Are mutations in POLG1 involved in MS?

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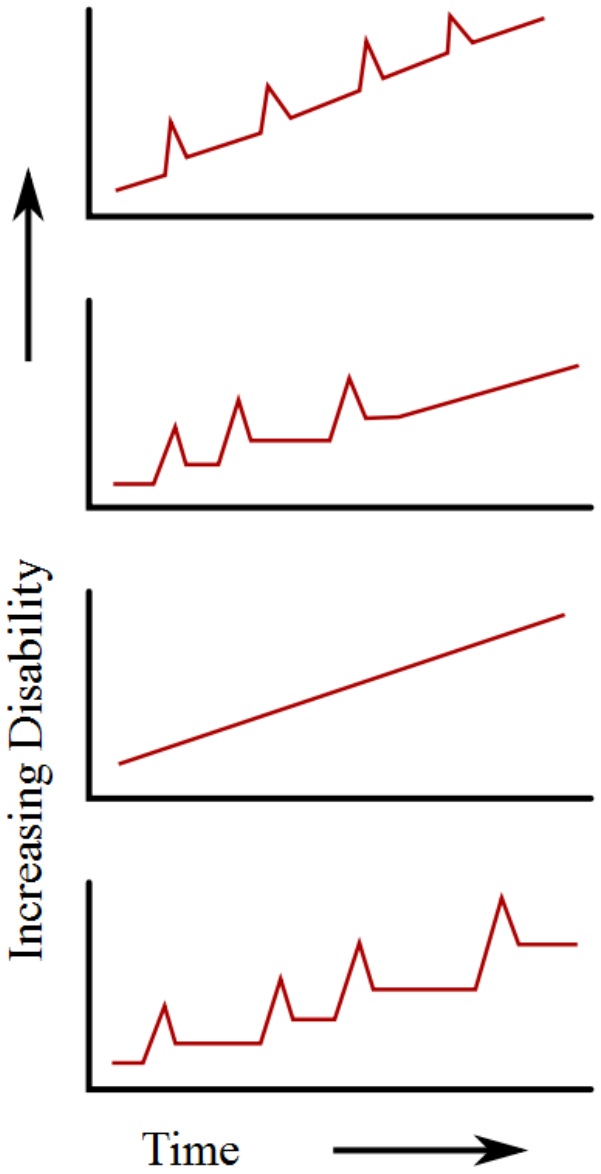


Progressive-relapsing multiple sclerosis

Steady decline since onset with super-imposed attacks.

<10% of cases

Secondary progressive multiple sclerosis

Initial relapsing-remitting multiple sclerosis that suddenly begins to have decline without periods of remission.

Follows on from relapsing/remitting

Primary progressive multiple sclerosis

Steady increase in disability without attacks.

10-20% of cases

Relapsing-remitting multiple sclerosis

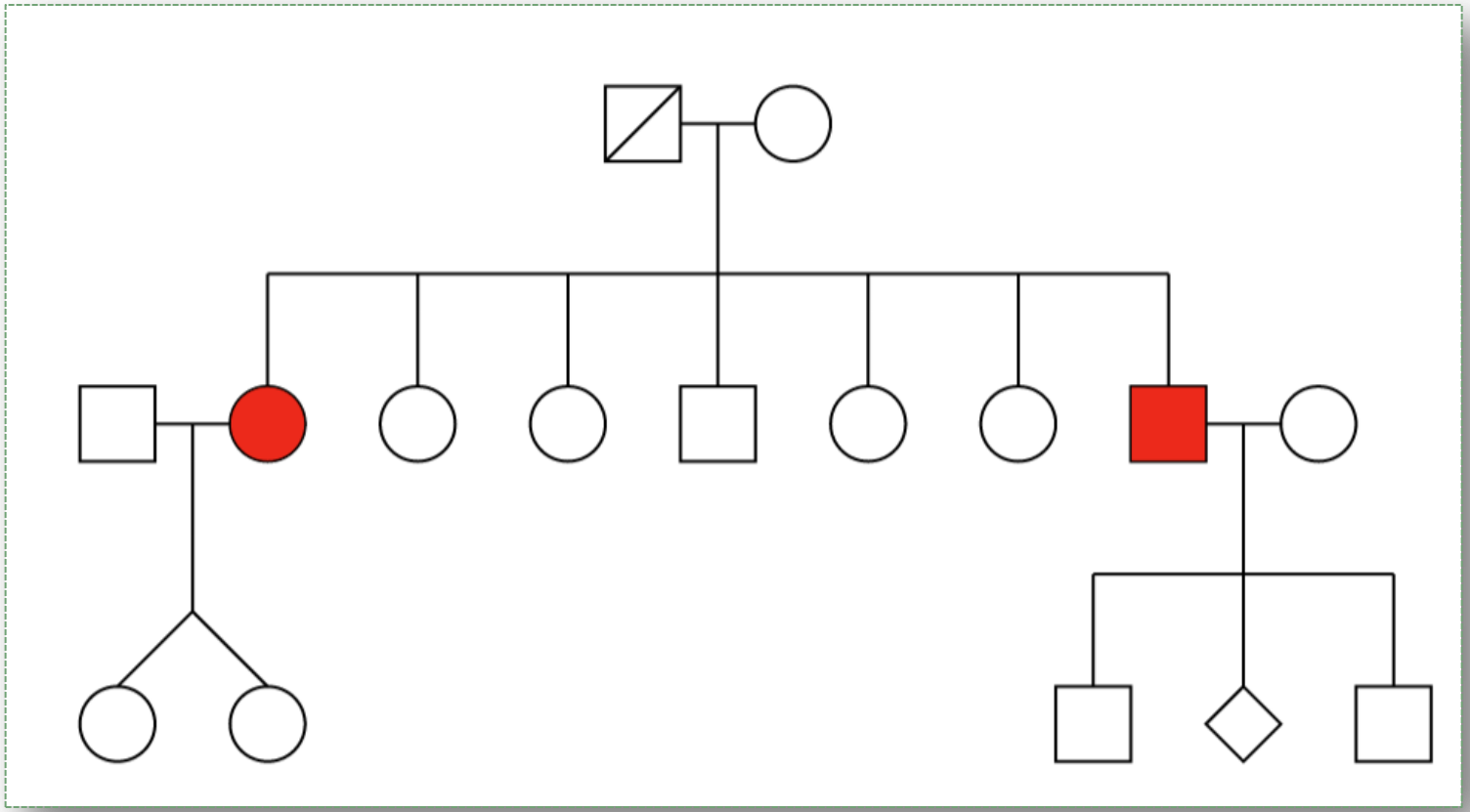
Unpredictable attacks which may or may not leave permanent deficits followed by periods of remission .

80-90% of cases

Why did the research begin?

- MS and genetics
- First patient
- Mutation – POLG1 gene (P587L, T251I).

Moshe's pedigree



POLG1-related disorders

- Wide spectrum of disorders:
  - Alpers-Huttenlocher syndrome
  - Childhood myocerebrohepatopathy spectrum disorders
  - Myoclonic epilepsy myopathy sensory ataxia
  - *POLG*-related ataxia neuropathy spectrum disorders
  - Autosomal recessive progressive external ophthalmoplegia
  - Autosomal dominant progressive external ophthalmoplegia
- MS-like symptoms and manifestations

The mutations in POLG1 gene

- Cytogenetic Location: 15q25, prevalence – <0.01
- Pol γ – trimeric protein, catalytic subunit encoded by POLG1
- The only DNA polymerase active in mitochondria and that can replicate mtDNA
- Mutations have been related to a wide variety of disorders – **mainly recessive**, also dominant.

Mitochondrial disorders

- Production of energy by mitochondria depends on:
  - mitochondrial DNA (mtDNA)
  - nuclear genome (nDNA)

- Disorders involving mtDNA replication:
  - **Qualitative defects (**multiple mtDNA deletions**)**
  - **Quantitative defects** (mtDNA depletion syndromes)

- Most subunits of the respiratory chain are of **nuclear origin**, as well as enzymes performing critical steps in metabolic pathways (and many more)

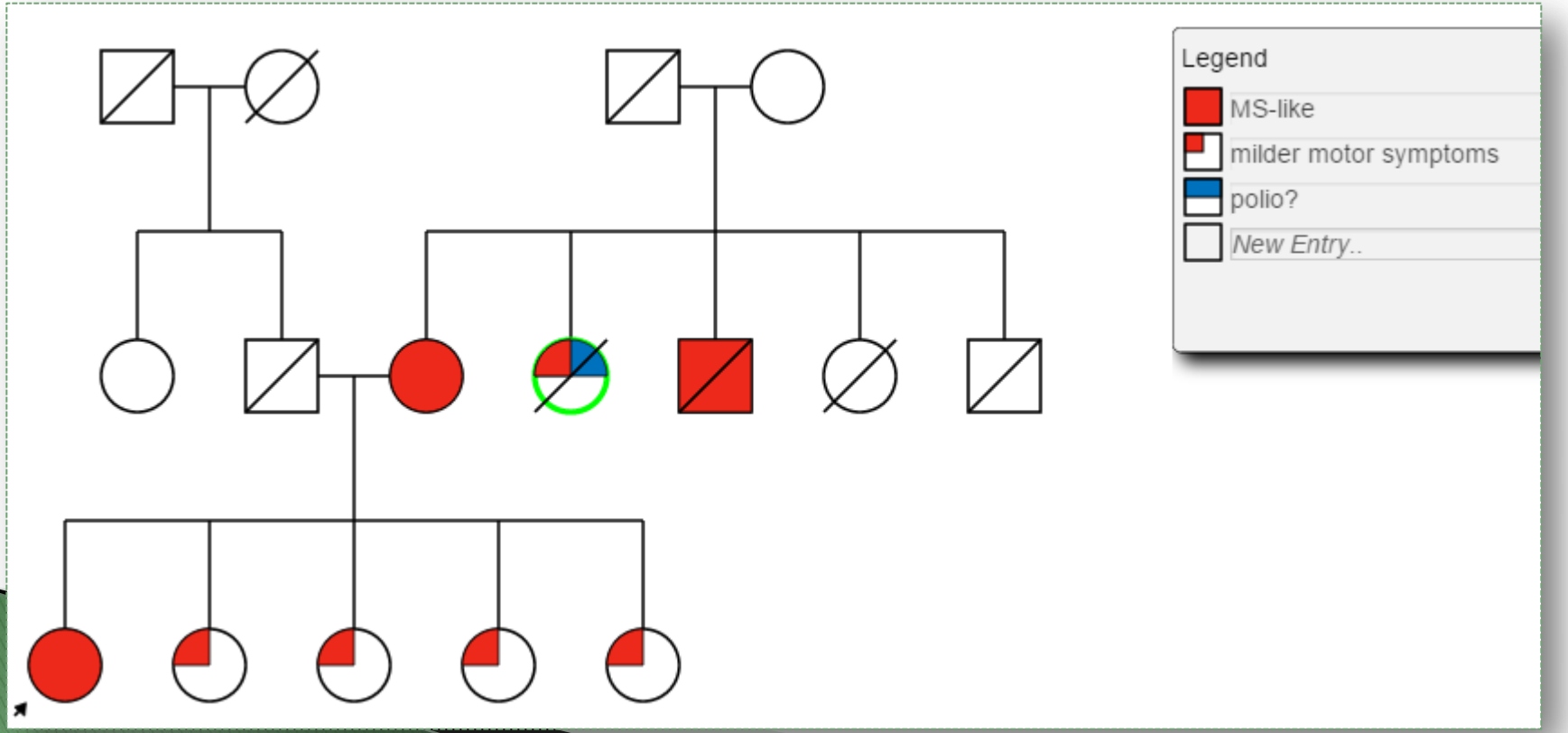
What did we do?

- Looked for relevant patients:
  - Georgians, familial story, preferable Primary Progressive MS

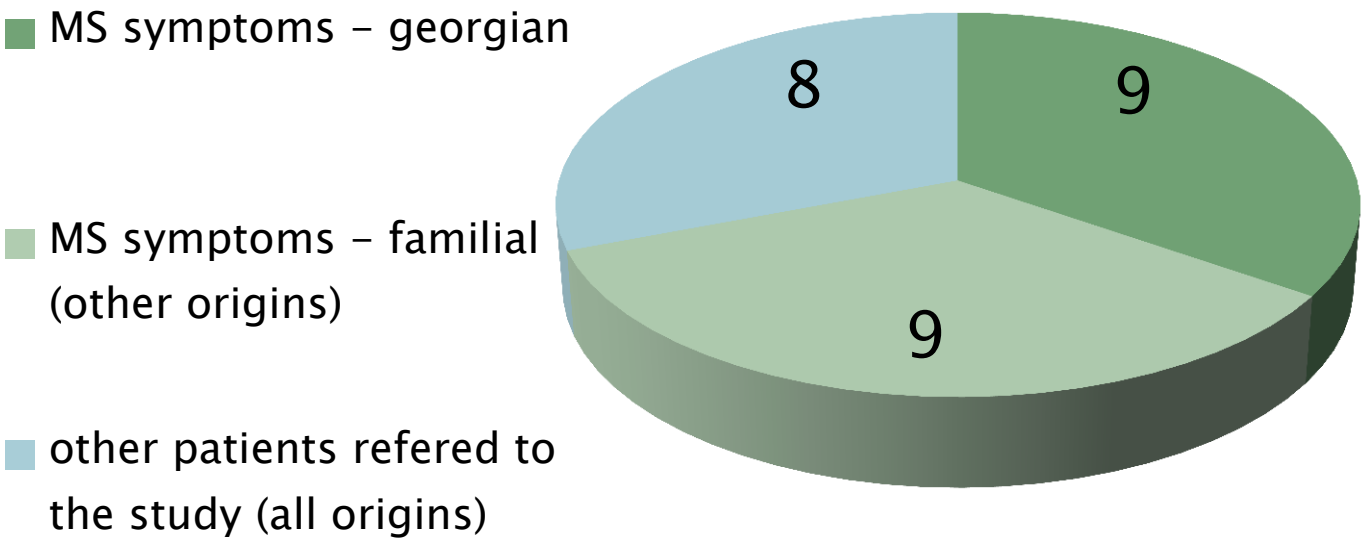
- Patients with familial background (all ethnic groups)

Nana's pedigree

- Our First positive patient and her familial background
  - Meri's symptoms
  - Sisters' mild symptoms



The patients in the study



- Prevalence in Georgians VS. wide population – 0.1 VS. 0.01

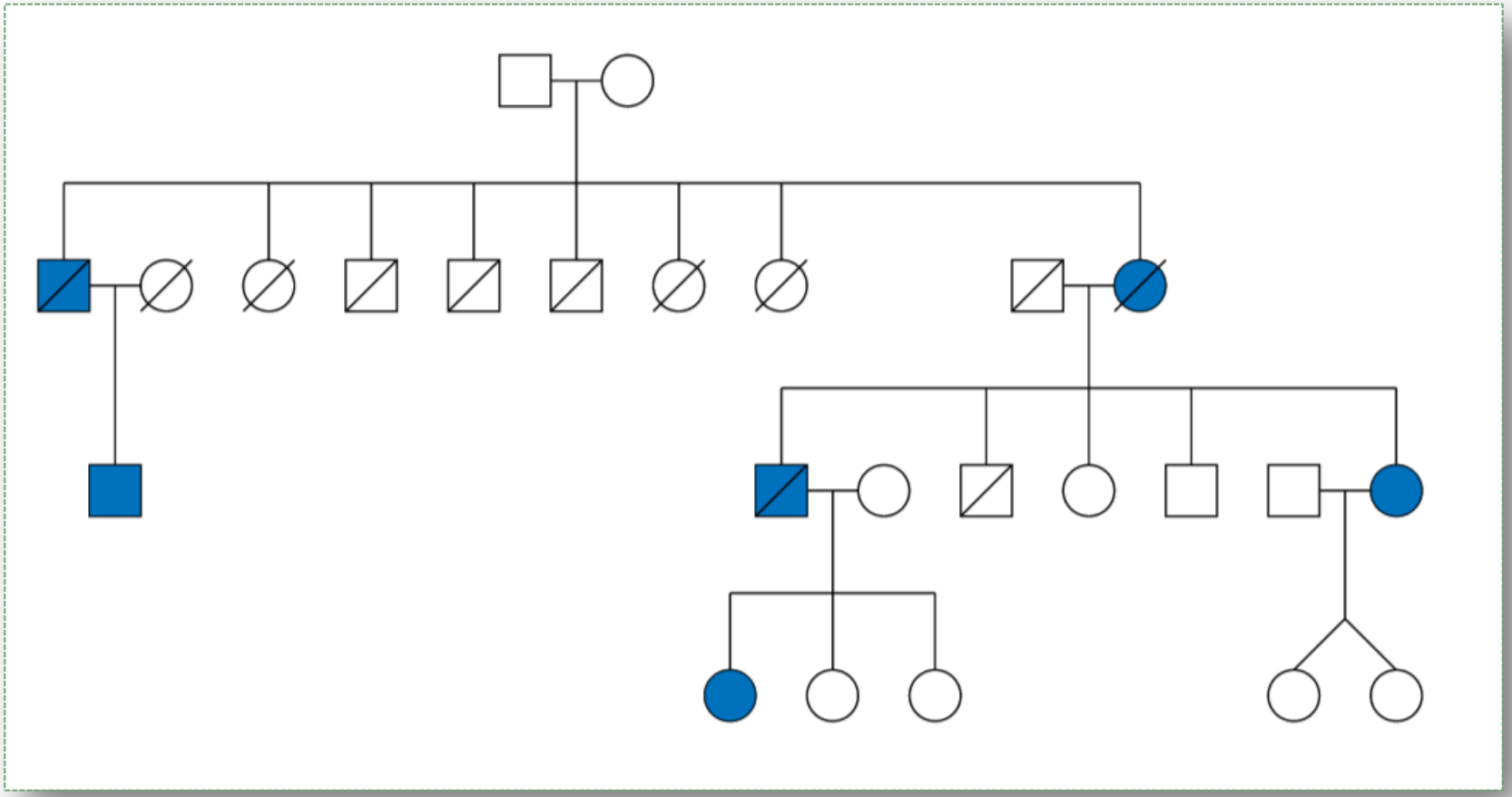
Our thoughts at this point

- Another mutation in the gene?
- Where are the homozygotes?

Interesting patient

- Rivka – 65 YO patient:
  - Progressive external ophtalmoplegia – 4 eyelid surgeries
  - “frozen” facial impression
  - familial background – AD
  - Dysphagia for the last 10 years
  - Normal reflexes
  - Walks normally
  - Lateral limitation in eyeball movements
  - coughs while drinking water
- The full symptoms indicate – Oculopharyngeal muscular dystrophy.

Rivka's pedigree



Oculopharyngeal muscular dystrophy (OPMD)

- Main symptoms :Ptosis and dysphagia
- Late onset
- Other symptoms such as tongue and facial muscle weakness might appear later on
- Autosomal Dominant or Recessive – PABPN1
  - Expansion of a GCN trinucleotide repeat
  - Prevalence – 1:600 among Bukhara Jews in Israel

What's next – PABPN1?

- Additional meeting with Rivka to discuss the results
  - Consequences on her daughters
  - Ethical aspects
- Search for more PEO patients and test them for OPMD

What's next – POLG1?

- Expand the prevalence inquiry to 200 Georgian patients
- Search for more Georgian patients with POLG1 symptoms

QUESTIONS?