CONGENITAL MYASTHENIC SYNDROMES: IMPROVED DIAGNOSTIC YIELD BASED ON COMBINED USE OF TARGETED NGS SEQUENCING AND DEEP PHENOTYPING

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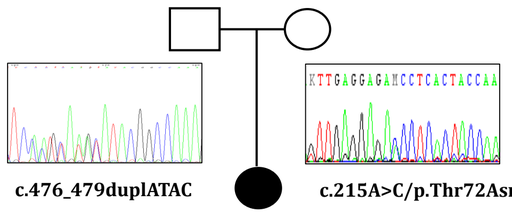
Background

Congenital myasthenic syndromes (CMS) are a genotypically and phenotypically heterogeneous neuromuscular disorders (NMD), due to mutations in over 25 genes encoding proteins involved in the neuromuscular junction structure and function. Although are collectively rare, CMS are probably underestimated due to diagnostic difficulties. In recent years, next-generation sequencing (NGS) has increasingly been used for the diagnosis of NMD and CMS.



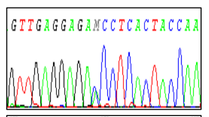
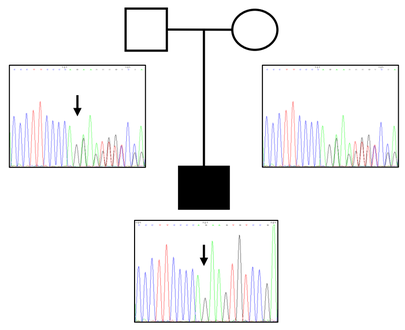
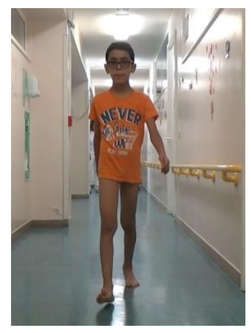




Fig.2 Patient with biallelic mutations in the *CHRND* gene





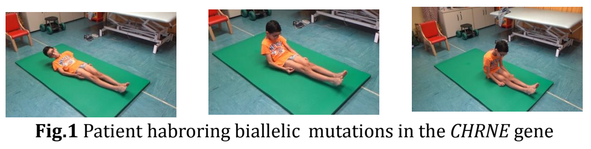


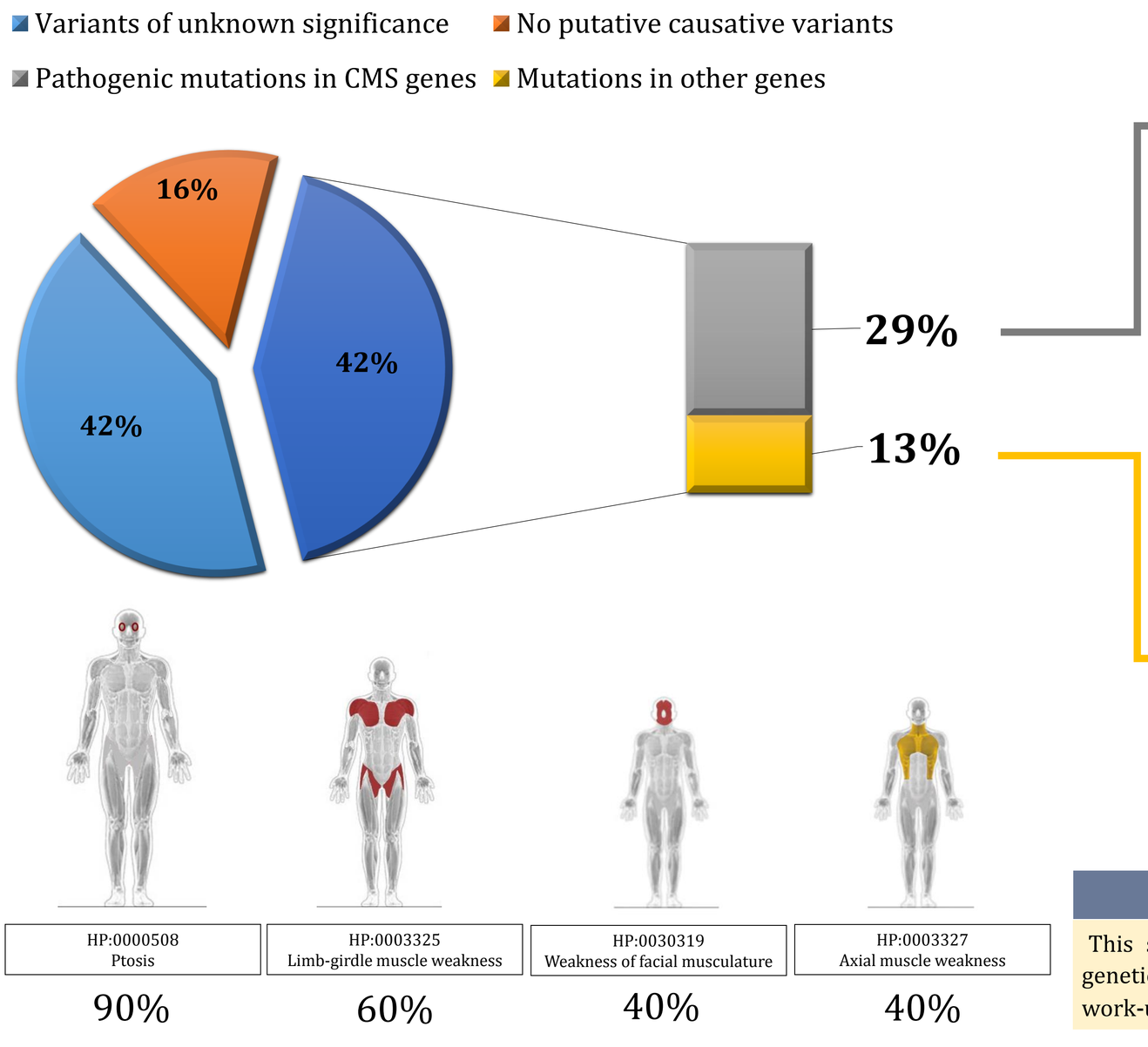
Fig.1 Patient habroring biallelic mutations in the *CHRNE* gene

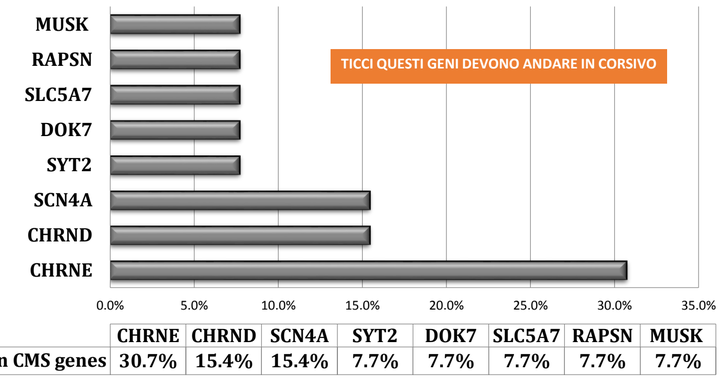
Methods

Between 2014 and 2018, among over 400 NMD patients referred to our center, we evaluated 45 patients with clinical suspicion of CMS. In all we tested the coding regions of 241 genes associated with NMD using a targeted NGS technology. In each case we also collected clinical and laboratory data as well as the results of familial segregation analyses. The distribution of the muscle weakness was recorded using the Human Phenotype Ontology (HPO) codes and nomenclature.

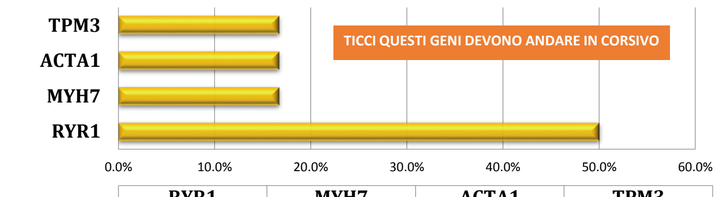
Results

A molecular diagnosis was reached in 19/45 cases (42%). Variants of unknown significance were found in 19 patients, whereas 7 cases remained molecularly undefined. Pathogenic mutations were identified in genes already associated with CMS in 13 individuals whereas 6 cases showed mutations in other genes not previously linked to defects of neuromuscular junction. Major features of the diagnosed CMS cases were ptosis and limb-girdle muscle weakness.





	CHRNE	CHRND	SCN4A	SYT2	DOK7	SLC5A7	RAPSN	MUSK
Mutations in CMS genes	30.7%	15.4%	15.4%	7.7%	7.7%	7.7%	7.7%	7.7%



	RYR1	MYH7	ACTA1	TPM3
Mutations in other genes	50.0%	16.7%	16.7%	16.7%

HP:0000508 Ptosis	HP:0003325 Limb-girdle muscle weakness	HP:0030319 Weakness of facial musculature	HP:0003327 Axial muscle weakness
90%	60%	40%	40%

Conclusions

This study highlights the advantages of NGS used as a first-tier diagnostic approach in genetically heterogeneous conditions and underlines the importance of a standardized clinical work-up as a component of the diagnostic pathway in CMS.