New FIG4 gene mutation causing fast progressing ALS phenotype: a case report.

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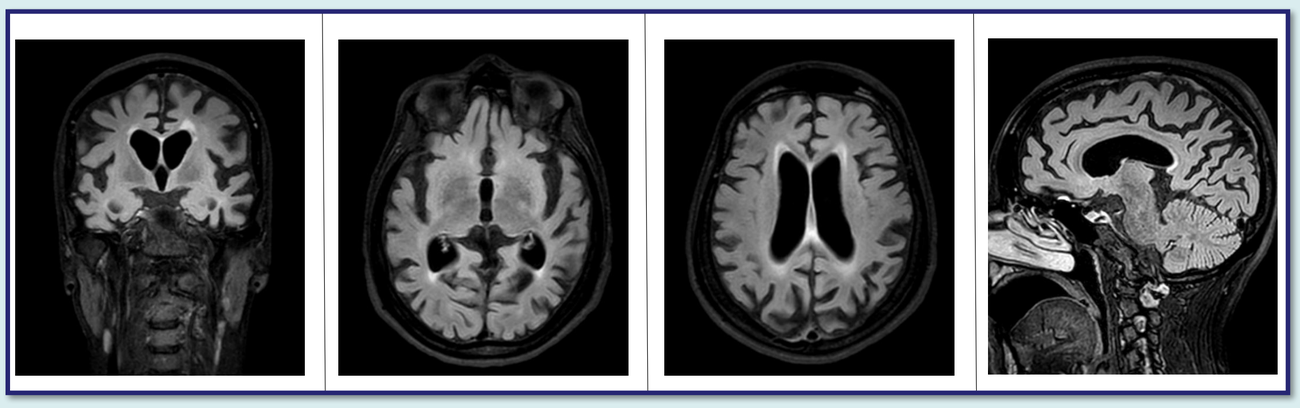
Case report

- A 27 years old woman was referred for rigidity in lower limbs associated with progressive verbal fluency impairment and dysphagia lasting for over one year.
- She was adopted and family history was unknown. Past medical history was characterized by moderate cognitive retardation known from the early infancy without motor deficits.
- As the patient came to our attention (May 2016), she presented ***severe motor aphasia and spastic paraplegia***. Mild proximal muscular weakness was identified in lower limbs together with fasciculations. Diffuse severe spastic hypertonia with brisk reflexes and bilateral Babinski sign were present. At cranial nerves examination, a *long-lasting multi-directional non-positional nystagmus* was observed.
- Later, symptoms rapidly worsened to a spastic tetraplegia associated with complete aphasia and severe dysphagia. The patient died after *ab ingestis* pneumonia 18 months after symptom onset.

Diagnostic exams

- Blood and cerebrospinal fluid analysis were normal as well as EMG and nerve conduction studies.
- **Brain MRI** showed diffuse ***cortical atrophy more evident in the temporal lobes and mild atrophy of the corpus callosum .***



- Muscle biopsy showed initial ***signs of neurogenic atrophy.***

Diagnosis of PROBABLE JUVENILE ALS

Genetic screening

- The pathological expansion of C9Orf72 gene was excluded by Repeat-Primed PCR.
- Extended genetic analysis was carried out with MND-related genes NGS panel, which evidenced **two mutations in the FIG4 gene (c.122T>C and c.1667C>T).**

Nucleotide change	Aminoacid change	Literature	European allele Frequency (ExAc browser)	Polyphen
c.122T>C	p.Ile41Thr	[1] [4]	0.001572	pathogenic
c.1667C>T	p.Thr556Ile	new	0	pathogenic

- Sanger sequencing of cloned cDNA encoding for muscular FIG4 gene of the patient verified that the two mutations are located on different chromosome (phased *in trans*).

Compound heterozygous mutations in the FIG4 gene

FIG4 phosphatidylinositol-3,5-bisphosphate **gene mutations**

CMT 4J	Epilepsy and polymicrogyria	ALS 11	Yunis-Varón syndrome
Onset in the childhood Prevalent motor involvement Minimal sensory symptoms	Abnormal cerebral lamination	Frequently PLS or slowly progressing phenotypes	Structural brain abnormalities, bone dysmorphisms, skin vacuolisation. Lethal in the childhood
Autosomal recessive Missense + null mutations	Autosomal recessive 2 Missense mutations	Autosomal dominant Frameshift or missense mutations	Autosomal recessive Missense + frameshift mutations
PARTIAL LOSS OF PROTEIN FUNCTION			COMPLETE LOSS OF PROTEIN FUNCTION

Conclusions and Discussion

- **Compound heterozygous mutations in the FIG4 gene** causing a juvenile fast progressive neurological syndrome characterized by severe spasticity and cognitive abnormalities.
- p.Ile41Thr (rs121908287) have already been reported in patients with ALS and PLS (autosomal dominant) and in CMT4J patients (autosomal recessive), while p.Thr556Ile was never described before and is absent from public databases of human variations. *In silico* analysis with bioinformatics prediction tools report a probable pathogenic role of this variation on protein function.

Even though a diagnosis of juvenile ALS was made, **the clinical phenotype may represent a novel clinical entity related to FIG4 gene mutation.**

The early onset and aggressive progression might be related to severe protein dysfunction caused by the combination of the two different mutations with very low levels of functioning protein.