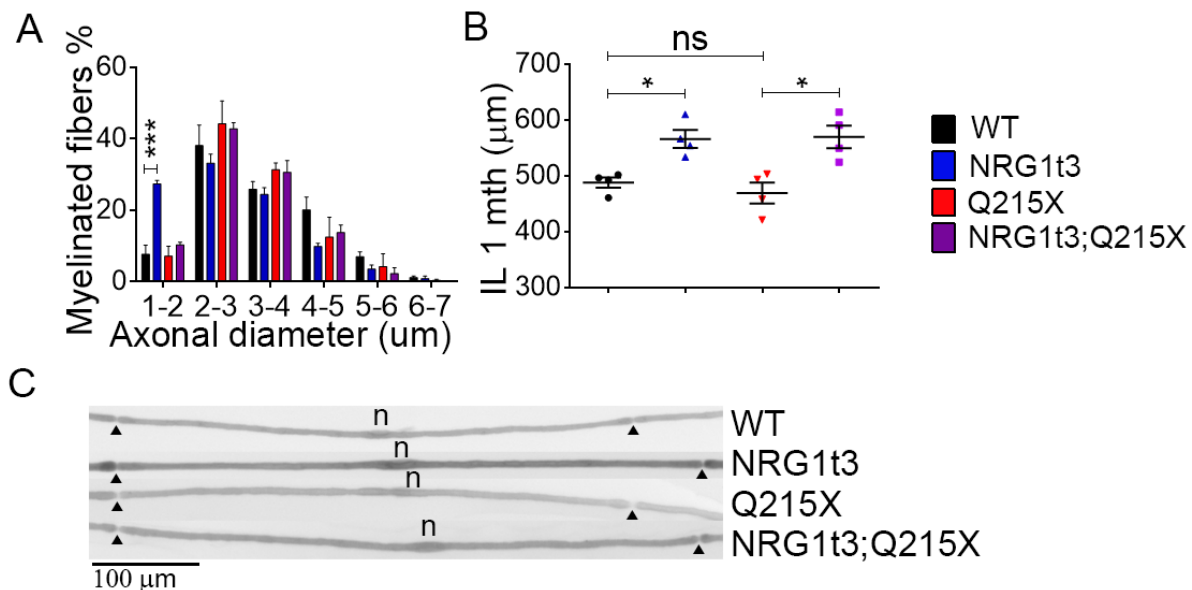


## Supplementary data

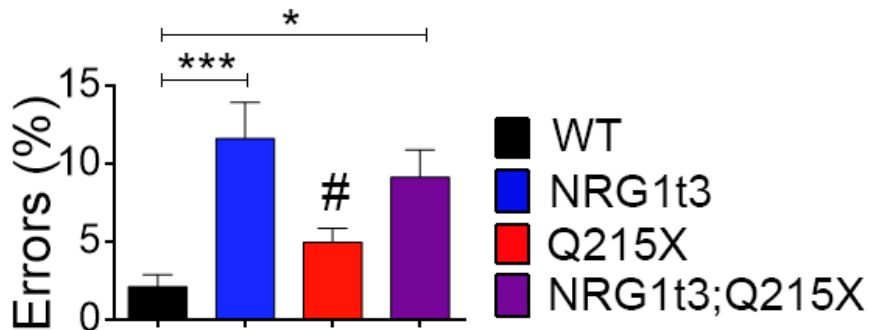
### Supplementary Figure 1. Expression of HA-NRG1 type III promotes a shift in the size of myelinated fiber population and an increase in internodal length

(A) The distribution of myelinated fibers shows a larger population of small myelinated axon (axon diameter from 1 to 2  $\mu\text{m}$ ) in Nrg1t3 compare to WT. (B-C) While no reduction in internodal lengths was measured in the Q215X, the internodal lengths were increased in both Nrg1t3 and Nrg1t3;Q215X and Nrg1t3 by approximately 15% (B). At least 100 internodes were measured (C). Scale bar 100  $\mu\text{m}$ . Analyses were performed using three mice per genotype. Error bars indicate s.e.m. Statistical analyses were performed using one-way ANOVA with Bonferroni's multiple comparison test. \*  $P < 0.05$ .



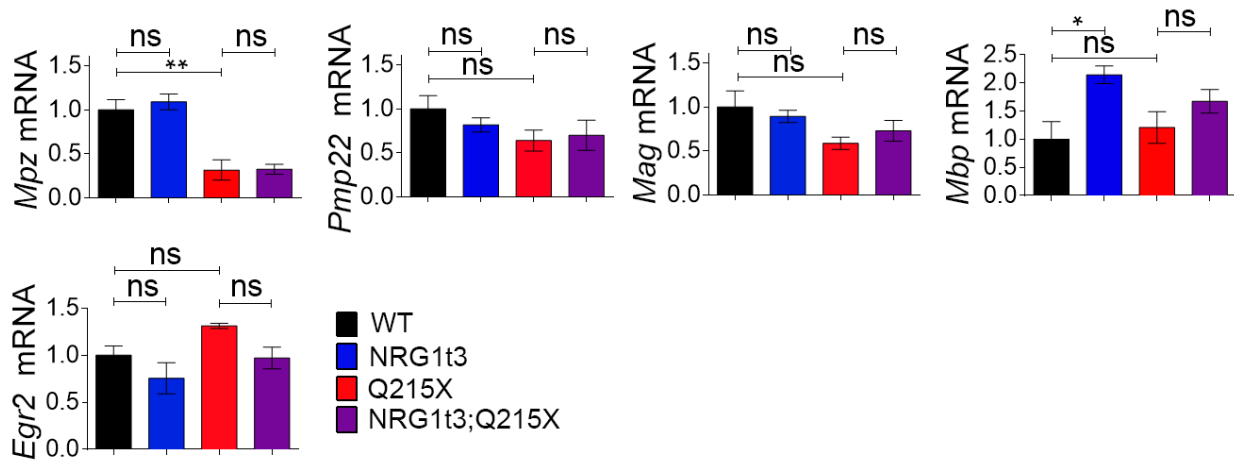
**Supplementary Figure 2. The exogenous expression of HA-NRG1 type III results in motor deficit in mutant mice**

Grid walking test done at 15 days of age, showed an unexpected motor defect due to HA-NRG1 type III exogenous expression. Analyses were performed using n=6 for WT, n=6 for NRG1t3, n=9 for Q215X and n=11 for Nrg1t3;Q215X. Error bars indicate s.e.m. Statistical analyses were performed using one-way ANOVA with Bonferroni's multiple comparison test. \*  $P < 0.05$ , \*\*\*  $P < 0.001$ , # not significant.



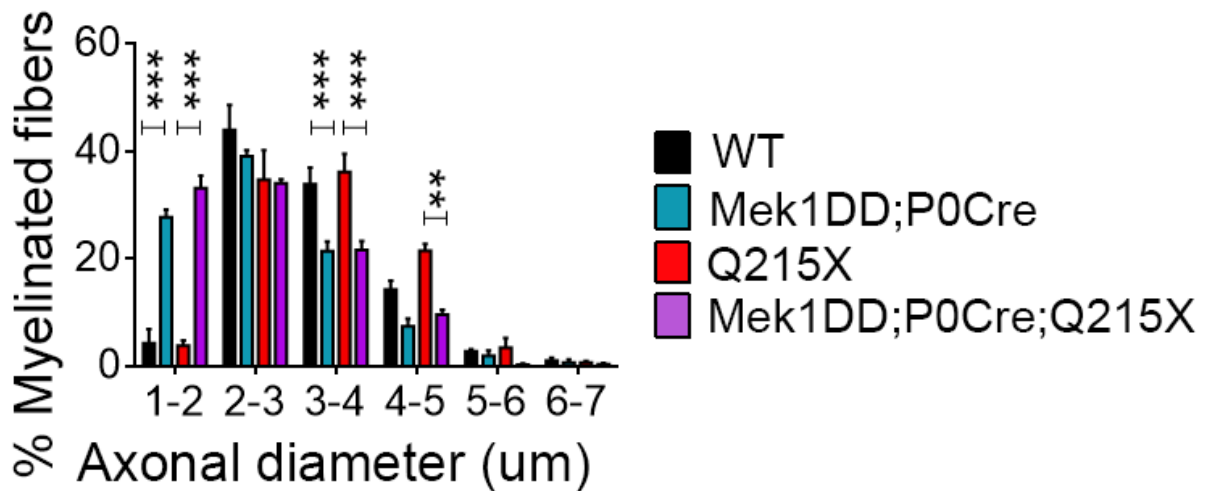
### Supplementary Figure 3. The hypermyelination mediated by HA-NRG1 type III transgenic expression does not correlate with an increase in major myelin components or in EGR2 activation

Relative quantification of *Mpz*, *Pmp22*, *Mag*, *Mbp* and *Egr2* mRNA from WT, *Nrg1t3*, Q215X, HA-*Nrg1t3*;Q215X sciatic nerves at P30. Analyses were performed using three mice per genotype. Error bars indicate s.e.m. Statistical analyses were performed using one-way ANOVA with Bonferroni's multiple comparison test. \*  $P < 0.05$ , \*  $P < 0.01$ .



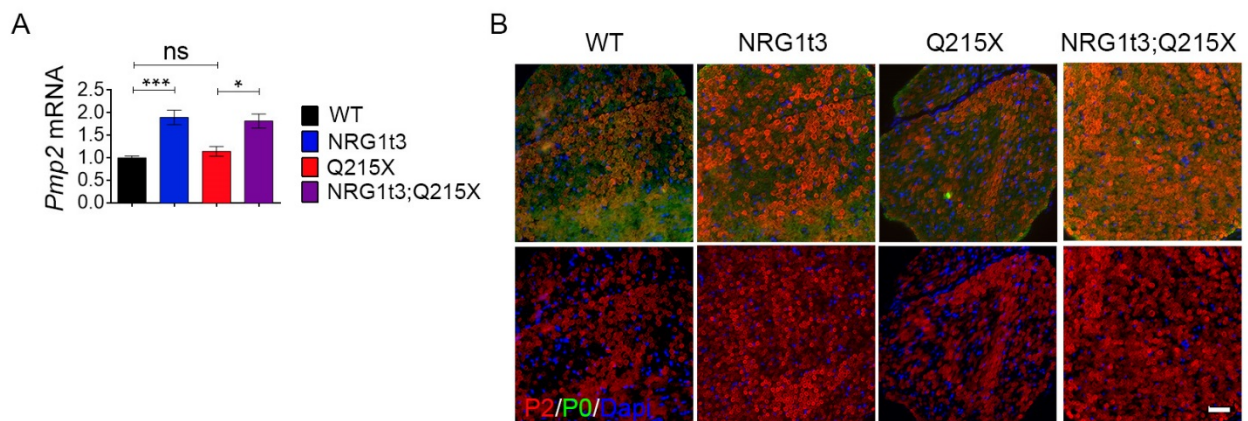
### Supplementary Figure 4. Mek1DD;P0Cre transgene promotes a shift in the size of myelinated fiber population

The distribution of myelinated fibers shows a larger population of small myelinated axon (axon diameter from 1 to 2  $\mu\text{m}$ ) in Mek1DD;P0Cre and Mek1DD;P0Cre;Q215X as compared to WT and Q215X at one month. Analyses were performed using three mice per genotype. Western blot were cropped. Statistical analyses were performed using one-way ANOVA with Bonferroni's multiple comparison test. \*  $P < 0.01$ , \*\*\*  $P < 0.001$ .



## Supplementary Figure 5. Expression of HA-NRG1 type III increases *Pmp2* mRNA and protein levels

(A) Relative quantification of *Pmp2* mRNA from WT, Nrg1t3, Q215X, Nrg1t3;Q215X sciatic nerves at one month. There is a significant up regulation of *Pmp2* ( $1.89 \pm 0.16$  folds in NRG1t3 and  $1.81 \pm 0.15$  in Nrg1t3;Q215X). Error bars indicate s.e.m. Analyses were performed using three mice per genotype. Statistical analyses were performed using one-way ANOVA with Bonferroni's multiple comparison test. \*\*\*  $P < 0.001$ . \*  $P < 0.05$ . (B) Immunolabelling for PMP2 (in red) and P0 (in green) in cross-section from WT, Nrg1t3, Q215X, Nrg1t3;Q215X sciatic nerves at one month. PMP2 staining is increased in Nrg1t3 and Nrg1t3;Q215X sciatic nerves. Scale bar, 25 $\mu$ m.



**Supplementary Table 1. *HA-NRG1 type III* decreases expression of NFATc4 target genes**

Number of genes and *P*-values revealed by a hypergeometric distribution test between genes identified by RNA sequence analysis performed on nerves of various genotypes, and genes enriched in Sox10/H3K27ac sites (at P15 and P30) with (+) or without (no) NFATc4 motif enrichment. Genes downregulated both in Nrg1t3 and Nrg1t3;Q215X were found to be significantly represented in the set of SOX10 target genes with an enrichment for NFATc4 motifs, suggesting a repressive effect of exogenous HA-NRG1 type III expression on NFATc4 target genes. Nrg1t3, *HA-NRG1 type III*; UP, upregulated; DOWN, downregulated; n, number; *P*, *P*-value.

		Nrg1t3 vs WT				Q215X vs WT				Nrg1t3;Q215X vs Q215X				
		UP		DOWN		UP		DOWN		UP		DOWN		
		715		762		306		388		818		612		
	Sox10 peak	Total genes	n	<i>P</i>	n	<i>P</i>	n	<i>P</i>	n	<i>P</i>	n	<i>P</i>	n	<i>P</i>
P15	+ Nfat motif	3006	110	0.02	190	3.15E-20	39	0.55	53	0.34	126	0.01	144	1.93E-13
	no Nfat motif	1229	33	0.80	50	0.06	14	0.74	19	0.60	31	0.98	39	0.12
P30	+ Nfat motif	2205	85	0.01	133	1.82E-12	28	0.59	36	0.56	101	3.09E-03	98	1.33E-07
	no Nfat motif	2374	70	0.65	100	4.61E-03	23	0.95	40	0.48	66	0.98	78	0.02