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Genetics of Domain-Specific and Time-Dependent Functional Recovery After Acute Ischemic Stroke

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Objective

- Stroke recovery varies widely among individuals despite standardized rehabilitation, suggesting the influence of biological factors beyond clinical severity.
- This study investigated whether genetic polymorphisms are associated with longitudinal functional recovery in patients with acute ischemic stroke undergoing intensive rehabilitation.

Methods

- Thirty-four patients were prospectively assessed at baseline, 1 month, and 6 months after stroke onset.
- Functional outcomes included upper and lower extremity motor function, balance, activities of daily living, emotion and cognition.
- Genotyping was performed for selected single nucleotide polymorphisms related to inflammation, neuromodulatory signaling, and neuroplasticity.
- Longitudinal associations between genotype and functional outcomes were analyzed using generalized estimating equation models.

Table 1. Baseline characteristics of study participants

Characteristics	n = 34
Gender, male/female, n (%)	22 (64.7) / 12 (35.3)
Age, years, mean ± SD (range)	62.9 ± 10.8 (43–85)
NIHSS, mean ± SD (n = 27)	4.2 ± 3.6
mRS, median (range) (n = 32)	3 (1–4)
Lesion side, n (%)	
Left	20 (58.8)
Right	13 (38.2)
Bilateral	1 (2.9)
Lesion location, n (%)	
BG / IC / CR	17 (50.0)
Brainstem	7 (20.6)
MCA territory	6 (17.6)
Other	4 (11.8)
Robotic hand therapy, n (%)	17 (50.0)
Onset-to-rehabilitation, days, median (range)	8 (0–22)
Baseline FMA-UE, mean ± SD	40.0 ± 23.3
Baseline FMA-LE, mean ± SD	24.8 ± 9.5
Baseline BBS, mean ± SD	24.7 ± 19.4
Baseline MBI, mean ± SD	45.0 ± 23.6
Completed 6-month follow-up, n (%)	29 (85.3)

Results

- Inflammation-related genetic variation in C-reactive protein was strongly associated with reduced early recovery in balance and lower extremity motor function.
- Neuromodulatory and plasticity-related genes, including PATJ and catechol-O-methyltransferase were associated with upper extremity motor recovery trajectory.
- LOC105372028 was associated with lower extremity motor recovery trajectory.

Table 2. Three-timepoint GEE analysis: Time × SNP interaction effects on functional outcomes

Outcome	SNP	Time point	β (Effect size)	SE	p-value	q-value (FDR)
FMA-UE	PATJ	1 month	+16.07	4.44	0.000299	**<0.001*** **
		6 months	+24.46	5.87	<0.001	**<0.001*** **
	COMT	1 month	−5.31	2.98	0.074	NS
		6 months	−14.04	3.41	<0.001	**<0.01** **
FMA-LE	LOC105372028	1 month	+10.05	3.00	0.000814	**<0.01** **
		6 months	+8.61	3.10	0.005	**<0.01** **
	CRP	1 month	−3.84	1.12	0.000643	**<0.001*** **
		6 months	+2.13	1.95	0.28	NS
BBS	CRP	1 month	−17.87	2.84	3.22×10^{-10}	**<0.001*** **
		6 months	−9.48	5.01	0.06	NS

Conclusion

- These findings indicate that genetic variation contributes to heterogeneity in post-stroke functional recovery and may help explain individual differences in rehabilitation outcomes.
- Further studies are warranted to validate these findings and explore their implications for precision neurorehabilitation.

Figure 1. Genotype-dependent functional recovery trajectories after acute ischemic stroke