Topical Review

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Stroke Recovery Genetics

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Clinical outcomes after stroke are highly variable, and reasons for these variations are often unexplained. Recovery after ischemic or hemorrhagic stroke begins immediately after acute onset, and many different levels of biological responses are involved.[1] These responses differ in time and between different areas of the affected brain.[2] Recovery after a cerebrovascular event may, therefore, vary from being rapid, without detectable remaining neurological deficits, to prolonged improvement, if any, over months or years. Outcome prediction is consequently difficult and unreliable and often depends on factors with unclear and limited impact.

Factors specific to pathophysiological subtypes of stroke add to the complexity of prediction. Stroke genetics research has shown that genome-wide association (GWA) results for stroke risk differ by subtype (for review on stroke genetics, see Lindgren[3]). The same might be true for stroke recovery because lesion locations vary between stroke subtypes, and different recovery mechanisms may depend on whether cortical/subcortical structures and gray or white cerebral matter are affected. Further indication for differences in outcome between stroke subtypes is that ischemic stroke patients classified as having a cardioembolic mechanism[4] have greater incidence of mortality and disability,[5,6] whereas for large vessel disease strokes, the risk of new events within 30 days is high, >18%.[5] However, it is also likely that some recovery pathways, for example, involved in cerebral ischemia are shared between stroke subtypes.

In addition, biological factors, prevention of recurrent stroke, treatment of concomitant conditions, as well as social supports and amount of poststroke rehabilitation therapies are all relevant during recovery.[7,8] But predictive models based on clinical factors remain limited by imprecision and difficulty with translation to the individual case.[9] This may improve when mechanisms such as brain plasticity[10] and brain stunning[11] and factors that influence these concepts become better defined.

Genetic factors also influence many different aspects of brain function and repair,[12–14] as well as recurrent stroke risk and response to pharmacological interventions, and can, thereby, account for hitherto unexplained variation in stroke recovery.

The majority of studies reviewed here used a candidate gene association design and investigated numerous gene variants' associations with outcomes of mortality, further vascular event, poststroke depression, functional ability, or rehabilitation treatment (Table 1). We categorized 3 different clinical types of stroke outcomes in line with the International Classification of Function and Disability (ICF[39]; Table 1) and also considered outcomes investigated by animal models and different surrogate/intermediate markers, such as biochemical and neuroimaging. The 3 ICF categories in this context are (1) neurological/physical deficit; (2) functional ability; and (3) social participation and illustrate different clinical aspects of stroke recovery. Notably, careful attention to timing is also essential in assessment of recovery because biological mechanisms are activated or deactivated at different time points (Table 2).

Neurological/Physical Deficit

Neurological deficit can be measured according to the National Institutes of Health stroke scale or other neurological assessment scales.[4] These measurements are often used for evaluation of recovery in the acute phase after stroke onset when more complex measurements, such as activity and social participation, are not feasible because of, for example, hospitalization. Several factors may influence the degree of initial neurological deficit (Table 3). These factors may be included in multivariate analyses assessing genetic impact. Until now, few studies have focused on the genetics of initial neurological deficit, although studies at 2 and 4 weeks post stroke have reported an association between brain-derived neurotrophic factor (BDNF) and outcome.[33,34] Large efforts on studying genetic impact on early treatment effects of thrombolysis are underway.[40]

Longer term prognosis on neurological/physical deficit can be grouped into neurological outcomes, stroke recurrence, and mortality. Alterations in the BDNF gene are often studied in stroke recovery. BDNF has a role in brain repair and plasticity and may have an effect on brain recovery.[10] The *BDNF* single nucleotide variation (rs6265, Val66Met; Table 1) influences excitability and outcome.[30,31,33] High-frequency repetitive transcranial magnetic stimulation over the primary motor cortex of the affected hemisphere induces positive effects on motor function, and subjects with the Val/Val genotype have better improvement.[29]

Long-term mortality after stroke and stroke recurrence genetics has been studied in several studies (Table 1). In a Chinese population of large-artery atherosclerosis stroke

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Table 1. Candidate Genetic Associations for Ischemic and ICH Stroke Recovery Outcomes

Gene	Variant/SNP rs Number	Chromosome	Phenotype Outcome Measured	HR/OR/RR; 95% CI	*P* Value	Result	Reference
Neurological/physical deficit							
COX-1	rs1330344, rs10306114, rs3842788, rs5788	9	Vascular outcomes, mortality	rs1330344, HR=1.958; 1.15–3.33	0.013	Increased risk of further event	Cao et al[15]
NINJ2	rs12425791	12	Recurrence in LAA	HR=2.52; 1.04–6.12	0.017	Recurrence of LAA subtype	Zhang et al[16]
	rs11833579	12	Recurrence in LAA	HR=2.13; 1.03–4.40	0.027	Recurrence of LAA subtype	Zhang et al[16]
TLR4	rs4986791, rs4986790	9	Neurological outcome	Haplotype adjusted OR=12.61; 1.42–111.9	0.023	Worsened	Weinstein et al[17]
COL3A1	rs2138533	2	Recurrence, prognosis, mortality	HR=2.98; 1.27–6.98	0.012	Increased death from cardiovascular disease or stroke in lacunar subtype	Lv et al[18]
	rs11887092	2	Recurrence, prognosis, mortality	HR=1.59; 1.04–2.44	0.035	Increased recurrence in atherothrombotic subtype	Lv et al[18]
	rs1800255	2	Recurrence, prognosis, mortality	HR=0.58; 0.36–0.96	0.024	Decreased recurrence in lacunar subtype	Lv et al[18]
GPIIIa, PAI-1, Factor VII, MTHFR, eNOS	GPIIIa PIA1/PIA2, PAI-1 4G/5G, FVII G10976A, MTHFR C677T, eNOS	Several	Stroke, myocardial infarction, death from all cause	N/S	N/S	N/S	Yeh et al[19]
Factor VII	Msp1, insertion	13	Poststroke mortality	N/S	N/S	N/S	Heywood et al[20]
APOE	rs7412, rs429358	19	Early death from stroke	Multiple analyses	Significant	Positive	Gromadzka et al[21]
APOE	rs7412, rs429358	19	1-y neurological impairment, severe functional disability, dependence	N/S	N/S	N/S	Gromadzka et al[22]
APOE	rs7412, rs429358	19	1-y outcome	N/S		N/S	Sarzynska-Dlugosz et al[23]
GPIIb	HPA-3 rs5911 ITGA2B	17	Poststroke mortality	Aa RR=2.42; 0.24–4.71 Ab RR=2.13; 1.09–4.17	<0.05	Significant	Carter et al[24]
Functional ability							
IGF-1	11 SNPs	17	Occurrence, severity, functional outcome	rs7136446, OR=1.46; 1.09–1.96	0.049	rs7136446 associated with favorable functional outcome 24 mo post stroke	Aberg et al[25]
MPO	rs1001179 (G-129-A)	17	Risk of brain infarct, functional short-term outcome—Rankin	A allele G-129-A polymorphism associated with brain infarct size	0.01	Significant	Hoy et al[26]
	rs2333227 (G-463-A)	17	Risk of brain infarct, functional short-term outcome—Rankin	A allele G-463-A polymorphism associated with poorer functional short-term outcome	0.02	Significant	Hoy et al[26]
SIGMAR1	5 SNPs	9	Outcome at 3 mo	N/S	N/S	N/S	Lovkvist et al[27]
APOD	5 SNPs	3	Outcome at 3 mo	N/S	N/S	N/S	Lovkvist et al[27]
GPIII a	rs5918	17	BI	OR=0.56; CI not reported	0.014	Protective	Maguire et al[28]
COX-2	rs20417	9	GOS	OR=2.18; CI not reported	0.015	Risk	Maguire et al[28]
	rs5275	9	mRS	OR=1.61; CI not reported	0.026	Risk	Maguire et al[28]
BDNF	rs6265 (–196 G>A)	11	BDNF polymorphism effect of rTMS on motor recovery post stroke	Upper extremity motor function changes over time: (a) Post-rTMS score minus pre-rTMS score, (b) Follow-up score minus pre-rTMS score	<0.05	Negative influence on rTMS effect in upper limb motor recovery	Chang et al[29]

(*Continued*)

Table 1. Continued

Gene	Variant/SNP rs Number	Chromosome	Phenotype Outcome Measured	HR/OR/RR; 95% CI	*P* Value	Result	Reference
BDNF	rs6265 (–196 G>A)	11	BDNF polymorphism influence on human motor cortex plasticity in acute stroke	Laterality index *t*=2.270	0.036	Excitability significantly higher with no variant	Di Lazzaro et al[30]
BDNF	rs6265 (–196 G>A)	11	Clinical parameters and functional outcome in patients with IS and ICH	Unfavorable outcome of stroke rehabilitation (Rankin Score >2): BDNF–196 GG polymorphism OR=2.18; 1.09–4.35	Not reported	Association with independent factors	Mirowska-Guzel et al[31]
BDNF	rs6265 (–196 G>A), –270 C>T	11	Allelic and genotypic distribution BDNF –196 G>A and –270 C>T polymorphisms; impact of rTMS on serum BDNF concentrations measured before rehabilitation	N/S differences in serum BDNF concentration were observed in patients with different BDNF –196 G>A or –270 C>T genotypes	N/S	No changes detected	Mirowska-Guzel et al[32]
BDNF	rs6265 (–196 G>A)	11	Recovery 1 mo post IS	Change scores	0.036	Poor recovery	Cramer et al[33]
			Recovery 3 mo post IS	Change scores	N/S	Poor recovery	Cramer et al[33]
BDNF	rs6265 (–196 G>A)	11	2 wk post stroke	OR=1.87; 0.92–3.78	0.027	Recovery	Kim et al[34]
			1 y post stroke	OR=1.53; 0.64–3.37	0.048	Recovery	Kim et al[34]
CYPC19	Loss-of-function alleles *2, *3	10	CYP2C19 polymorphisms on clinical outcomes in IS patients treated with clopidogrel: Functional ability (mRS)	CYP2C19 independent predictor of poor prognosis: OR=3.01; 1.23–7.38	0.016	Carriers significant influence on clopidogrel response and prognosis	Qiu et al[35]
APOE	rs7412, rs429358	19	Recovery 1 mo post IS	Change scores	0.023	Significantly poorer recovery in presence of APOE ϵ4	Cramer et al[33]
			mRS 3 mo post IS	Change scores	0.029	Significantly poorer mRS in presence of APOE ϵ4	Cramer et al[33]
CRP	rs1130864	1	Functional ability	Additive adjusted OR=1.51; 1.09–2.09 Recessive adjusted OR=1.27; 1.08–1.50	0.013 0.008	T allele of rs1130864 TT+CT genotypes of rs1130864 strongly predicted functional disability	Guo et al[36]
COMT	rs4680	22q11	BI, RMA, on admission, after 4 wk, after 6 mo	Multiple ANOVA	0.002	Carriers of COMT Val/Val alleles better results in BI and RMA than COMT Met/Met carriers at all 3 time points	Liepert et al[37]
Social participation							
SERT	rs25531	17	PSD	N/S	N/S	N/S	Kohen et al[38]
	5-HTTLPR	17	PSD	5-HTTLPR s/s genotype higher odds of PSD compared with l/l or l/xl genotype carriers OR=3.1; 1.2–8.3	0.045	3-fold higher risk if carrier	Kohen et al[38]
	STin2 VNTR	17	PSD	*STin2* 9/12 or 12/12 genotype higher odds of PSD compared with *STin2* 10/10 genotype carriers OR=4.1; 1.2–13.6	0.01	4-fold higher risk if carrier	Kohen et al[38]

BDNF indicates brain-derived neurotrophic factor; BI, Barthel index; GOS, Glasgow outcome scale; HR, hazard ratio; ICH, intracerebral hemorrhage; IS, ischemic stroke; LAA, large-artery atherosclerosis; mRS, modified Rankin Scale; N/S, not significant; OR, odds ratio; PSD, poststroke depression; RMA, Rivermead motor assessment; RR, relative risk; rTMS, repetitive transcranial magnetic stimulation; and SNP, single nucleotide polymorphisms.

cases, a signal on Chr12p13 predicted stroke recurrence,[16] and this variant has also been associated with stroke risk in some but not all populations of European descent.[41,42]

Functional Outcome

Several genetic studies focus mainly on functional ability after stroke at a range of time points (Table 1). Many have concentrated on Apolipoprotein E (APOE) and BDNF gene variants. Functional ability can be measured with several assessments, including the modified Rankin Scale, Barthel index, Glasgow outcome scale, and other measures of activities of daily living.[43]

APOE gene variants have been related to stroke risk[44] and may also play a role in stroke recovery, although results have

Table 2. Key Points for Studies on Stroke Recovery Genetics

Categorization of variables
Primary outcome variable may differ between studies
Neurological/physical impairment
Functional outcome
Social participation
Animal models
Surrogate/intermediate markers
Concomitant/confounding factors including the following
Premorbid conditions
Stroke phenotype definition: infarct/hemorrhage; TOAST classification
Highly predictive clinical variables, for example, age, sex, stroke risk factors, measure of stroke severity, and lesion size
Treatment post stroke
Time points for evaluation: days, weeks, months, years
General key points
Stroke outcomes are highly heterogeneous and unpredictable
Reported findings from genetic studies for stroke outcome often used candidate approaches, and many results have not been replicated
Other approaches such as genome-wide association studies are currently in progress

TOAST indicates Trial of Org 10172 in Acute Stroke Treatment.

been equivocal (Table 1).[33,45,46] See also below in Surrogate/Intermediate Markers and Intracerebral Hemorrhage (ICH) sections.

The BNDF (rs6265, Val66Met) variation has been reported to be associated with improved recovery, although subsequent findings showed somewhat contradictory results.[47,48] Another study reported less favorable effect of rehabilitation on outcome after stroke in patients with the BDNF −196 GG (Val) polymorphism[31] (see also the BDNF section in the Neurological/Physical Outcome section earlier and the Surrogate Marker section later).

Other examples of genes reported to be related to functional outcome, for example, Aberg et al,[25] Hoy et al,[26] Maguire et al,[28] and Liepert et al,[37] are mentioned in Table 1, although these studies need replication.

Social Participation

This category of stroke recovery can be assessed with metrics, such as quality of life scores. It is also possible to include depression into this category because social engagement is diminished in people experiencing depression.[49,50] Several covariates known to influence psychosocial aspects are included in multivariate models examining genetic influence on social participation after stroke (Table 3).

Genetic signals associated with poststroke depression and emotional incontinence have mostly been limited to serotonin pathways or regions of serotonergic genes.[51] The serotonin transporter (SERT) gene has been widely investigated for association with depression, but the exploration of association with poststroke depression has been limited. One study reported an association between poststroke depression and the SERT gene polymorphisms STin2 VNTR and 5-HTTLPR after adjustment for age, sex, and National Institutes of Health stroke scale scores[38] (Table 1), and another small case–control study found the S_A and L_G alleles of 5-HTTLPR/rs25531 to be more common in depressed stroke participants.[52]

Animal Models and Surrogate Markers for Studying Stroke Recovery Genetics

Because of space limitations, this review does not contain a detailed account on stroke recovery genetics in animal models. However, some examples can be mentioned: animal model results support the presence of genetic determinants of outcome[53] and indicate genetic impact on cerebrovascular collateral density and infarct lesion size.[54] Animal models can also examine if genetic variations detected in humans have an impact on poststroke outcome.[47]

Surrogate/intermediate markers for studying stroke recovery genetics are increasingly being explored and include biochemical and neuroimaging analyses.

Biomarkers associated with cellular repair, reorganization, and remodeling after an acute event may have effect on outcome after stroke. In apoptosis and cell activation after ischemic injury, many complex signaling pathways are at work, and to identify those relevant to stroke recovery requires integrated understanding of involved multifaceted molecular processes.[1]

Even though one approach is to study how genetic factors influence stroke outcome in patients with similar or identical cerebral lesions, another method is to search for genetic factors related to lesion volume because the infarct size predicts stroke outcome.[55] The use of magnetic resonance imaging for stroke outcome prediction shows that several magnetic resonance imaging parameters correlate highly with favorable stroke outcome,[56] and this may increase the potential to detect genetic information related to recovery. Diffusion and perfusion-weighted magnetic resonance imaging can be used to measure infarct volume in patients with and without a specific genetic trait, for example, APOE ε4 genotype[57] (Table 1).

Cortical plastic changes after acute stroke may also be influenced by genetic factors. One study showed that repetitive transcranial magnetic stimulation inducing long term potentiation-like activity differed less between the affected and unaffected hemisphere in patients with the BDNF rs6265, Val66Met polymorphism than those without, and the authors proposed that this may be beneficial in less severe strokes but unfavorable in severe strokes,[30] suggesting that genetic variations may play alternative roles in different settings.

ICH and Recovery

Some genetic variations have similar effects in both ischemic and hemorrhagic stroke, whereas other variations have specific influence on outcome for certain stroke subtypes, for example, ICH or a particular subtype of ICH. There are several remarkable studies on genetic influence on ICH outcome: APOE studies have yielded results where poor outcome and increased mortality after lobar ICH have been associated with the APOE ε2 variant.[58] In addition to candidate gene studies, a genome-wide complex trait analysis using data from GWA analyses calculated that apart from

Table 3. Factors That May Influence Different Types of Clinical Outcomes After Stroke

Group of Factors	Specific Factor	Example of Measurement Types/Specific Factors	Possible Influence on Outcome Type:
Demographic	Age	Years	IND, FO, SP
	Sex	Female/male	IND, FO, SP
Premorbid	Premorbid disability	Modified Rankin Scale	IND, FO, SP
	Concomitant diseases	Vascular risk factors (eg, hypertension, heart disease, diabetes mellitus, smoking)	IND, FO, SP
	Education	Educational level	SP
Acute stroke situation	Initial stroke severity	NIH stroke severity scale	IND, FO, SP
	Stroke subtype	Ischemic/hemorrhagic stroke	IND, FO, SP
		Ischemic stroke according to TOAST/CCS criteria	IND, FO, SP
	Lesion characteristics	Lesion volume (mL)	IND, FP, SP
		Lesion location (cortical/subcortical/ brain stem/cerebellum)	IND, FP, SP
Poststroke situation	Rehabilitation	Yes/no	FO, SP
	Depression	MADRS	FO, SP
	Social support	Access to services	FO, SP
	Living situation	Alone/with someone	FO, SP
	Housing situation	Home/institution	FO, SP
	Complications after stroke	Infection	FO, SP
		Deep vein thrombosis	FO, SP
		Falls	FO, SP
		Nutritional problems	FO, SP
	Recurrent stroke	Yes/no	FO, SP
	Concomitant medications	Antidepressants (SSRI, tricyclics, etc)	FO, SP
		Stimulating drugs (eg, amphetamines)	FO, SP
Genetics	Genetic variants	Description of genetic variation	IND, FO, SP

CCS indicates the Causative Classification of Stroke System; FO, functional outcome; IND, initial neurological deficit; MADRS, Montgomery-Asberg Depression Rating Scale; NIH, National Institutes of Health; SP, social participation; SSRI, selective serotonin reuptake inhibitor; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

the APOE loci, there was a 41% heritability for 90-day ICH mortality.[59] A recent study found an association between a haptoglobin allele variant and lower odds of favorable modified Rankin Scale (described as modified Rankin Scale score 0–2) outcome.[60] Also genetic factors influencing intermediate ICH risk factors may influence outcome because a report showed that a genetic risk score based on 42 single nucleotide polymorphisms related to blood pressure was related to poor clinical outcome at 90 days specifically for individuals with deep ICH.[61]

Epigenetics and Gene–Gene Interaction

Epigenetic mechanisms regulating the DNA transcription have a potential role in stroke recovery and can modulate several downstream pathways—for review see Elder et al.[62] Micro-RNA in an ischemic brain area can be up- and down-regulated during different time points of the spontaneous recovery phase of ischemic stroke,[53] indicating how different biochemical pathways are controlled. Genetic influence on epigenetic mechanisms and epigenetic influence on genetic expression are potentially important targets for understanding and enhancing stroke recovery.

Even though most studies have examined only 1 or 2 candidate genes with regard to stroke recovery, it is possible that gene–gene interaction also plays a role in the stroke recovery genetics. One example is a study showing that epistatic interactions between the BDNF, fibroblast growth factor 2, and vascular endothelial growth factor genes may influence stroke recovery.[63]

Pharmacogenetics and Stroke Recovery

Evidence is emerging on the modulation and influence of certain pharmacological agents on brain plasticity and subsequent improved stroke functional outcome. It other complex diseases, pharmacological responses vary depending on genetic variations, and effect sizes are compelling. One example is how genetic polymorphisms affect the response to L-dopa treatment.[64,65]

One class of medications showing promise in stroke is the selective serotonin reuptake inhibitor class. For patients with moderate to severe strokes, fluoxetine plus physiotherapy resulted in enhanced motor recovery at 3 months that seemed to persist ≤12 months.[66,67] Whether the stroke recovery response to selective serotonin reuptake inhibitor treatment is influenced by genotype, for example, the SERT 5-HTTLPR genotype, discussed earlier, remains to be investigated.

Of great clinical interest is whether response to tissue-type plasminogen activator treatment is influenced by genetic factors. A study of 140 single nucleotide polymorphisms in ischemic stroke patients treated with tissue-type plasminogen activator reported that variants in the *IL1B* and *vWF* genes were associated with early recanalization and suggested a relation to activity of coagulation factors.[40] In a microarray study, patients with hemorrhagic transformation after tissue-type plasminogen activator treatment had altered expression of genes related to apoptosis and neutrophil regulation pathways.[68]

The genetic impact on metabolism and response to anticoagulation therapy would have important clinical consequences for stroke recovery. Genetic polymorphisms in the cytochrome P-450 enzyme *CYP2C9* gene are related to metabolism of vitamin K antagonists. Variants in the *VKORC1* gene coding for vitamin K epoxide reductase are associated with variability of the anticoagulation effect of warfarin.[69] The risk of warfarin-related lobar ICH may be increased in *APOE* ε2 and *APOE* ε4 carriers,[61] although it is unclear whether these observations can be used in clinical practice. One study reported that presence of the *CES1* rs2244613 minor allele resulted in lower active dabigatran metabolite levels and lower risk of hemorrhagic complications, although no increased risk of ischemic events was detected.[70] Future studies may show other genetic variants related to the effect of non–vitamin K antagonist oral anticoagulants.

The clinical effect of genetic variations affecting clopidogrel metabolism is not clearly established. However, a study of ischemic stroke patients treated with clopidogrel showed worse prognosis at 6 months in carriers of the *CYP2C19* loss of function allele.[35]

Future Directions

There are several long-term goals of genetic studies on stroke recovery. These include the understanding of genetic influence on brain plasticity and repair with subsequent intervention possibilities; detection of metabolic pathways that can be targeted with different types of treatments; pharmacogenetics for individualized treatment; improved prognostic accuracy; and improved rehabilitation methods. Alternative approaches to candidate gene studies are emerging. GWA studies examine many thousands of genetic variations simultaneously and have been highly successful in establishing new genetic factors influencing stroke risk.[3] The ongoing multicenter GISCOME (Genetics of Ischemic Stroke Outcome) study uses GWA data to search for single nucleotide polymorphism variants associated with stroke recovery.[71] Strengths of GWA studies are that they have no preconceived assumption that a specific gene causes the phenotypic observation and that large parts of the genome are examined. GWA study limitations include inadequate capacity to detect rare genetic variants, that advanced statistical analyses involved carries a risk of misinterpretation, and that imbalance between included subject groups may produce biased results. New, recently developed techniques for copy number variation studies, exome sequencing, whole genome sequencing, and epigenetic studies, plus the aid of sophisticated mathematical analyses will lead to better understanding of stroke recovery genetics.[3] To quantify the genetic heritability component influencing stroke recovery, the recently developed genome-wide complex trait analysis method can be applied in a similar way as described for stroke risk and mortality,[59,72] using data from GWA studies, for example, GISCOME. Replication attempts for already reported preliminary associations and gene–environment, gene–phenotype, and gene–gene interactions also need to be considered. Most importantly, future research in recovery requires clarity and consensus about time points for assessing different types of outcome, outcome phenotype definitions—preferably adhering to the ICF classification, and consideration of rehabilitation and other interventional treatments that may have influence in outcome studies.[73] Pharmacogenetic implications and other treatment methods may be the most likely clinical goals to profit from stroke recovery genetics research in the nearest future. Pooling data from large cohorts in, for example, the International Stroke Genetics Consortium (ISGC) (http://www.strokegenetics.org/) will be pivotal to obtain the large sample sizes required for many of these complex genetic studies. The ISGC supports several groups working on short- and long-term outcome after stroke, publication efforts in the field, and project proposals for recovery studies. ISGC workshops, occurring twice a year, allocate time for sessions on stroke recovery, including planning of forward directions.

Conclusions

Until now, many studies on stroke recovery genetics have been candidate gene studies. Several results warrant further investigation. Other methods have also been used, and recent advances in biochemistry and bioinformatics hold promise for the future. However, careful description of clinical phenotypes, interventional treatment, and appropriate selection of clinical or surrogate/intermediate primary outcome variables describing the recovery is crucial. A better understanding of genetic influence on stroke recovery is expected to support the development of new beneficial treatments for stroke patients.

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