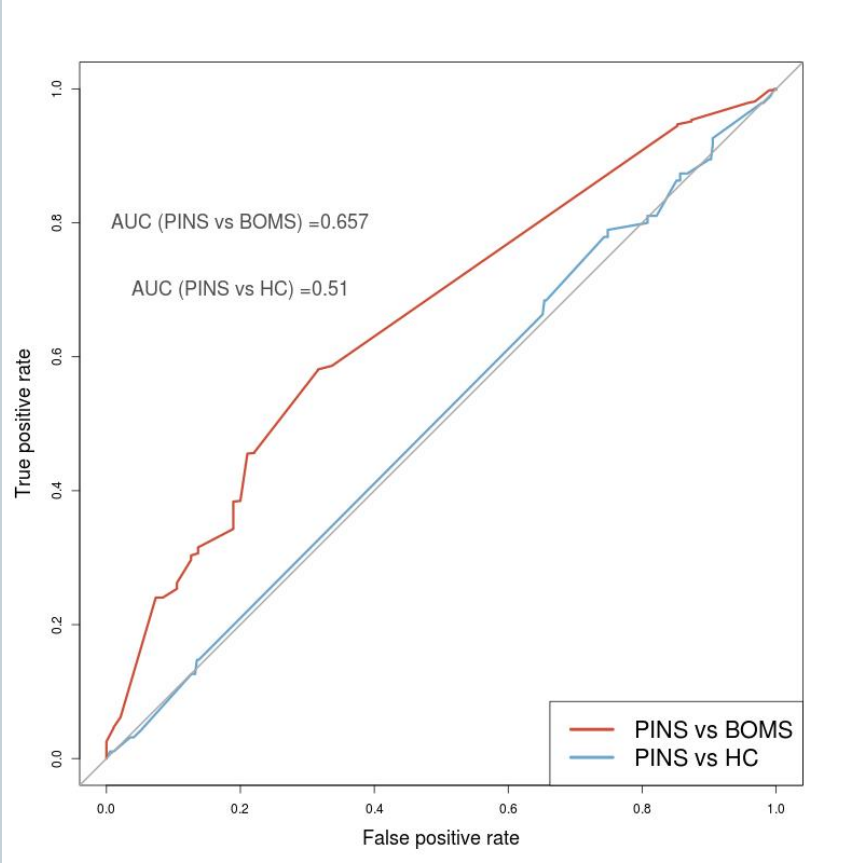


Results – VI

wGRS



HLAGB



Conclusions

- To date, no direct comparison between genetic susceptibility to MS and PINS has been done, apart from pediatric cohort of patients
- Our study suggests that the genetic background of these two conditions differs, and supports the need to discriminate them with clinical, prognostic and therapeutic implications
- There is also genetic heterogeneity between PINS with and without peripheral involvement
- Main limits of the study are represented by the retrospective nature, the low sample size and the unequal size of cohorts

- What to be expected in the future?

  a) GWAS tools could be used to discriminate between MS and PINS

  b) an increase in sample size can help to identify additional different genetic drivers of PINS condition

Acknowledgements

IRCCS Neurological National Institute C. Mondino, Pavia

Dr. Riccardo Currò
Dr.ssa Giulia Berzero
Dr. Angelo Guglielmi
Dr.ssa Elisa Vegezzi
Dr.ssa Ilaria Callegari
Dr. Andrea Cortese
Dr. Enrico Marchioni

Department of Neurology, San Raffaele Hospital
Dr. Vittorio Martinelli
Prof. Massimo Filippi

Laboratory of Human Genetics of Neurological Diseases, San Raffaele Hospital (Milan)

Dr.ssa Federica Esposito
Dr. Ferdinando Clarelli
Dr.ssa Silvia Santoro
Dr.ssa Laura Ferre'
Dr.ssa Melissa Sorosina

Multiple Sclerosis Research Unit and Department of Neurology
(University of Milan, IRCCS Ospedale San Donato)

Prof. Filippo Martinelli-Boneschi
Dr.ssa Chiara Starvaggi Cucuzza
Dr. Alessandro Cagol
Dr. Mattia Pozzato
Dr.ssa Manuela Valsecchi
Prof. Giovanni Meola