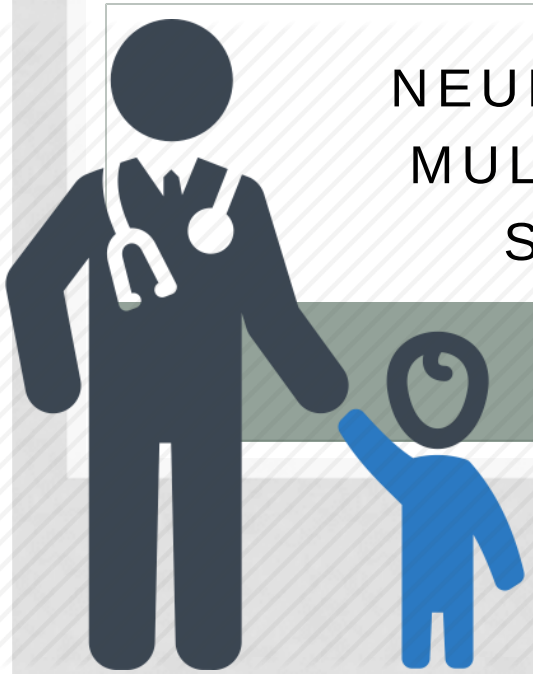
PEDIATRIC MULTIPLE SCLEROSIS

NEUROGENOMICS LABORATORY
MULTIPLE SCLEROSIS CENTER
SHEBA MEDICAL CENTER



Definitions

Multiple sclerosis (MS), a chronic inflammatory autoimmune disease of the central nervous system commonly diagnosed in adults in age between 20 to 40 years.

MS develops in genetically predisposed subjects affected by some environmental factors

An estimated 2%–5% of all patients with MS have onset of clinical symptoms before reaching the age of 18 years defined as Pediatric MS.

Although adults and children share basic aspects of the disorder, children have different clinical, neuroimaging, laboratory features, and courses of the disease.

Why it is important to study pediatric MS?

- Pediatric MS represents an important unmet clinical need

- Pediatric MS is a unique opportunity to investigate early disease mechanisms.

Epidemiology

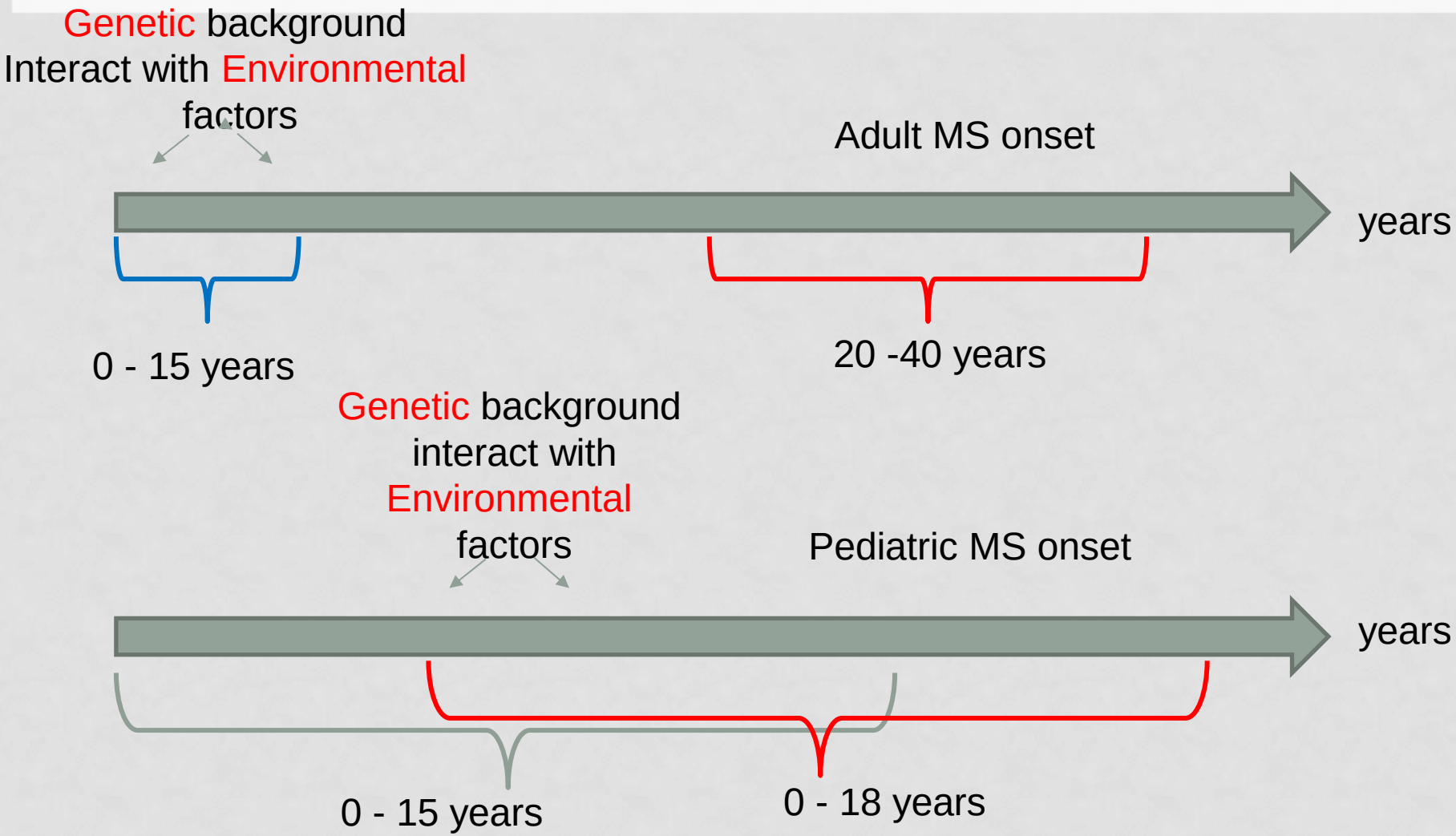
MS have geographical prevalence

Place of residence during childhood is a determinant factor for the development of MS.

Migrants <15 years old moving from an area of lower risk to one of higher risk tended to retain the lower MS risk

Synergy between genetic and environmental factors in first 15 years determined MS risk.

Time scale of disease development in Pediatric versus Adult MS



In Pediatric MS:

The shorter time between environmental exposures and disease onset may provide insight into specific environmental factors

The load of genetic factors and environmental exposures may be higher than in adults

Risk factors information could be implicated to adult-onset MS

Potential risk factors for pediatric multiple sclerosis

Genetic susceptibility

Vitamin D level

Infection exposure

Smoking

Genetic susceptibility

The same genetic risk factors implicated in pediatric and adults MS:

HLA-DRB1*1501 – the most strongly implicated risk gene in adult onset – found overrepresented

Total 36 or 57 of 110 genetic variants associated with adult MS are also associated with disease in children

In general genetic susceptibility evaluated in adult MS also relevant to pediatric MS

Vitamin D

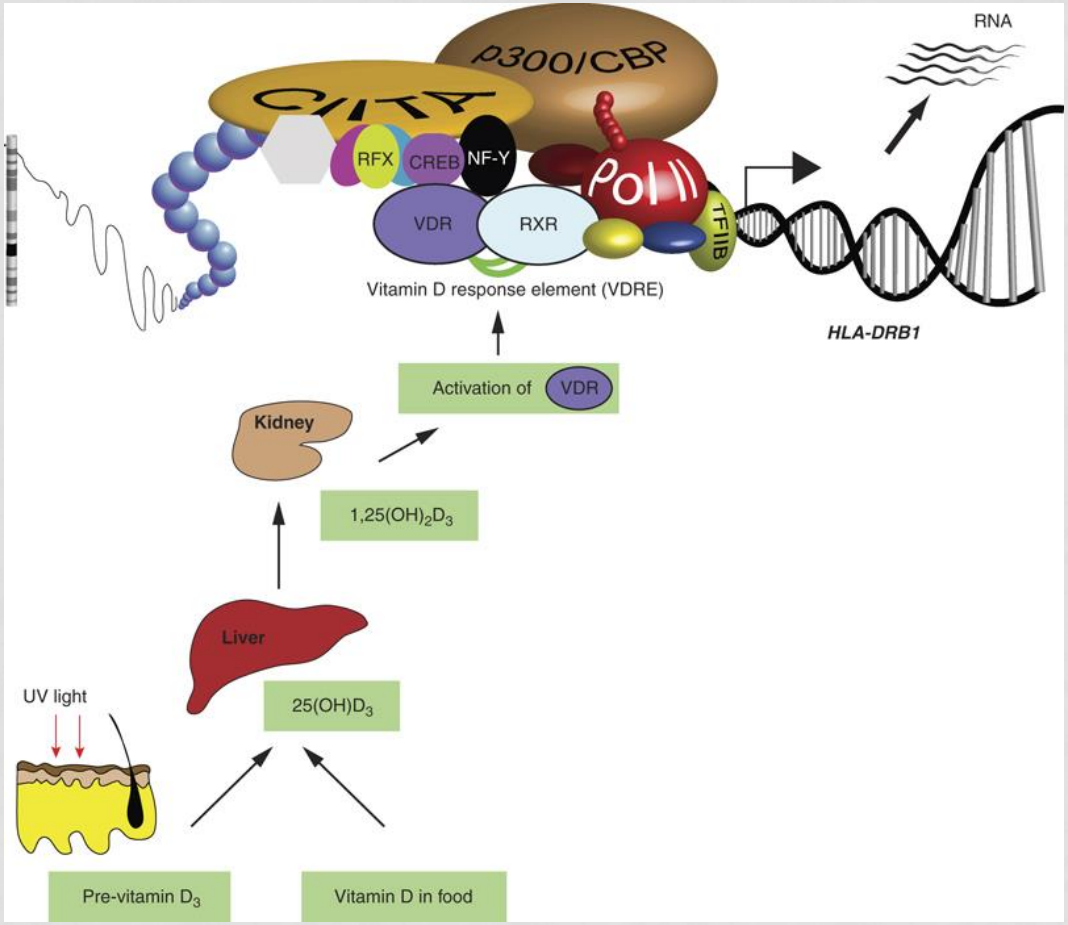
As in adult MS higher serum level of 25-hydroxyvitamin D level associated with reduced risk of MS

Mechanism of VitD effects:

Reduce Th1, Th17 response
Inducing TH2 response
Induce Treg
Inhibit B cells

Link between VitD and MS genetic susceptibility

Expression of HLA-DRB1*1501 is modulated by VitD responsive element in the promotor region of the HLA-DRB1*1501



Infection exposure

Serological evidence of EBV infection increase 3 fold Pediatric MS Risk

1. EBV infected memory B Cells, produced LMP1 (latent membrane protein) that mimicking CD40 and activate pathogenic T cells
2. Molecular mimicry of EBV based on shared sequence with MBP

EBV infection, low VitD level and HLA-DRB1*15 could contribute as independent risk factor

Absence off all 3 factors is associated with significant reduce of disease risk.

Demographical and clinical features

Pediatric MS onset most frequently between 12-16 years
Before 10 years is rare

Relapsing-remitting MS course in >98% of pediatric MS

Primary Progressive MS in <2% (in adult about 15%)

Characterized by higher relapse rate and shorter interval to second relapse than adult MS

Children experience more severe relapses but characterized by better recovery.

The F/M ratio depend on patient's age

Age (y)	F/M ratio
10 to 18	2.1:1 to 3:1
6 to 10	1.6:1
<6	0.8:1

Clinical Outcome

EDSS score utilized in both pediatric and adult MS

In pediatric MS time to EDSS 4 (able to walk at least 500 m) occurred after 20 years, vs 8 years in adults

In pediatric MS development of SPMS occurring at median 28.1 years, in adult 10 years early

Project 1. Yulia Khavkin. Pediatric multiple sclerosis: Clinical features and outcome

Motivation

Majority of pediatric MS data related to comparison of pediatric and adult MS

In the proposed project we will focused on pediatric MS subgroups.

We will compare clinical features and outcomes in childhood and juvenile pediatric MS patients and evaluate gender effect on disease progression.

Methods

Patients will be selected retrospectively from MSC database.

Comparison between childhood (onset <12 years) and juvenile (onset 12-18 years) patients as well as between genders will be performed by following parameters:

MS type, age of onset, EDSS at onset, functional systems involvement at onset, mono or poly-symptomatic presentation at onset, EDSS after 5 and 10 years of disease, time to second relapse, annual relapse rate at 5 and 10 years of disease, recovery after relapse, F/M ratio, OCB, MRI and origin.

Treatment of Pediatric MS

There is limited approval for interferon (IFN)–b and glatiramer acetate (GA) use in children >12 years of age

Current clinical trials in Pediatric MS included
Fingolomod (Gilenia)
Teriflunomide (Aubagio)
Dimethil fumarate (Tecfidera)

Natalizumab

Humanized monoclonal AB targeting a4 subunit of a4b1-integrin
Characterized by 68% reduction of ARR
42% reduction in EDSS
Risk factor Progressive Multifocal Leucoencephalopathy (PML) (4cases/1000 patients)
No pediatric PML cases reported today
Pediatric use demonstrated similar efficacy as in adult MS
However, effect of Natalizumab on children development is not fully covered.

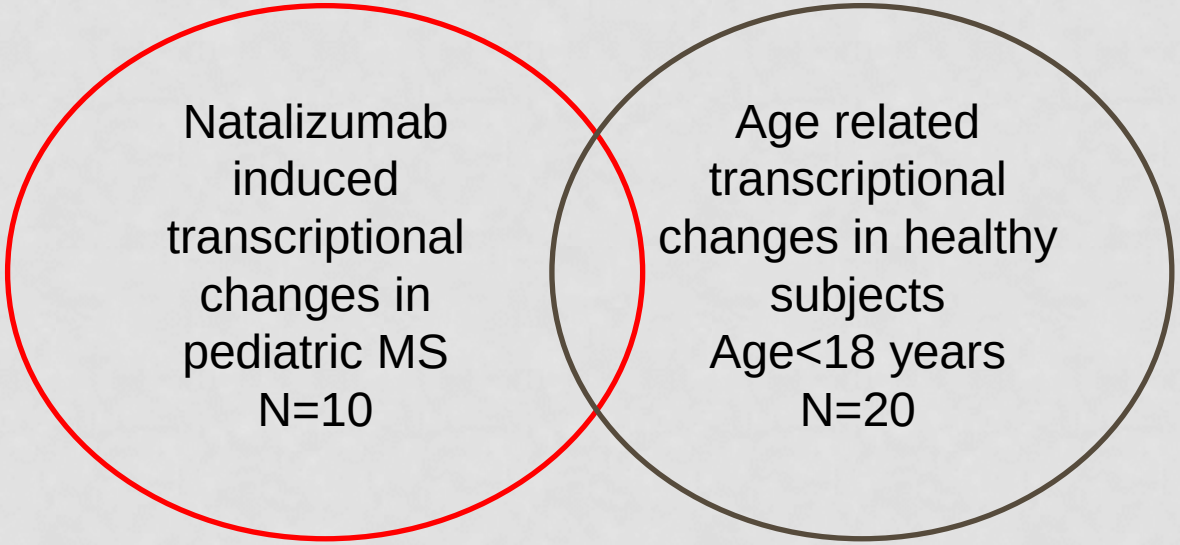
Project 2. Bracha Robinson. Studying the safety of Natalizumab treatment in pediatric MS patient.

We intent do investigate whether or not Natalizumab treatment affect expression of essential childhood and adolescent developmental genes

We will analyze blood transcriptional profile associated with Natalizumab treatment of Pediatric MS patients in comparison with age related transcriptional changes of healthy children.

Methods:

Microarray gene expression using Affymetrix Inc. technology



THANK YOU