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Supplemental information

The severity of *MUSK* pathogenic variants is predicted by the protein domain they disrupt

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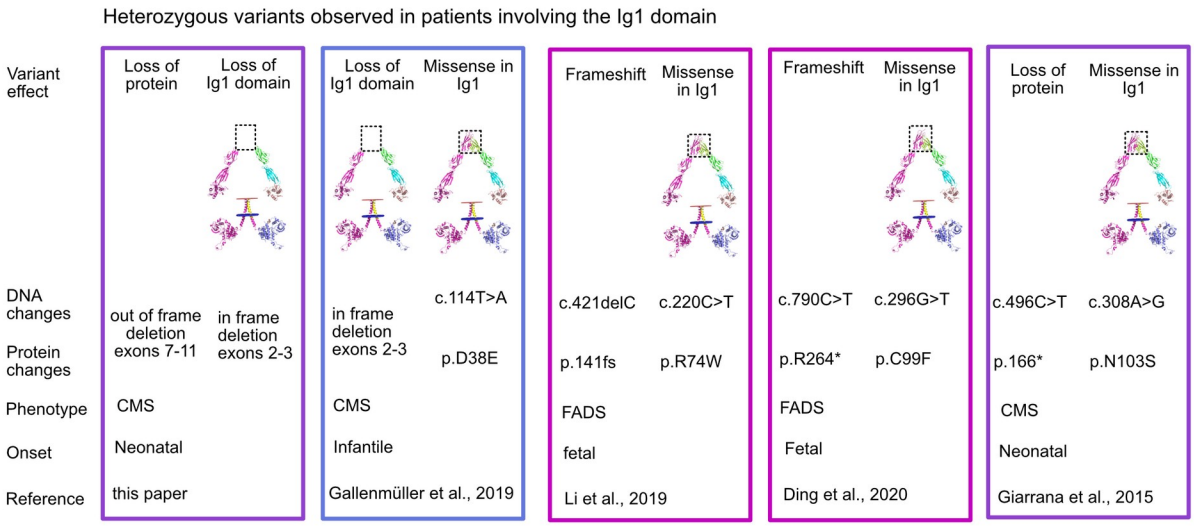
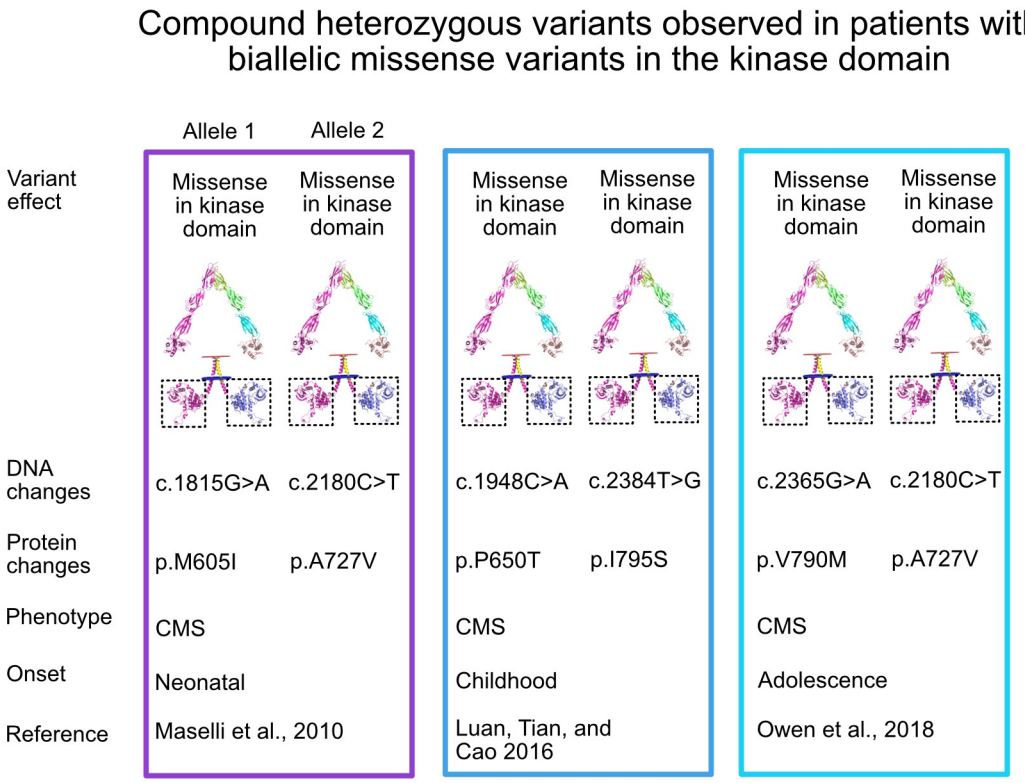
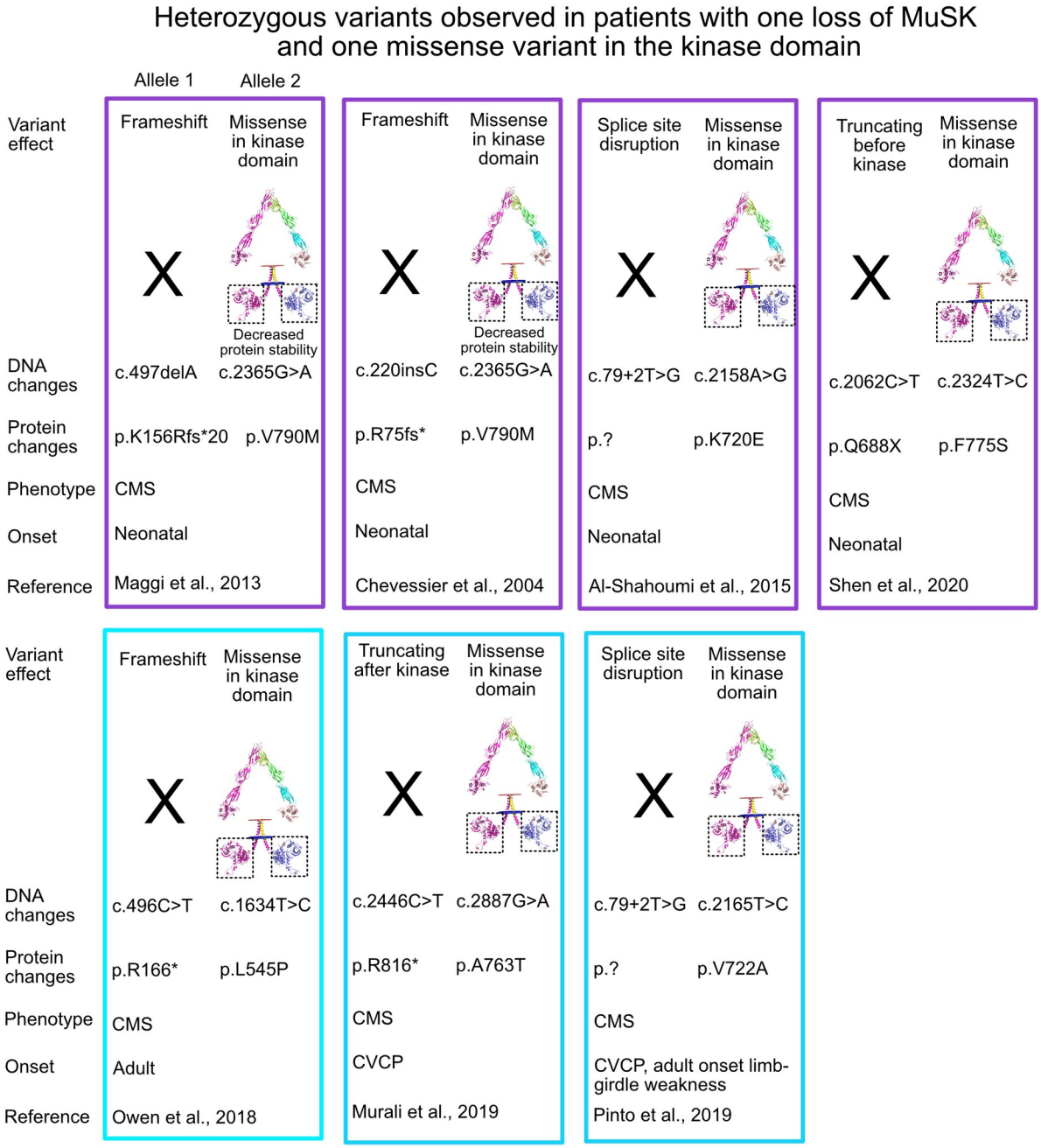


Supplemental Figure 1: Compound heterozygous allele combinations with missense variants in the Ig1 domain. Five allele combinations in compound heterozygosity involve the Ig1 domain. They all result in fetal or neonatal presentation, with the exception of the p.N103S which has a variable presentation (observed as neonatal, infantile, adolescent, and adult). Two cases have been reported with the in-frame deletion of Ig1. The p.R74W and p.C99F allele, when in combination with a null allele, result in FADS. The p.N103s allele is the most variable and most common pathogenic allele observed in the cohort.



Supplemental Figure 2: Compound heterozygous allele combinations with missense variants in the kinase domain. Three combinations of variants were observed with two separate missense variants in the kinase domain. The p.A727V appeared in both a neonatal case in combination with p.M605I and an adolescent case with p.V790M, suggesting that either (1) the p.M605I is a more severe variant or (2) additional genetic or environmental modifiers were present in the patients reported. The p.V790M, when paired with a null allele, leads to neonatal onset CMS (Supplemental Figure 3).



Supplemental Figure 3: Compound heterozygous allele combinations with one null and one missense variant. The most common allele class observed in compound heterozygous patients is one null and one missense allele (11/15 observations). Patients with one null allele and one kinase missense variant had variable phenotypes from neonatal CMS to isolated CVCP. Even residues that are very close in space (p.V722A and p.K720E) had disparate clinical presentations.

Gene	DNA change	Protein change	Zygosity	dbSNP rsID	Variant interpretation	Related Disease (inheritance)
MUSK	Deletion exons 7-11	Premature stop codon	Heterozygous	N/A	Pathogenic (maternally inherited)	Congenital Myasthenic Syndrome (AR)
MUSK	Deletion exons 2-3	In frame	Heterozygous	N/A	Pathogenic (paternally inherited)	Congenital Myasthenic Syndrome (AR)
MUSK	c.667G>A	p.Val223Ile	Heterozygous	rs774463260	Uncertain significance (paternally inherited)	Congenital Myasthenic Syndrome (AR)
CHRND	c.68A>T	p.Asn23Ile	Heterozygous	Not reported	Uncertain significance	Congenital Myasthenic Syndrome (AR)
HNRNPDL	c.273A>G	Silent mutation	Heterozygous	rs372961029	Uncertain significance	Limb girdle muscular dystrophy (AD)
SPEG	c.3017G>A	p.Arg1006His	Heterozygous	rs571127512	Uncertain significance	Centronuclear myopathy (AR)
GAA	c.2065G>A	p.Glu689Lys	Heterozygous	rs1800309	Benign (Pseudodeficiency allele)	Pompe Disease (AR)

Supplemental Table 1: Results from a comprehensive neuromuscular panel revealed two pathogenic variants in *MUSK*, four variants of uncertain significance, and a benign pseudodeficiency allele in *GAA* were detected. This result is consistent with a diagnosis of *MUSK*-related CMS.