UNIVERSITÀ DEGLI STUDI DI MILANO

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico

Sistema Socio Sanitario Regione Lombardia

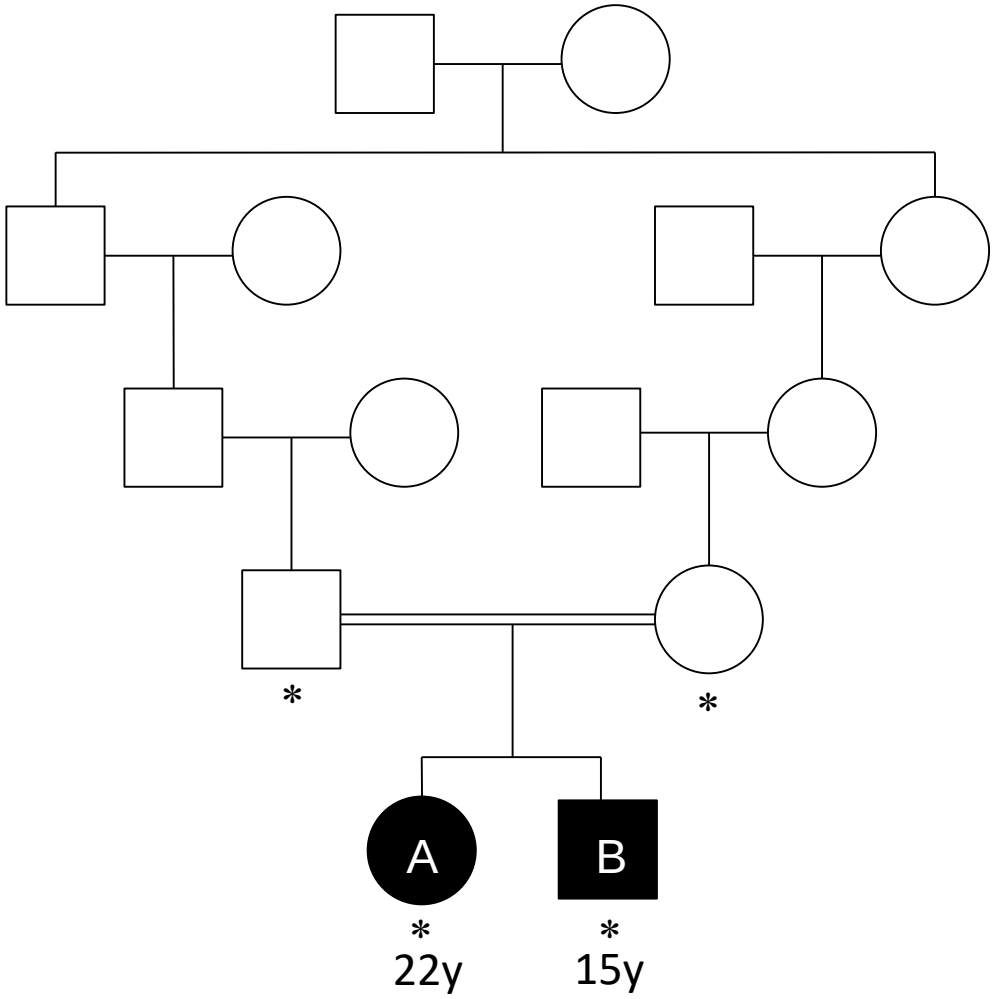
Neurofascin (*NFASC*) is a novel gene causing hereditary ataxia

A family-based approach to find the genetic cause of a new neurological disease

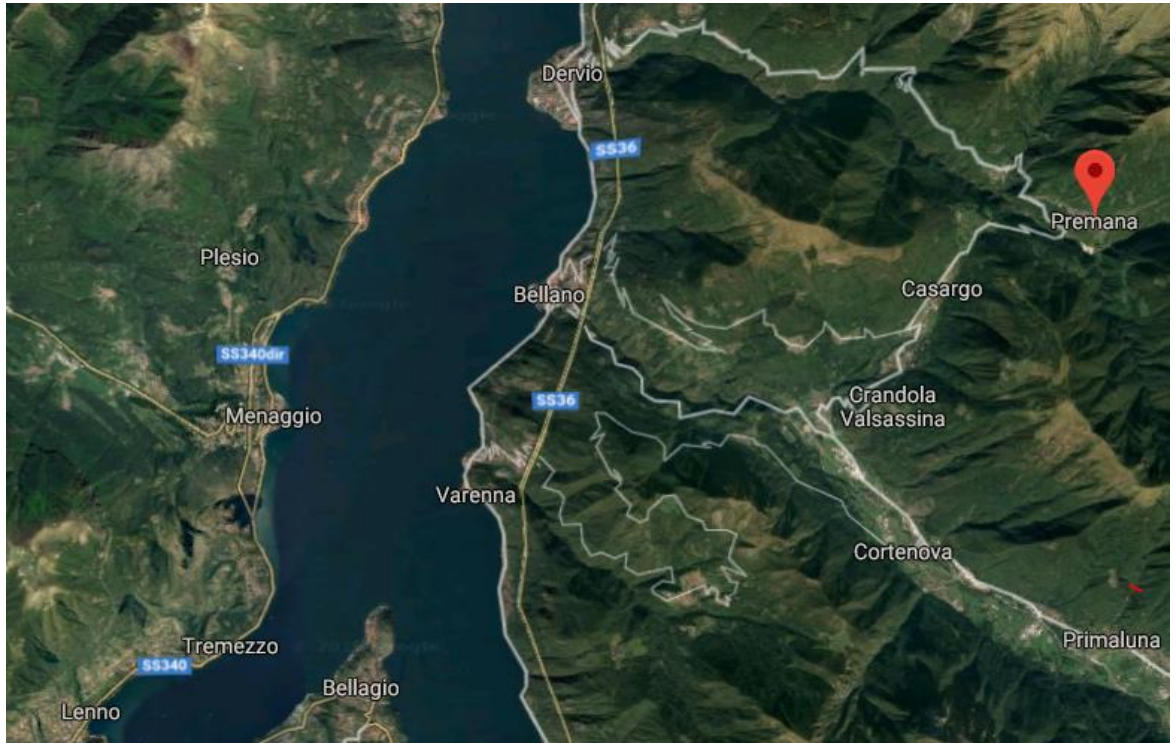
8ª GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA

Edoardo Monfrini
Specializzando in Neurologia

Early-onset ataxia in an Italian consanguineous family



The parents are related (cousins)



The family originated from an isolated valley of Lombardia region.

Clinical features of the patients

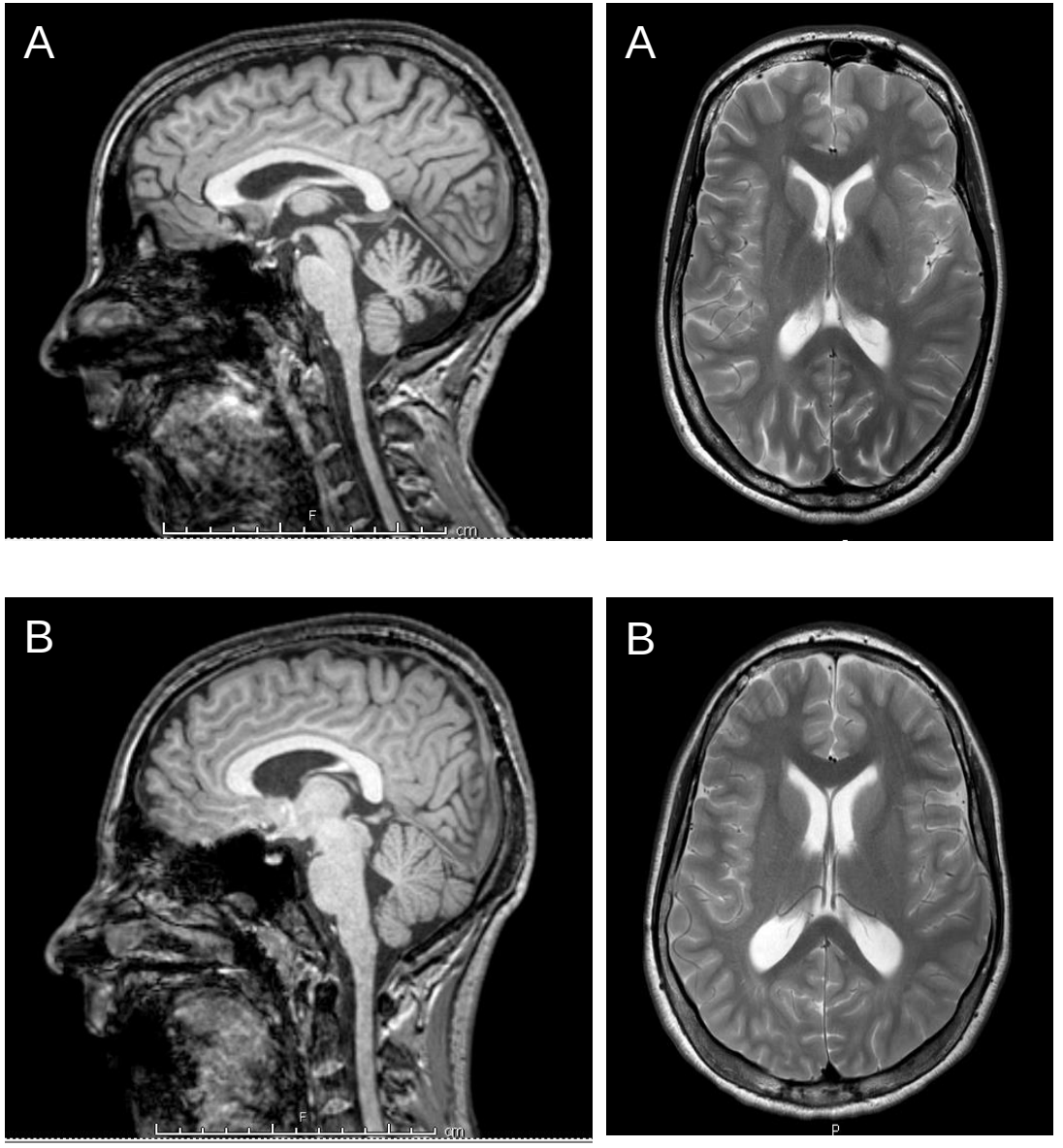
Early psychomotor delay was present. They started to walk at 3 years of age with an unsteady **wide-based ataxic gait**.

Prominent cerebellar signs: cerebellar dysarthria, intention tremor, dysmetria, pursuit saccadization, and dysdiadochokinesia were observed.

From the age of 11 years, subject A developed progressive **spastic hypertonia of the limbs with hyperreflexia**, lower limbs intra-rotation, ankle clonus, and bilateral **Babinski sign**.

Nerve conduction studies showed a length-dependent **demyelinating sensory-motor peripheral neuropathy**.

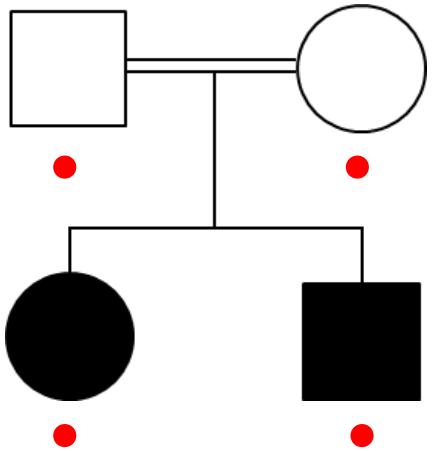
→ **Known etiological genes** for hereditary ataxias **were excluded**.



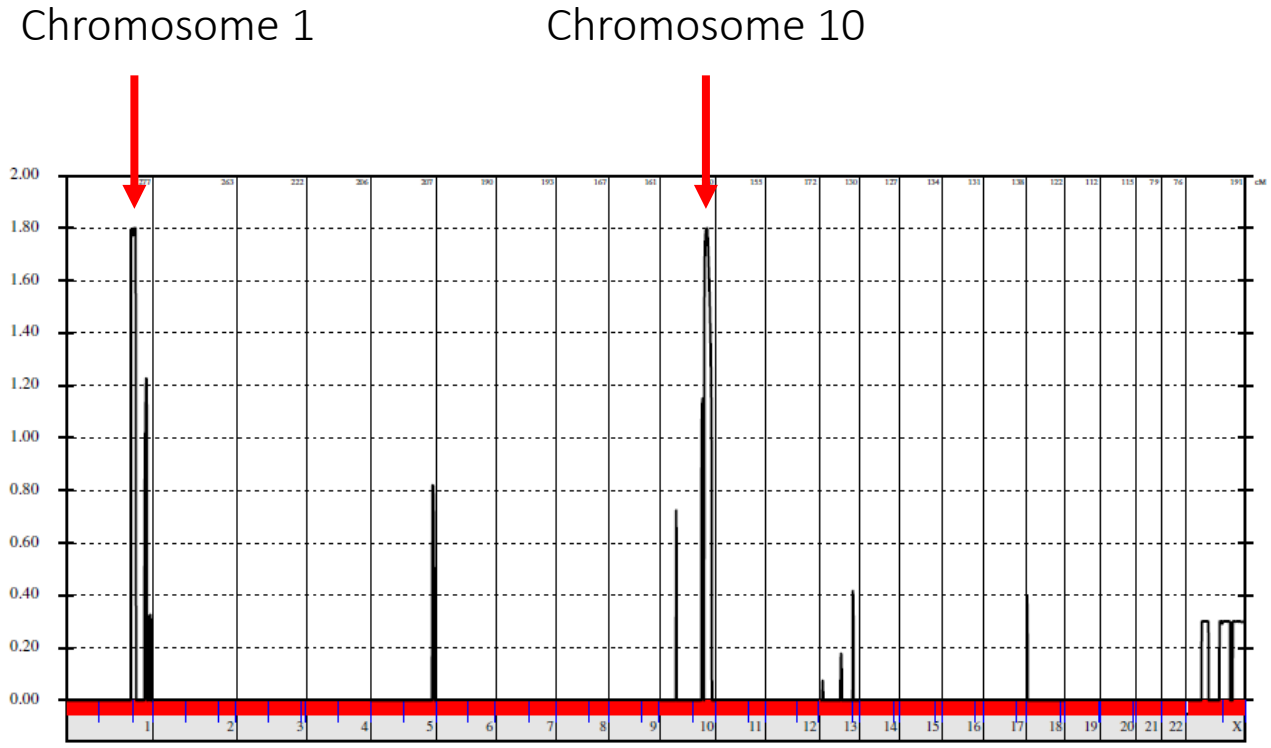
Linkage analysis – Homozygosity mapping

A homozygous mutation was suspected to be the cause of disease in this family

Illumina beadchip SNP-array

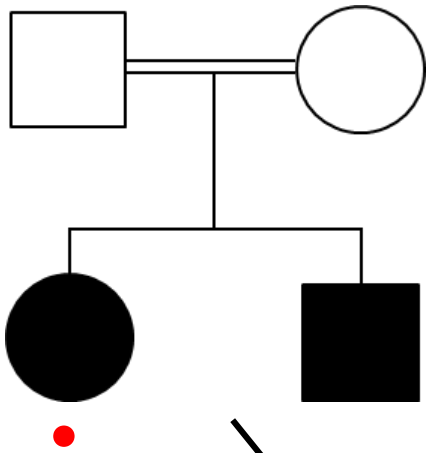


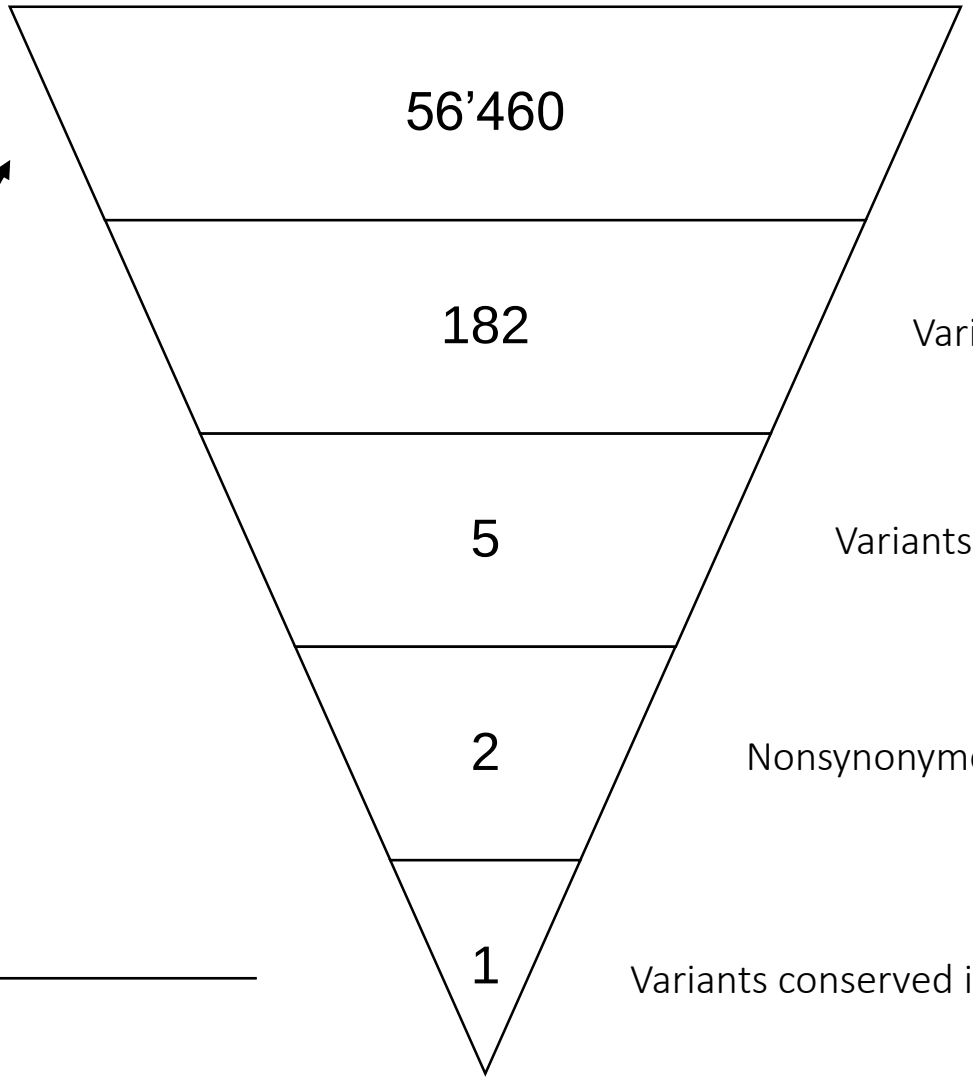
Genotyping of all core family members



Two homozygous regions shared by the two affected siblings

Whole-exome sequencing – filtering analysis





Total variants

Variants in homozygous linkage regions

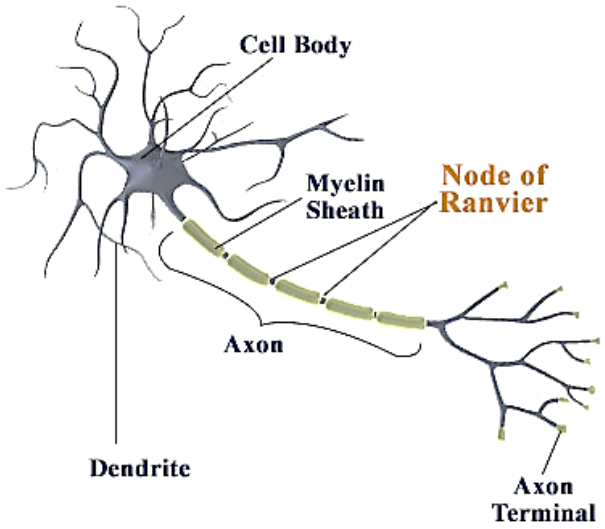
Variants with allele frequency ≤ 0.1

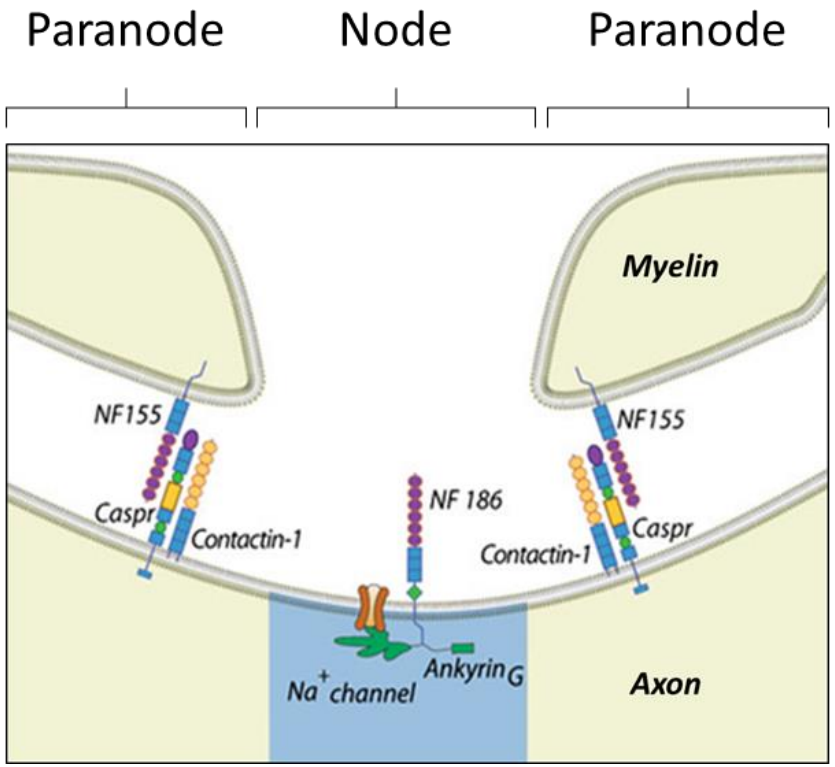
Nonsynonymous variants

Variants conserved in mammals

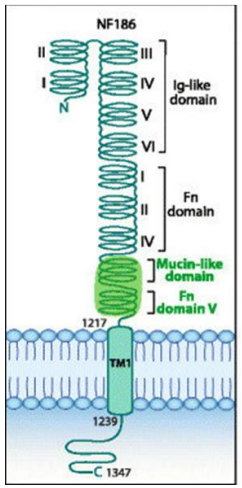
Neurofascin (NFASC)
c.3693T>A
p.V1122E

Neurofascin and the node of Ranvier

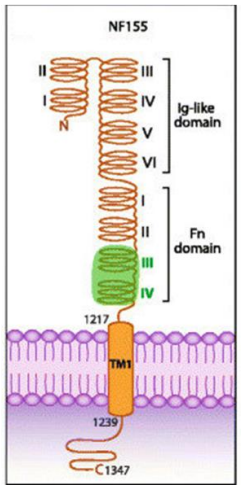




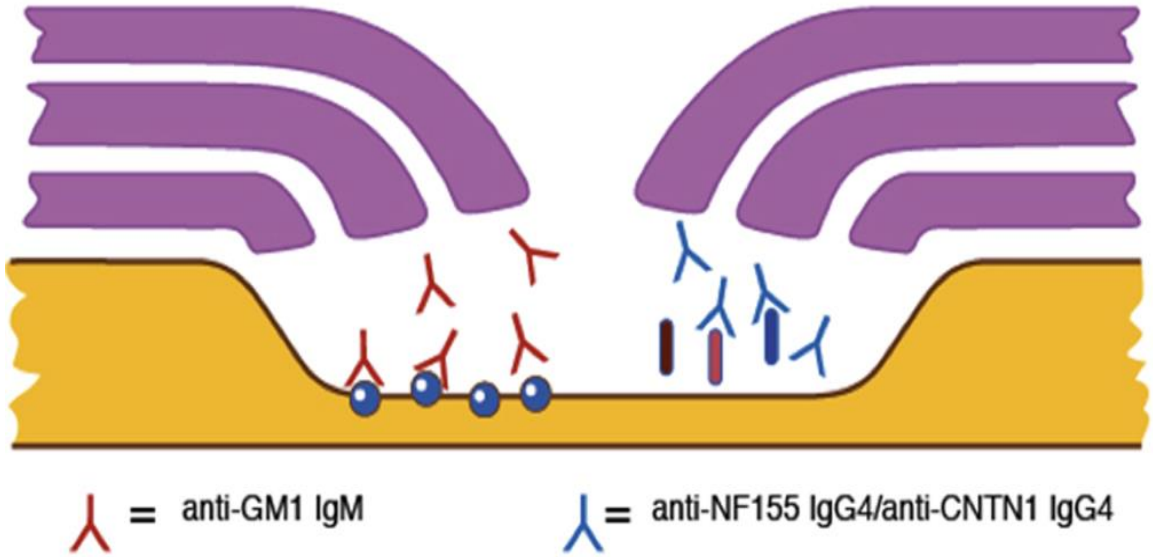
Nfasc186 (Neurons)



Nfasc155 (Glia)



Neurofascin and human disease (CIDP)



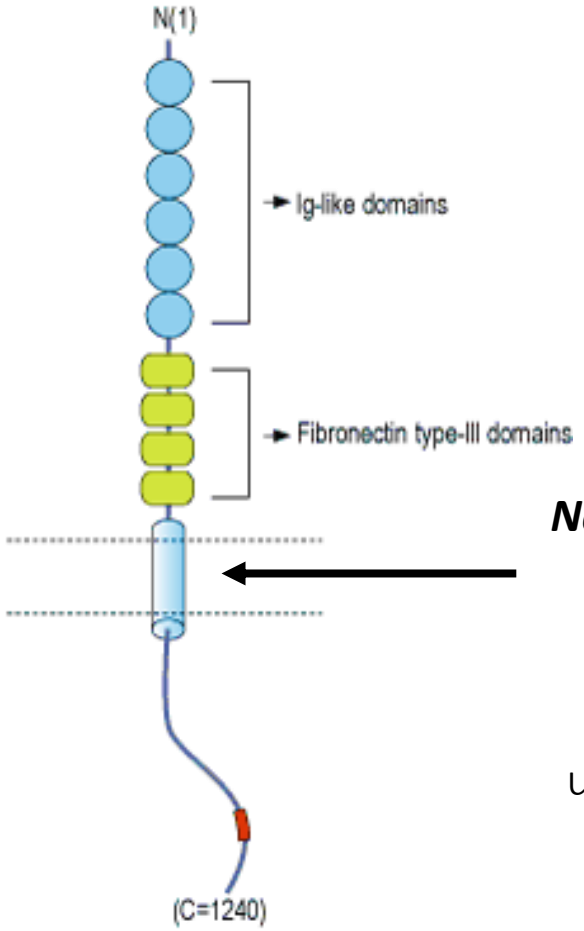
CIDP
(autoantibodies
against Neurofascin)

Neuropathology on nerve biopsies showed a **predominant injury to the nodes of Ranvier**

Nodopathies

Typical clinical features include:
- Cerebellar ataxia
- Tremor

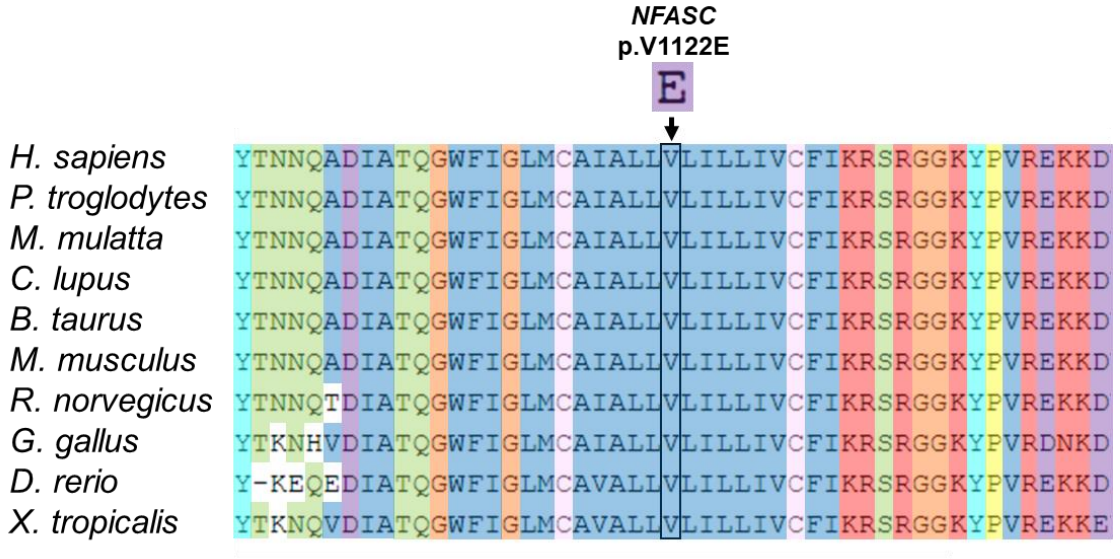
In silico evidence of mutation pathogenicity



Neurofascin protein domains

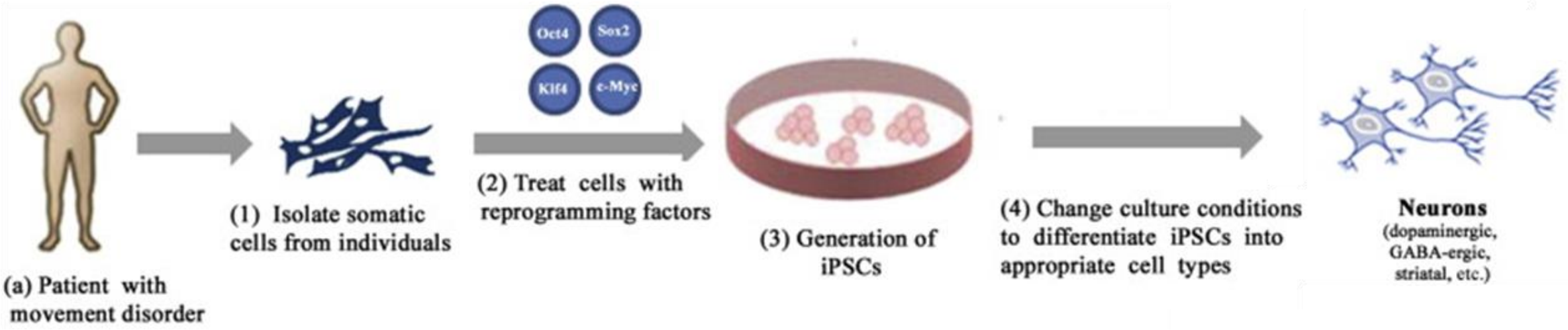
Neurofascin (NFASC)
c.3693T>A
p.V1122E

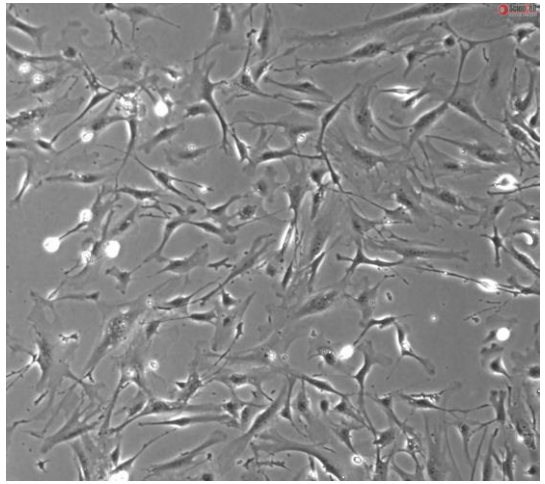
Localized in the unique Neurofascin transmembrane domain

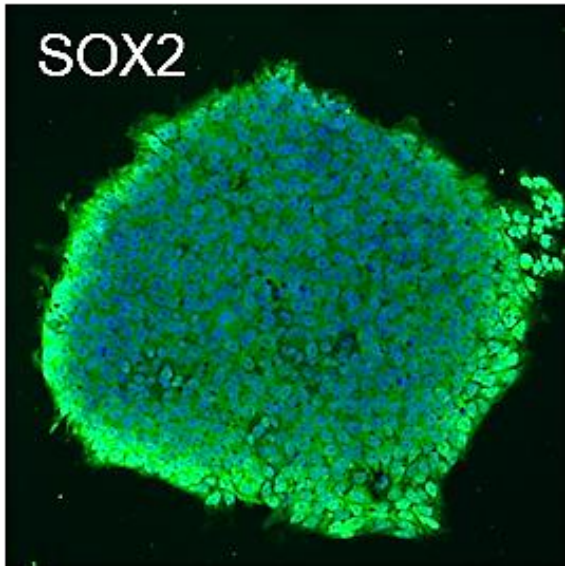


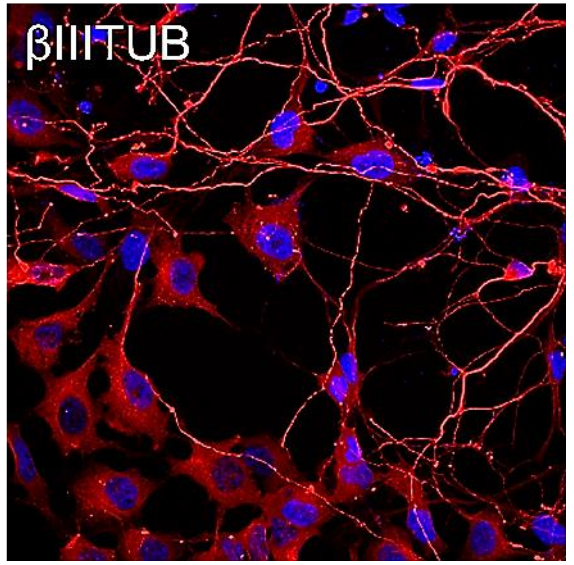
NFASC **- c.3693T>A - p.V1122E**	
SIFT	Damaging (0.001)
Provean	Deleterious (-5.06)
Polyphen2	Probably damaging (0.997)
Mutation taster	Disease causing (0.999)
Condel	Damaging (0.565)
CADD - PHRED	Deleterious (26.4)

In vitro evidence of mutation pathogenicity



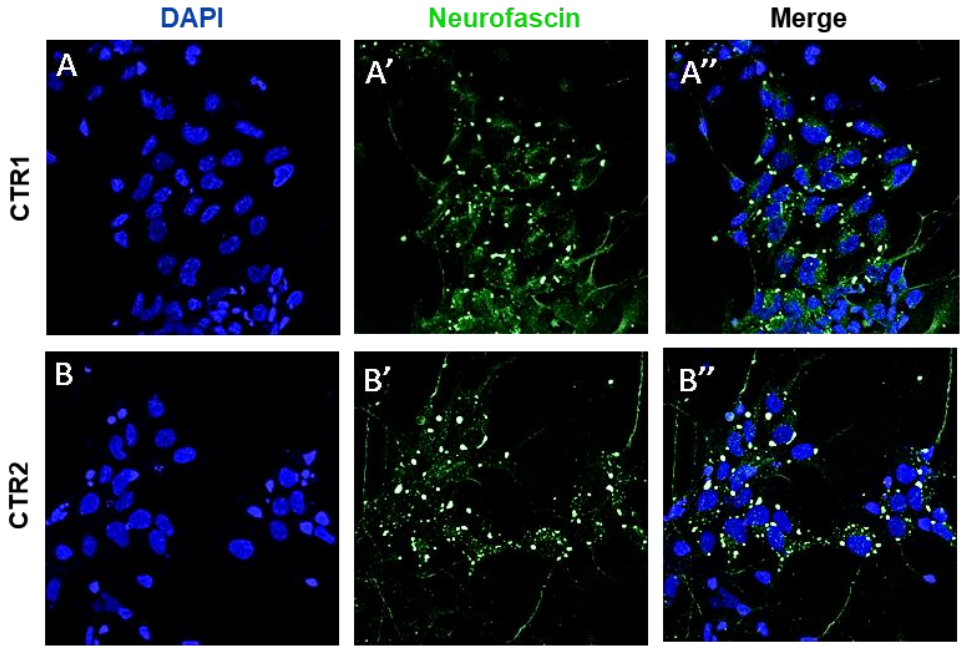




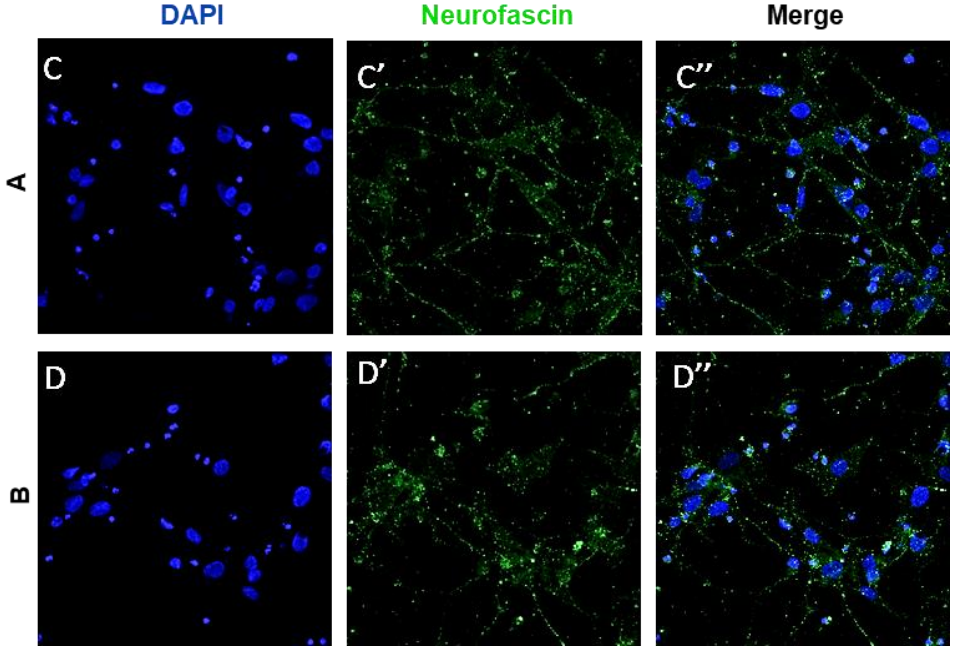


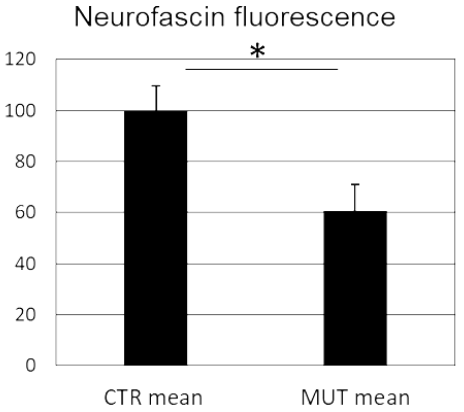
Immunocytofluorescence

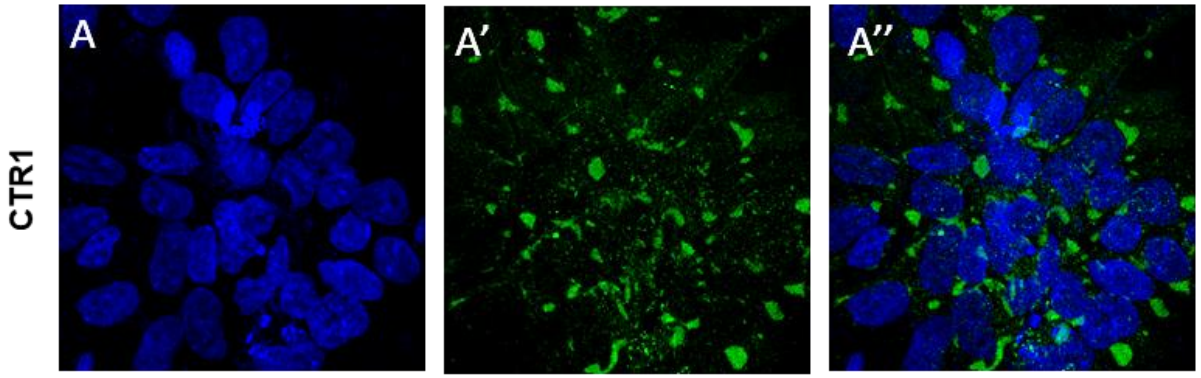
Healthy controls

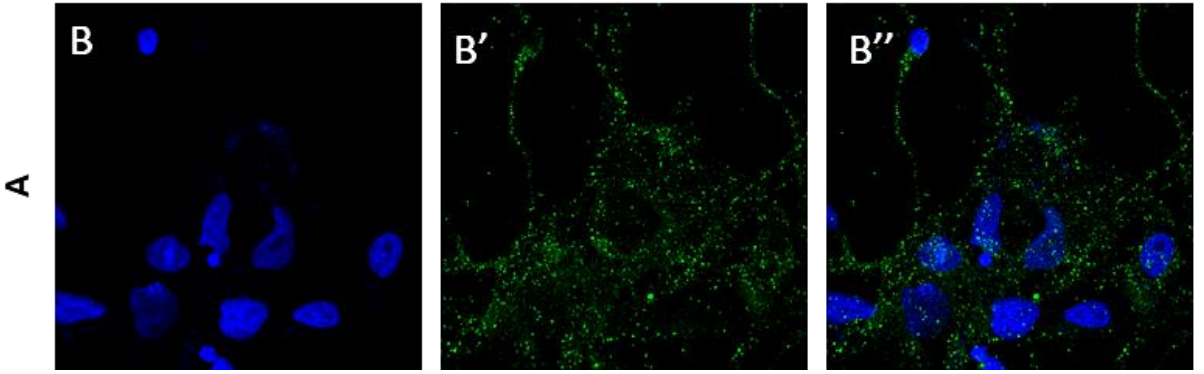


Mutated



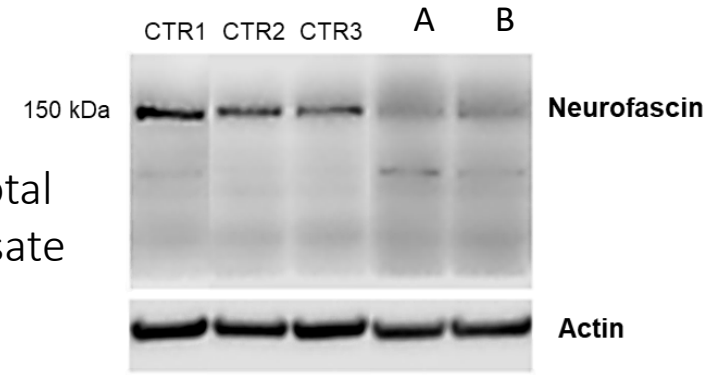


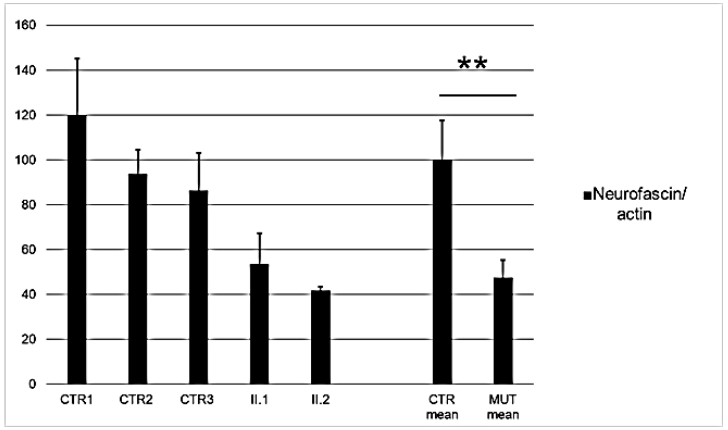




Western blot (Healthy controls vs patients)

Total Lysate



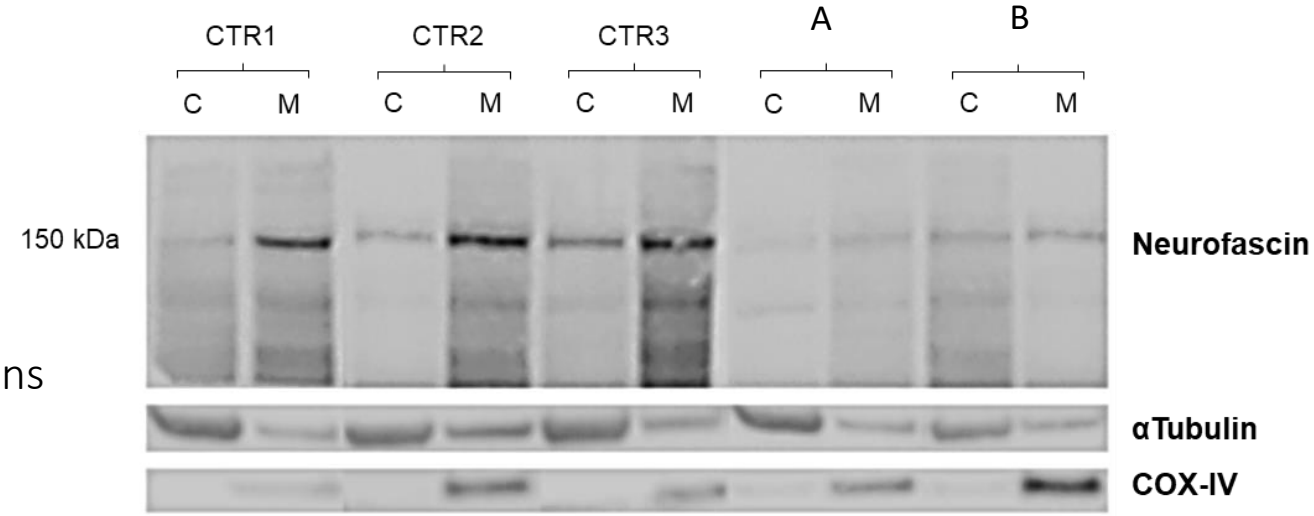


Neurofascin mRNA is not reduced

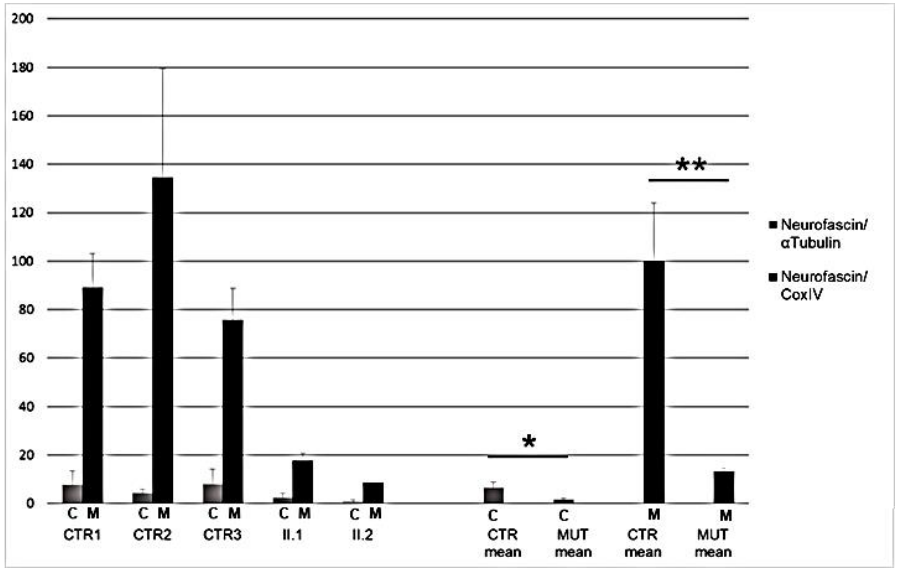
↓

Increased protein degradation

Cell fractions



C = cytosol
M = membranes



Publications

ELSEVIER

Parkinsonism & Related Disorders

Available online 1 March 2019

In Press, Corrected Proof

Neurofascin (*NFASC*) gene mutation causes autosomal recessive ataxia with demyelinating neuropathy

Edoardo Monfrini [a, b], Letizia Straniero [c, d], Sara Bonato [a, b], Giacomo Monzio Compagnoni [a, b], Andreina Bordoni [a, b], Robertino Dilena [e], Paola Rinchetti [a, b], Rosamaria Silipigni [f], Dario Ronchi [a, b], Stefania Corti [a, b], Giacomo P. Comi [a, b], Nereo Bresolin [a, b], Stefano Duga [c, d], Alessio Di Fonzo [a, b]

CORRIERE DELLA SERA

La storia di [redacted], paziente 1 e paziente 2: affetti da una malattia rarissima

Fratello e sorella, colpiti da una mutazione genetica della coordinazione muscolare. Il loro è l'unico caso conosciuto al mondo Un male per il quale a oggi non esiste cura

di Barbara Gerosa

Homozygous mutation in the *Neurofascin* gene affecting the glial isoform of Neurofascin causes severe neurodevelopment disorder with hypotonia, amimia and areflexia

Robert Smigiel, Diane L Sherman, Małgorzata Rydzanicz, Anna Walczak, Dorota Mikolajkow, Barbara Krolak-Olejnik, Joanna Kosińska, Piotr Gasperowicz, Anna Biernacka, Piotr Stawinski ... Show more

Human Molecular Genetics, Volume 27, Issue 21, 1 November 2018, Pages 3669–3674,
https://doi.org/10.1093/hmg/ddy277

Published: 13 August 2018 **Article history** ▾

Conclusions and take-home messages

1. Neurofascin (*NFASC*) mutations are associated with **autosomal recessive hereditary ataxia and demyelinating neuropathy**.

2. ***NFASC*** gene should be included in **NGS gene-panels** for hereditary ataxias and genetic neuropathies.

3. Neurofascin-related hereditary ataxia with neuropathy is the **first described "genetic nodopathy"**.

Dip. Di Fisiopatologia Medica e Dei Trapianti – Università degli Studi di Milano
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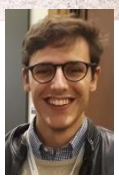


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