

Variants in *SNAP25* are targets of natural selection and influence verbal performances in women

Rachele Cagliani¹, Stefania Riva¹, Cecilia Marino¹, Matteo Fumagalli¹, Maria Grazia D'Angelo¹, Valentina Riva², Giacomo P. Comi³, Uberto Pozzoli¹, Diego Forni¹, Mario Cáceres^{4,5}, Nereo Bresolin^{1,3}, Mario Clerici^{6,7}, Manuela Sironi¹

ELECTRONIC SUPPLEMENTARY MATERIAL

Figure 1. GENETREE analysis of the *SNAP25* gene region carrying rs363039.

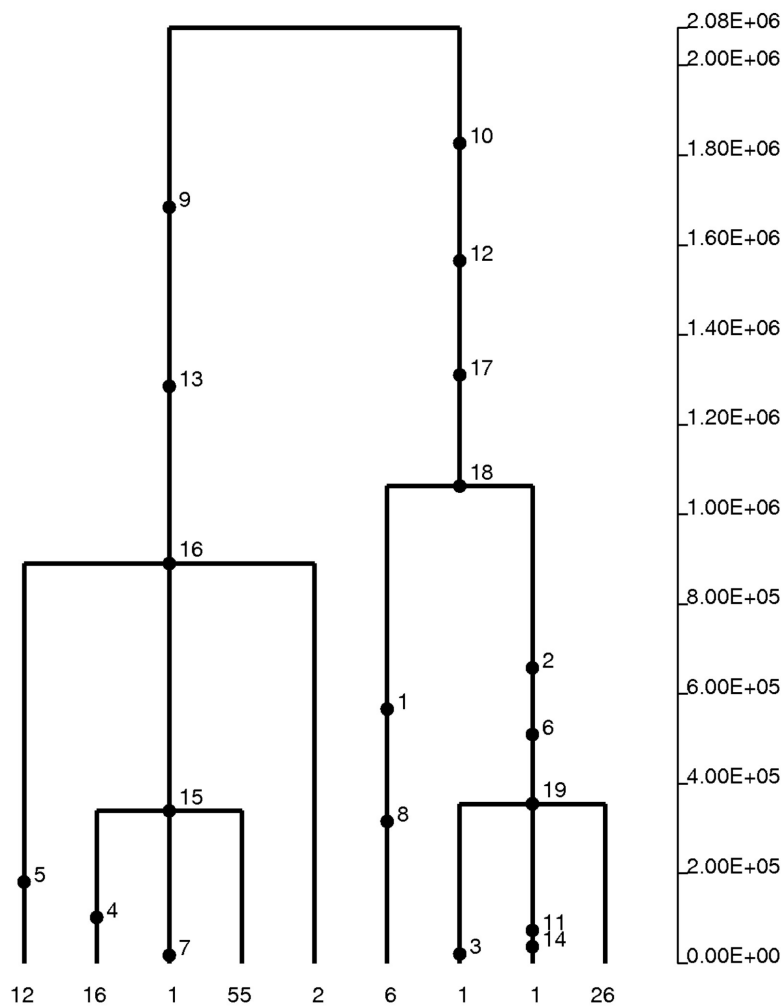


Table 1. Neuromuscular cohort. Age, FIQ, VIQ and PIQ are reported separately for males and females and divided on the basis of disease

Disease	Limb-girdle muscular dystrophy	Spinal muscular atrophy	Facioscapulo humeral muscular dystrophy	Congenital myopathy	Hereditary peripheral neuropathy	All
Males (n)	22	4	3	4	3	36
Females (n)	15	3	4	5	7	34
Males, age (SD)	27.23 (13.95)	12.75 (5.5)	27 (6.8)	26.25 (10.76)	36.33 (11.72)	26.25 (14.01)
Females, age (SD)	30.44 (15.15)	21.33 (16.8)	31.25 (9.31)	20.8 (9.23)	30.86 (20.82)	28.46 (16.97)
Males, FIQ (SD)	101.5 (12.88)	103.05 (17.75)	96.00 (14.11)	95.50 (27.39)	82.67 (6.43)	99.03 (15.36)
Females, FIQ (SD)	97.93 (13.63)	95.33 (4.04)	100.50 (2.52)	101.40 (9.79)	103.67 (9.81)	99.59 (10.63)
Males, VIQ (SD)	100.55 (13.25)	101.74 (14.71)	97.33 (13.01)	95.75 (29.5)	87.67 (3.51)	98.81 (14.96)
Females, VIQ (SD)	97.13 (15.49)	94.33 (6.43)	98.50 (5.80)	97 (5.72)	107.57 (13.19)	98.67 (13.13)
Males, PIQ (SD)	103.09 (16.56)	104.50 (23.53)	92.33 (10.69)	97.25 (23.60)	80.33 (17.21)	99.80 (12.18)
Females, PIQ (SD)	102.2 (13.69)	98.67 (11.06)	103.50 (5.92)	108.25 (16.50)	107.45 (7.13)	101.94 (11.56)

Table 2. Results for the MLHKA test performed over the *SNP25* gene region where rs363039 is located.

Fixed substitutions	MLHKA					
	YRI		CEU		EAS	
	k ^a	p	k ^a	p	k ^a	p
30	3.89	1.60x 10 ⁻³	4.46	4.74x 10 ⁻⁴	4.46	4.42x 10 ⁻⁴

^a selection parameter (k>1 indicates an excess of polymorphism compared to divergence; k< 1 indicates the opposite situation)

Table 3. Association analysis of rs363043, rs6039787 and rs3787297 with cognitive performance in the child cohorts

SNP	age group	Sex (n)	Test	Score (SD)			F	P
rs363043	3-8 years	Males (81)	V/I	CC	CT	TT	0.88	0.42
			Block	9.65 (2.39)	10.28 (3.16)	10.79 (3.29)		
	3-8 years	Females (104)	V/I	12.12 (2.82)	11.86 (3.44)	10.14 (4.29)	1.8	0.17
			Block	9.38 (2.66)	9.78 (2.92)	9.57 (3.82)	0.23	0.79
	9-12 years	Males (81)	V/I	11.50 (2.96)	10.87 (3.50)	12.57 (1.90)	1.09	0.34
			Block	8.69 (3.55)	8.70 (3.01)	8.40 (4.51)	0.02	0.98
	9-12 years	Females (75)	V/I	10.43 (3.44)	11.11 (2.95)	13.00 (4.42)	1.46	0.24
			Block	9.09 (3.77)	8.11 (2.76)	9.00 (3.65)	0.73	0.49
	combined	Males (189)	V/I	10.73 (2.98)	10.92 (2.97)	10.29 (1.98)	0.20	0.82
			Block	9.16 (3.05)	9.39 (3.15)	10.16 (3.67)	0.74	0.48
	combined	Females (179)	V/I	11.26 (3.24)	11.44 (3.17)	10.89 (4.40)	0.20	0.82
			Block	9.27 (3.07)	9.11 (2.96)	9.29 (3.60)	0.06	0.94
rs6039787	3-8 years	Males (81)	V/I	CC	CT	TT	0.97	0.38
			Block	10.18 (3.05)	9.27 (1.74)	13.00 (n.a.)		
	3-8 years	Females (104)	V/I	11.28 (3.40)	12.91 (2.84)	14.00 (n.a.)	1.39	0.26
			Block	9.64 (2.82)	9.00 (3.19)	n.a.	0.56	0.45
	9-12 years	Males (108)	V/I	11.18 (3.15)	10.62 (3.28)	n.a.	0.36	0.55
			Block	8.23 (3.36)	9.50 (2.47)	n.a.	1.58	0.21
	9-12 years	Females (75)	V/I	10.40 (3.50)	10.67 (2.31)	n.a.	0.06	0.80
			Block	8.84 (3.09)	6.43 (3.46)	n.a.	3.72	0.06
	combined	Males (189)	V/I	10.78 (2.56)	10.86 (1.95)	n.a.	0.01	0.94
			Block	9.06 (3.36)	9.39 (2.10)	13.00 (n.a.)	0.83	0.44
	combined	Females (179)	V/I	10.78 (3.47)	11.74 (2.78)	14.00 (n.a.)	1.21	0.30
			Block	9.32 (2.95)	8.10 (3.43)	n.a.	2.86	0.09
rs3787297	3-8 years	Males (81)	V/I	CC	CT	TT	1.13	0.32
			Block	10.06 (3.08)	9.64 (2.42)	12.00 (2.94)		
	3-8 years	Females (104)	V/I	11.08 (3.44)	12.05 (3.17)	14.00 (1.41)	1.82	0.17
			Block	9.45 (2.76)	9.88 (2.96)	9.25 (4.56)	0.23	0.79
	9-12 years	Males (108)	V/I	11.24 (3.30)	11.08 (2.28)	9.00 (5.35)	0.95	0.39
			Block	8.52 (3.57)	8.06 (2.66)	10.00 (3.61)	0.58	0.56
	9-12 years	Females (75)	V/I	10.26 (3.85)	10.85 (2.48)	10.33 (2.08)	0.33	0.71
			Block	8.94 (3.12)	7.67 (3.31)	n.a.	2.01	0.14
	combined	Males (189)	V/I	10.98 (2.44)	10.28 (2.61)	n.a.	1.03	0.31
			Block	9.22 (3.43)	8.68 (2.66)	11.14 (3.13)	1.99	0.14
	combined	Females (179)	V/I	10.63 (3.68)	11.32 (2.80)	12.43 (2.51)	1.48	0.23
			Block	9.24 (2.91)	8.98 (3.26)	9.25 (4.57)	0.11	0.89
combined	Males (189)	V/I	11.13 (2.97)	10.75 (2.42)	9.00 (5.35)	1.23	0.30	
		Block	9.24 (2.91)	8.98 (3.26)	9.25 (4.57)	0.11	0.89	

Abbreviations: V/I, Vocabulary/Information; block, Block design; P, uncorrected P value; n.a., not available