[Frontiers In Bioscience, Landmark, 23, 1338-1359, March 1, 2018]

Towards precision medicine in ischemic stroke and transient ischemic attack

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1. ABSTRACT

Although there is no consensus on the exact definition of precision medicine, it is generally agreed upon that the term entails diagnosis and therapy tailored to the individual patient. Precision medicine has seen major advances in the past two decades, many of which are relevant to ischemic stroke or transient ischemic attack (TIA). Advances include substantial improvements in high-throughput technologies, collaborations between the fields of biology and medicine, increasingly advanced biomedical informatics, the development of multimodal brain imaging techniques, as well as the widespread usage of electronic medical records and big data. Precision medicine in ischemic stroke or TIA is still in its infancy, but there have already been changes in clinical care from a one-size-fits-all model to a more precise, individualized approach. However, further studies are urgently needed to bridge the gaps between clinical studies and precision clinical practice. We discuss here the advances and challenges for precision medicine in ischemic stroke or TIA at its current stage, focusing on genetic predispositions, pharmacogenetics, omics, brain imaging and big data.

2. INTRODUCTION

The concept of precision medicine (PM), or the use of prevention and treatment strategies that take individual variability into account, can be traced back to more than a century ago. The ABO blood group system, identified by Karl Landsteiner in 1900, is the foundation of modern transfusion therapy. In 2011, the report “Toward Precision Medicine” was approved by the Governing Board of the National Research Council and emphasized the urgency of building a knowledge network for biomedical research to modernize disease taxonomy. The report addressed the feasibility, need, scope, impact, and consequences of creating a “new taxonomy of human diseases based on molecular biology” (1). With the innovation of human genome

sequencing technology and powerful methods to analyze biomedical informatics and big data, precision medicine can and should be incorporated into patient care. (2)

In 2015, the President of the United States announced a research initiative that aims to accelerate progress toward a new era of precision medicine (www.whitehouse.gov/precisionmedicine) (2). In 2016, China launched a national key research and development program for precision medical research. These initiatives represent unprecedented opportunities for experts in ischemic stroke to develop more detailed patient profiles, obtain more in-depth understanding of responses to treatment, and ultimately identify an optimal treatment for a given patient (3). Although the PM for ischemic stroke or TIA is still in its infancy, clinical care has already begun to shift from a one-size-fits-all model toward a more precise, individualized approach. In this review, we summarize the current progress of precision medicine for ischemic stroke or TIA, focusing on disease-causing genes, genetic predispositions, pharmacogenetics, omics, brain imaging and big data.

3. MONOGENIC STROKE DISORDERS

Several mendelian disorders can cause stroke, defined as monogenic stroke (4-6). Testing of the disease-causing genes is the gold standard for the diagnosis of monogenic stroke (Table 1). With the improvements in next-generation sequencing technologies, the potential causative genes are directly distinguished (7). The primary and secondary preventions of sporadic stroke might not be suitable for all monogenic stroke. For example, an enzyme replacement therapy (ERT) with recombinantα-galactosidase A (α-gal) has shown benefits for patients with Fabry' disease early in their disease. Drugs affecting mitochondrial respiratory chain could not be used for patients with MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke). Detail discussion of these monogenic disorders is beyond the scope of this review. Although the monogenic stroke is relatively rare, our understanding of monogenic stroke would help us to further reveal of the etiology and pathophysiology of sporadic stroke.

4. GENETICS OF SPORADIC ISCHEMIC STROKE

Most strokes are sporadic strokes, which are complex diseases. In the past, the candidate gene association study approach was the most common method used for analysis. Using the the genome-wide linkage analysis, the genes encoding phosphodiesterase 4D (PDE4D) and 5-lipoxygenase activating protein (FLAP) conferred risk of ischemic stroke in an Icelandic population (DeCODE) (8, 9). However, some studies failed to replicate these findings and others reported conflicting conclusions (10-12).

The genome-wide association studies (GWAS) approach has revolutionized the field of complex genetics and is now having a major impact on the understanding of stroke genetics, confirming the heritability of ischemic strokes (4, 13). Studies have shown that heritability was 37.9% for all patients and varied markedly among different stroke subtypes, with 40.3% for large-vessel, 32.6% for cardioembolic and 16.1% for small-vessel stroke (14). The GWASs of ischemic stroke are listed in Table-2, though not all of them were further validated in the following replicated studies and large-scale meta-analysis (15-18). The METASTROKE collaboration was established by the ISGC (International Stroke Genetics Consortium) to combine the GWAS datasets for ischemic stroke, including 15 cohorts for the discovery stage and 18 cohorts for the replication stage (19). This meta -analysis verified previous associations for cardioembolic stroke near *PITX2* (pituitary homeobox 2) and *ZFHX3* (zinc finger homeobox 3 gene), as well as for large-vessel stroke at a 9p21 locus (Cyclin-Dependent Kinase Inhibitor, *CDKN2A/CDKN2B*) and *HDAC9* (Histone deacetylase 9) (19). More and more studies have shown that beyond these specific genetic variations, the susceptible SNPs among European, African, and Asian populations were identical (20-22). The genetic variants confirmed in the METASTROKE collaboration were nominally associated (p<0.0.5). with ischemic stroke in the COMPASS (Consortium of Minority Population Genome-Wide Association Studies of Stroke) trial in African Americans (20).

The NINDS-SiGN (National Institute of Neurological Disorders Stroke Genetics Network) is an international consortium that has taken a systematic approach to phenotyping and has produced the largest GWAS in ischemic stroke to date. The results of the GWAS on NINDS-SiGN have confirmed four loci robustly associated with ischemic stroke, including *PITX2* and *ZFHX3* for cardioembolic stroke and *HDAC9* for large-vessel stroke (22). The EuroCLOT study further confirmed the subtype-specific associations between genetic variants and ischemic stroke. The rs505922 of the *ABO* (ABO histo-blood group) gene has been associated with large-vessel and cardioembolic stroke, but not with small-vessel stroke (23). Ischemic stroke (IS) and coronary artery disease (CAD) share several risk factors, especially for large-vessel stroke. A large-scale meta-analysis was conducted to evaluate the extent of shared genetic determination between the two diseases, including GWAS data from METASTROKE, Coronary Artery Disease Genome wide Replication and Meta-analysis (CARDIoGRAM), and Coronary Artery Disease (*C4D*) Genetics consortia (24). In this joint meta-analysis, 17

Table 1. Summary of several monogenic stroke

Syndrome	Inheritance	Chromosome	Gene	Stroke subtype	Symptoms
CADASIL	Autosomal dominant	19p13	NOTCH3	Small-vessel stroke	Migraine, stroke, depression, cognitive diaorders, seizures,
CARASIL	Autosomal recessive	10q26.3	HTRA1	Small-vessel stroke	Premature baldness; severe low back pain, spondylosis, stroke, cognitive problems
Fabry's disease	X-linked	X	GLA	Large-artery stroke, and small-vessel stroke	Episodes of pain in hands and feet, acroparaesthesis angiokeratomas, stroke, corneal opacities, cataract, renal and cardiac failure
MELAS	Maternal	Mitochondrial DNA	mtDNA (Several)	Complex (microvascularand neuronal factors)	Developmental delay, short stature, stroke-like episodes, Muscle weakness, sensorineural hearing loss, diabetes, migraine-like headache, seizures, cognitive decline
Sickle cell disease	Autosomal recessive	11p15.5	HBB	Large-artery stroke, small-vessel stroke, hemodynamic insufficiency and prothrombotic state	Anemia, stomachache or headache episodes, infections, stroke, affection of lungs including pulmonary hypertension, renal impairment, Splenomegaly, Sickle-cell crisis, myelopathy
Homocystinuria	Autosomal recessive	21q22.3, 1p36.3 and other	CBS, MTHFR, and other	Large-artery stroke, cardioembolism,small-vessel stroke, arterial dissection	multi-systemic disorder. Mental retardation, cognitive problems, myopia, osteoporosis, skeletal abnormalities, thromboembolic events, lens dislocation, thromboembolic events
Marfan's syndrome	Autosomal dominant	15q21.1	FBN1	Cardioembolism stroke and arterial dissection	Lens dislocation, cataract, myopia, aortic aneurysm, dilation or dissection of the ascending aorta, cerebral aneurysms, cerebral hemorrhage, arthritis, tall habitus, Pectus carinatum or excavatum, lumbosacral dural ectasia,
Pseudoxanthoma elasticum	Autosomal recessive		ABCC6	Large-artery stroke ,small-vessel stroke, and arterial dissection	Papules in flexor areas of skin, increased elasticity and yellow-orange papular lesions, visual loss, hypertension, arterial dissection
Ehlers-Danlos syndrome type IV	Autosomal dominant	2q31	COL3A1	Arterial dissection	Joint hypermobility and easy bruising, easily bruised skin, arterial dissection, cerebral aneurysm, short stature, intestinal and uterine fragility, joint subluxation, internal bleeding
HERNS	Autosomal dominant	3p21.31	TREX1	Small-vessel disease	Stroke-like episodes, White matter lesions, Visual loss, cognitive problems, renal dysfunction
Familial cerebral amyloid angiopathy	Autosomal dominant	21q21.3 and other	APP and other	Rupture of cortical cerebral small vessels	starting in mid-adulthood: white-matter lesions, cognitive impairment, Cerebral lobar hemorrhages
COL4A-related brain small vessel disease	Autosomal dominant	13q34	COL4A1, and COL4A2	Rupture of cortical and subcortical cerebral small vessels	white matter lesions, seizures, migraine, transient ischaemic attacks lobar and non-lobar hemorrhagic stroke, congenital porencephaly

CADASIL: Cerebral autosomal dominant subcortical infarcts and leukoencephalopathy; CARASIL: Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; HERNS: Hereditary endotheliopathy with retinopathy, neuropathy and stroke; MELAS: mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke; NOTCH3: Neurogenic locus notch homolog protein 3; HTRA1: HtrA Serine Peptidase 1; GLA: Galactosidase Alpha; mtDNA: mitochondrial DNA; HBB: hemoglobin subunit beta; CBS: cystathionine-beta-synthase; MTHFR: methylenetetrahydrofolate reductase; FBN1: fibrillin 1; ABCC6: ATP binding cassette subfamily C member 6; COL3A1: collagen type III alpha 1 chain; TREX1: three prime repair exonuclease 1; APP: amyloid beta precursor protein; COL4A1: collagen type IV alpha 1 chain; COL4A2: collagen type IV alpha 2 chain.

loci passed genome-wide significance for large-vessel stroke or CAD (24). These included variants at the 9p21 locus (25, 26), *ABO* and *HDAC9* (27, 28). Several novel loci, which were associated with ischemic stroke or large-artery stroke, have been identified recently, including *MMP12*(29), *PTCSC3* (30), and *ALDH2* (31). All of these studies shed light on the different pathogenic pathways underpinning stroke subtypes. It is necessary to further evaluate the functions and mechanisms of these susceptible genetic variants (32).

The prediction of genetic predispositions allowed for the identification of individuals at elevated risk of ischemic stroke. The CHARGE risk score project attempted to improve the prediction of future strokes based on associated SNPs and risk factors, but there was only limited improvement when compared to the classic Framingham stroke risk score (33). The polygenic risk score (polyGRS) is based on the idea that a few strong indicators, as well as several weaker indicators, can be jointly informative to determine IS risk. It was recently investigated and shown to be superior to weighted multi-locus genetic risk scores as an IS prediction model (34).

To date, GWASs have yielded relatively few loci associated with ischemic stroke, in spite of the large sample sizes. In addition to SNPs, CNVs should

Table2. Genetic variants associated with ischemic stroke in GWASs

Chromosomal	Gene	Stroke subtype	Ref	SNP ID	Minor Allele	RAF
6p21.1.	CDC5L/SUPT3H	Large-artery stroke	(15)	rs556621	A	0.2.9
7p21	Hdac9	Large-artery stroke	(22, 24, 27, 28)	rs2107595	A	0.2.5
9p21	CDKN2A / CDKN2B	Large-artery stroke	(24-26)	rs2383207	A	0.3.1
9p21	CDKN2B-AS1 (ANRIL)	Large-artery stroke	(24, 25)	rs1333040	C	0.3.8
11q22	MMP12	Large-artery stroke	(29)	rs660599	A	0.2.2
14q13	PTCSC3	Large-artery stroke	(30)	rs2415317 rs934075 rs944289 rs2787417 rs1952706	G A T T C	0.4. 0.4.4 0.3.9 0.4.2 0.3.9
9q34	ABO	Large-artery stroke; Cardioembolic stroke	(23, 24)	rs505922	C	0.3.5
4q25	PITX2	Cardioembolic stroke	(22)	rs6843082	G	0.4.6
16q22	ZFHX3	Cardioembolic stroke	(22)	rs879324	A	0.2.1
14q22	PRKCH	Small-vessel stroke	(18)	rs2230500	A	0.3.4
11q12	AGTRIL1	All ischemic stroke	(16)	rs9943582	A	0.3.1
12p13	NINJ2	All ischemic stroke	(17)	rs12425791	A	0.2.2
12q24	ALDH2	All ischemic stroke	(31)	rs10744777	T	0.3.0

CDC5L : cell division cycle 5 like; SUPT3H : SPT3 homolog, SAGA and STAGA complex component; HDAC9: histone deacetylase 9; PTCSC3: encoding papillary thyroid carcinoma susceptibility candidate 3; CDKN2A: Cyclin-Dependent Kinase Inhibitor 2A; CDKN2B: Cyclin-Dependent Kinase Inhibitor 2A; CDKN2B-AS1 (ANRIL) : CDKN2B antisense RNA 1; MMP12 : matrix metallopeptidase 12; PTCSC3: encoding papillary thyroid carcinoma susceptibility candidate 3; ABO: ABO histo-blood group, alpha 1-3-N-acetylgalactosaminyltransferase and alpha 1-3-galactosyltransferase; PITX2: paired like homeodomain 2; ZFHX3: zinc finger homeobox 3; PRKCH: protein kinase C eta; AGTRIL1: angiotensin receptor like-1; NINJ2: ninjurin 2; ALDH2: aldehyde dehydrogenase 2 family.

also be accounted for when determining susceptibility to stroke, but there is limited data. Furthermore, most studies focus on common variants, but the rare genetic variants might also contribute to the risk of developing stroke and influence its prognosis. Whole-genome sequence (WGS) and exome-based analysis have already been used in studies of genetic risk factors in ischemic stroke. Participants in the Genetics of Early Onset Stroke (GEOS) have been genotyped by the exome array, which revealed four highly associated variants for all strokes, and several others that were specific for stroke subtypes (35).

There are two major challenges for GWAS in terms of identifying genomic underpinnings of ischemic stroke, which are similar to the process for other complex diseases. One challenge is to identify causal genes within a GWAS-implicated locus, and the other is to identify causal variants for polygenic traits (36). Network analysis of GWAS data is a novel approach that uses information in protein–protein and protein–DNA interaction networks to address these two challenges (36). A Weighted Gene Co-expression Network Analysis (WGCNA) of carotid atherosclerotic plaques has been explored to identify biologically tractable candidates for stroke and stroke subtypes (35).

5. PHARMACOGENETICS AND PRECISION MEDICINE IN ISCHEMIC STROKE

Pharmacogenetics deals with the influence of genetic variants on drug response, including the efficacy and toxicity of drugs (37). It seeks to develop the optimal drug therapy with maximum efficacy and minimal adverse effects, with respect to patient genotypes. The Pharmacogenomics Knowledgebase (PharmGKB, http://www.pharmgkb.org), is a publicly available online knowledgebase responsible for the aggregation, curation, integration and dissemination of related knowledge. It was founded in 2000 and jointly funded by the National Institutes of Health (NIH) and the National Institute of General Medical Sciences (NIGMS), and is a partner of the NIH Pharmacogenomics Research Network (PGRN). The CPIC (Clinical Pharmacogenetics Implementation Consortium) and the DPWG (Dutch Pharmacogenetics Working Group) have updated freely-available, peer-reviewed drug-dosing guidelines for clinicians with access to pre-emptive genetic testing results. These guidelines are available in the PharmGKB.

The biggest challenge was the application of pharmacogenetic markers to clinical decisions related to drug prescription. There are more than 200 Food

and Drug Administration (FDA) drug labels referring to pharmacogenetic biomarkers of drug safety or efficacy. However, only a very small proportion of these drug labels mandate clinicians to test for pharmacogenetic markers. Here, we focus on the pharmacogenetics of antiplatelet and anticoagulation agents, for which we have strong evidence for stroke preventions (Table 3).

5.1. Antiplatelet agents

Platelets contribute to ischemic strokes by playing a key role in the development of atherosclerotic lesions at sites of endothelial activation (38). Antiplatelet agents are commonly used to prevent cerebrovascular events, but the response to antiplatelet therapy is highly variable (39, 40). Up to 20 % of patients treated with antiplatelets continue to experience new thrombotic events, and 8.2.% of patients treated with dual antiplatelet therapy of clopidogrel with aspirin in the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) trial experienced a new stroke within 90 days (41).

5.1.1 Aspirin

Aspirin irreversibly inhibits the cyclo-oxygenase (COX)-1 enzyme by acetylating the serine residue at position 529 (37). The relationship between the response to aspirin with genetic variants of *COX*-1 and several receptors on platelet surfaces was evaluated based on candidate gene association studies (42). Among healthy volunteers and patients with coronary artery disease, participants who were heterozygous for the -842A>G/50C >T haplotype showed significantly greater inhibition of platelet aggregation by aspirin when compared with common allele homozygotes (43, 44). However, these *COX*-1 polymorphisms were not associated with clinical outcomes (45, 46). The platelet glycoprotein (GP) IIb/IIIa receptors are responsible for binding with fibrinogen and cross-linking of platelets, and for the von Willebrand factor (vWF) (47, 48). In a meta-analysis, which included 11 related studies before Dec. 2007, the $PI^{A1/PIA2}$ polymorphism of platelet glycoprotein IIIa (*GP IIIa*) gene was associated with aspirin resistance in healthy subjects, but not in patients with cardiovascular disease (42, 47, 49). No relation was found between aspirin resistance and genetic variants in the 807 C>T of GPIa, the 1622A> G of *P2Y1*, or the H1/H2 of *P2Y12* (42).

In 2013, a GWAS explored the common related genetic variations for response to aspirin (50). The study populations included 565 Amish PAPI (Pharmacogenomics of Anti-Platelet Intervention) study subjects, 227 nonemergent PCI patients from the Sinai Hospital of Baltimore Study and 1,000 patients from the INVEST-GENES (International VErapamil SR/trandolapril Study GENEtic Substudy). This GWAS showed that the rs12041331 in the platelet endothelial aggregation receptor-1 (*PEAR1*) gene was strongly associated with both platelet response and cardiovascular events in patients treated with aspirin alone, as well as in those treated in combination with clopidogrel (50). The rs12041331 reproducibly influenced platelet aggregation in aspirin-treated Danish patients with coronary artery disease (51). *PEAR1* is a platelet trans-membrane protein that becomes activated upon platelet contact. The precise biological mechanism of activation remains unclear.

Both the GWAS and the whole-exome sequencing study reported that several common variants of supervillin (*SVIL*). were associated with inhibition of platelet aggregation as detected by both the PFA-100 and optical aggregometry (52). In spite of the different SNPs in these two studies, these data suggest that genetic variants in SVIL expression contribute to variations in human platelet reactivity and indicate that SVIL plays a role in arterial thrombosis (52).

5.1.2 Clopidogrel

Clopidogrel is widely used for secondary prevention of ischemic stroke and TIA. Recently, the combination of clopidogrel with aspirin has been recommended for initiation within 24 hours of a minor ischemic stroke or TIA (39, 40). Clopidogrel inhibits adenosine diphosphate (ADP) and stimulates platelet aggregation by binding irreversibly to a specific platelet receptor of ADP, $P2Y_{12}$ (53). Clopidogrel requires transformation into an active metabolite by cytochrome P450 (CYP) isoenzymes for its anti-platelet effect. CYP2C19 has a crucial role in the metabolism of clopidogrel (54).

The *2 (681G>A, dbSNP rs4244285), *3 (636G>A, dbSNP rs4986893) and *17 (−806C>T, dbSNP rs12248560) polymorphisms were the most common variants in the *CYP2C19* gene (55, 56). A number of studies have suggested that the carriage of *CYP2C19* loss-of-function alleles (*2 and *3) were associated with increased cardiovascular events in patients treated with clopidogrel, particularly after coronary stenting (57-62). The gain-of-function variant is associated with a lower risk of cardiovascular events and with a higher risk of bleeding (63-65). However, substantial heterogeneity was observed among the studies. The carriers of *CYP2C19* loss-of-function alleles did not increase the risk for cardiovascular events, with a sample size of ≥500 patients (63). Although there was an association between the *CYP2C19* genotype and clopidogrel responsiveness, there was no significant association between genetic variants and cardiovascular events in the original randomized controlled trial (RCT), which included the ACTIVE-A, CURE, CHARISMA and CLARITY-TIMI 28 trials (66, 67).

Table 3. The association between several common SNPs and therapy effects of Aspirin, Clopidogrel and Warfarin

Drug	Gene	Gene Product	Nucleotide change or alternative name	SNP ID	Minor Allele	MAF	Conclusion
Aspirin	PTGS1	COX-1	-842A>G/50 C >T	rs10306114/ rs384287	G/T	0.05/0.24	No association
	PTGS2	COX-2	-765G>C	rs20417	G	0.20	No association
	ITGB3	GPIIIa	PIA1/A2, 176T>C	rs5918	C	0.09	Potential association
	ITGA2	GPIa	807 C>T	rs1126643	T	0.34	No association
	P2RY1	P2Y1	1622A> G	rs701265	G	0.37	No association
	P2RY12	P2Y12	H1/H2	constituted by rs10935838/ rs2046934/ rs5853517/ rs6809699	A/G/T/A	0.13	No association
	PEAR-1	platelet endothelial aggregation receptor-1	G>A	rs12041331	A	0.33	Potential association
	SVIL	Supervillin	1663C>A	rs7070678	A	0.38	Potential association
Clopidogrel	CYP2C19	cytochrome P450 family 2 subfamily C member 19	*2, 681G>A	rs4244285	A	0.22	Association
			*3,636G>A	rs4986893	A	0.01	Association
			*17,−806C>T	rs12248560	T	0.15	Association
	ABCB1	ATP binding cassette subfamily B member 1	3435C>T	rs1045642	T	0.40	Potential association
			1236C>T	rs1128503	T	0.42	Potential association
	PON1	paraoxonase 1	575A>G	rs662	A	0.46	Potential association
	P2RY12	P2Y12	G>A	rs2046934	G	0.13	No association
	CES1	carboxylesterase 1	G143E, 428G>A	rs71647871	A	0.01	No association
			A>C	rs8192950	C	0.37	Potential association
Ticagrelor	CYP2C19	cytochrome P450 family 2 subfamily C member 19	*2, 681G>A	rs4244285	A	0.22	No association
			*3,636G>A	rs4986893	A	0.01	No association
	ABCB1	ATP binding cassette subfamily B member 1	3435C>T	rs1045642	A	0.40	No association
	SLCO1B1	Solute carrier organic anion transporter family member 1B1	T > C	rs113681054	C	0.22	Potential association
	CYP3A4	cytochrome P450 family 3 subfamily A member 4	G > A	rs62471956	A	0.01	Potential association
			167G>A	rs56324128	T	<0.01	Potential association
	UGT2B7	UDP-Glucuronosyltransferase-2B7	T>C	rs61361928	C	<0.01	Potential association
Warfarin	CYP2C9	cytochrome P450 family 2 subfamily C member 9	* 2, 430C> T	rs1799853	T	0.05	Association
			* 3, 1075A> C	rs1057910	C	0.05	Association
	VKORC1	Vitamin K epoxide reductase complex subunit 1	−1639G>A	rs9923231	T	0.36	Association

The CHANCE trial was a randomized, double-blind, multicenter, placebo-controlled clinical trial, which clarified that for minor ischemic stroke or TIA, greater protection against recurrent stroke could be realized through means other than treatment with aspirin alone. The pre-specified pharmacogenetics sub-study of the CHANCE trial had shown an association between *CYP2C19* genetic variants and clinical efficacy of clopidogrel (41, 68). Clopidogrel combined with aspirin reduced the risk of stroke only in patients without any *CYP2C19* loss-of-function allele (HR, 0.51; 95% CI, 0.35-0.75), when compared to treatment with aspirin alone. In noncarriers, the absolute risk reduction of stroke recurrence was 5.7% between patients on dual- versus mono-antiplatelet therapies. However, carriers did not benefit from clopidogrel in addition to aspirin (HR, 0.93; 95% CI, 0.69 to 1.26). The proportion of carriers was 58.5% among Chinese patients, which is much higher than the proportion among Europeans (68). The SPS3 (Secondary Prevention of Small Subcortical Strokes) study was an international multicenter randomized trial evaluating antiplatelet and antihypertensive approaches to prevent stroke recurrence. The genetic substudy of SPS3 enrolled white, black and hispanic patients. Among white patients, there was a higher probability of recurrent stroke in carriers with at least one *CYP2C19* loss-of-function allele when compared to noncarriers (OR 5.19, 95%CI, 1.08-24.90). However, the association was not significant in the overall cohort (69). A recent meta-analysis of reports published through June 2016 was undertaken, which included 15 studies on patients with ischemic stroke or TIA on clopidogrel. This analysis further confirmed that carriers of loss-of-function alleles have a greater risk of stroke and composite vascular events when compared with non-carriers (RR, 1.92; 95% CI,1.57-2.35) (70-76). Patients carrying two loss-of-function alleles have a higher risk of recurrent stroke than those carrying one loss-of-function allele (70). Non-genetic factors might affect the association between *CYP2C19* and the variability of responses to clopidogrel. A post-hoc analysis of the CHANCE trial has found that the interactions between the carriage of *CYP2C19* loss-of-function allele and clinical efficacy of clopidogrel were attenuated by poor glycemic control, defined as the glycemic albumin level >15.5% (77).

The influence of genetic polymorphisms other than *CYP2C19* on clopidogrel efficacy for acute ischemic stroke or TIA was also evaluated in this meta-analysis (70). In a case-control study that enrolled a total of 268 stroke patients undergoing extracranial or intracranial stenting on clopidogrel with aspirin, the SNPs of *P2Y12* (rs2046934), *PON1* (rs662). and *COX-1* (rs1330344) were associated with recurrent clinical events (78). However, no association was found between the risk of vascular event recurrence and the allelic gene variants modulating clopidogrel absorption (*ABCB1*), metabolic activation (*CES1, CYP3A5, CYP2B6, CYP2C8, CYP2C9* and *CYP3A4*), or biologic activity (*P2Y1* and *ITGB3*), especially in patients with ischemic stroke or TIA (70-73, 75, 78-80).

5.1.3 Ticagrelor

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor $P2Y_{12}$. It is primarily metabolized by the *CYP3A4* enzyme, and has faster onset and produces more pronounced platelet inhibition than clopidogrel (81). The ONSET/OFFSET and RESPOND genotype studies have suggested a superior pharmacodynamic effect of ticagrelor when compared to clopidogrel, irrespective of *CYP2C19* genotype. There was no effect of *CYP2C19* loss-of-function allele on the antiplatelet effect of ticagrelor, when assessed by ADP-induced platelet aggregation, VerifyNow $P2Y_{12}$ assay and vasodilator-stimulated phosphoprotein (VASP) -phosphorylation assay (82). A GWAS based on the PLATO (Platelet Inhibition and Patient Outcomes). trial has found modest effects of three genetic loci (*SLCO1B1, UGT2B7, and CYP3A4*). on ticagrelor plasma levels, which could not be translated into any detectable effects on clinical efficacy or safety (83). Another genetic substudy of the PLATO trial has shown that ticagrelor was more effective for acute coronary syndromes than clopidogrel, irrespective of *CYP2C19* and *ABCB1* polymorphisms (84). To date, there is no pharmacogenetic data for stroke patients treated with ticagrelor.

5.2. Anticoagulation agents

Warfarin has been widely used as an oral anticoagulant for secondary prevention of cardioembolic stroke. It is a mixture of the enantiomers of S-warfarin and R-warfarin. The S-warfarin is 3-5 times more potent than R-warfarin, and 85% of the S-warfarin are metabolized by cytochrome P450 2C9 (85). The *CYP2C9** 2 (430C> T) and *CYP2C9* * 3 (1075A> C) variants are two common variants of *CYP2C9* that have observably reduced enzyme activity when compared to the wild genotype (86, 87). Patients with *CYP2C9* *2 or *3 required a lower dose of warfarin and had a higher risk of bleeding. Vitamin K epoxide reductase complex subunit 1(*VKORC1*). is the main rate-limiting step in the biosynthesis of vitamin K-dependent proteins, and is the target for warfarin-based anti-coagulants. It has been documented that the SNP in *VKORC1* gene (−1639G>A) was associated with a necessary decrease in warfarin dosage. The FDA has approved pharmacogenetic testing of *CYP2C9* and *VKORC1* for warfarin, and has provided genotype-specific ranges of doses. However, the combination of *CYP2C9* and *VKORC1* polymorphisms accounted only for about 30 to 40% of the total variation in the warfarin dose (88). The final dose of warfarin might be influenced

by other clinical and demographic factors such as age, body weight, concurrent disease, as well as concomitant interactions with medication and food. The pharmacogenetic-based therapy of warfarin is still being debated. In the COAG (Clarification of Optimal Anticoagulation Through Genetics) trial, which was designed to test the effect of genotype-tailored dosing on anticoagulation control, genotyping-guided dosing was not shown to be superior to conventional warfarin dosing (89). In contrast, in the EU-PACT (EUropean Pharmacogenetics of AntiCoagulant Therapy-Warfarin) trial, the genotype-guided dosing was shown to improve anticoagulation control (90). There are some genetic clues for the response to this new oral anticoagulant. A GWAS analysis, which was performed on patients in the RELY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial, identified that carrying the *CES1* rs2244613 was associated with lower exposure to the active metabolite of dabigatran (91).

6. PROTEOMIC AND PRECISION MEDICINE IN ISCHEMIC STROKE

In a symposium titled “2D Electrophoresis: from protein maps to genomes” held in Siena, Italy in 1994, Marc Wilkins coined the term “proteome”, and the term subsequently appeared in print in 1995 (6). The term originated from the combination of “protein” and “genome”, and refers to the entire complement of proteins expressed by genomes, cells, tissues and organisms. In recent years, theory and approaches to proteomics have been applied to explore the risk factors of stroke and to understand response variability to drugs. A proteomic study was conducted on stable coronary ischemic Spanish patients taking aspirin (100mg/day). In has been suggested that the level of expression of proteins associated with mechanisms such as energetic metabolism, cytoskeleton, oxidative stress and cell survival is associated with variations in patient responses to aspirin (92, 93). However, to date, the data for stroke patients is limited in this area. The MITICO study was designed to assess the prognostic value of markers for inflammation as they might relate to the risk of recurrence of vascular disease (94). The proteomic substudy of MITICO indicated that increased desmoplakin I levels during the first 1-3 months after symptom onset could be a biomarker for statin responsiveness against a new vascular event (95). Platelet basic protein (PBP). has been identified by mass spectrometry as a candidate serum biomarker for TIA in a small-sample proteomics study (96). This proteomic approach might be a promising method for finding novel biomarkers to more precisely predict, diagnose and treat ischemic stroke. The CHANCE trial has identified that the glycated albumin (GA) could be a potential biomarker to predict the effects of dual- and mono-antiplatelet therapy in patients with minor stroke or TIA (97). It has been suggested that glycomics might be proposed as a new approach for precise antiplatelet therapy.

7. OTHER OMICS AND PRECISION MEDICINE IN ISCHEMIC STROKE

Reports of the “omics” on oncology and cardiovascular disease have spurred an interest in other types of studies that may promote further understanding of ischemic stroke. In one study, a total of 194 RNA samples from 76 acute ischemic stroke patients were analyzed on whole-genome microarrays. Two gene profiles were identified in this study, one comprised of 40 genes, and the other of 37 genes. With sensitivity and specificity of > 90%, these two studies were capable of differentiating cardioembolic stroke from large vessel stroke and differentiating cardioembolic stroke due to atrial fibrillation from non-atrial fibrillation causes, respectively (98). Another 41-gene profile has been able to discriminate lacunar from non-lacunar stroke with high sensitivity and specificity (99). The combination of the above three gene expression profiles in conjunction with a measure of infarct location can predict a probable cause for cryptogenic strokes. Among a total of 131 patients, cryptogenic strokes were predicted to be 58% cardioembolic, 18% arterial, 12% lacunar and 12% of unclear etiology (100). A case-control study employing methylation microarray analysis has identified obesity-induced, stroke-dependent changes in the *KCNQ1* methylation pattern (101, 102). In a prospective nested case-control study that included 42 ischemic stroke patients, over 480 000 DNA methylation sites were analyzed across the genome. Lower cg03548645 DNA methylation levels of TRAF3 (tumor necrosis factor receptor-as ociated factor 3) were correlated with increased platelet aggregation on clopidogrel treatment. It suggested, for the first time, that epigenetics may significantly contribute to the response variability of clopidogrel and to the recurrence of ischemic events in patients with ischemic stroke (102). Metabolomic analysis was performed by liquid chromatography coupled to mass spectrometry in plasma samples from a total of 131 TIA patients. This study has identified that lysophosphatidylcholine (LysoPC(16:0), LysoPC(20:4) and LysoPC(22:6) is significantly associated with stroke recurrence and that assessment of lysophosphatidylcholine levels could improve the predictive power of conventional predictors (103).

8. BRAIN IMAGING AND PRECISION MEDICINE IN STROKE

Imaging should be regarded as the core of precision stroke research (104). Unlike tumor biopsies, lesion tissue samples cannot be obtained routinely in stroke research or in clinical practice. Brain imaging can detect lesions in stroke patients in-

vivo and provide information fundamental to precise clinical determination of treatment and can also be an effective predictor of outcomes. In clinical practice, imaging plays a vital role in stroke assessment, diagnosis, etiology, management, treatment, and prevention (105, 106). In the hyper-acute phase of ischemic stroke, noncontrast CT scans are pivotal to precise selection of patients eligible for implementation of intravenous tissue-type plasminogen activator, as CT scans can rule out hemorrhages and more precisely identify the area of cerebral infarction (106). The combination of multimodal imaging techniques, such as diffusion-weighted imaging, noninvasive angiography, perfusion imaging with CT and MRI can provide clinicians with a wider eligibility window for administration of IV tPA in order to treat patients beyond the accepted therapeutic window of 4.5. hours (107). When endovascular therapy is considered, noninvasive intracranial vascular imaging is strongly recommended during the initial imaging evaluation of the acute stroke (105). The collateral status in proximal middle cerebral artery occlusion may have a radical impact on the response to endovascular therapy for acute ischemic stroke (104). Brain imaging provides extensive information on baseline pathophysiology, necessary when selecting eligible patients for novel treatments as well as for prediction of patient outcomes.

In stroke clinical trial design, brain imaging biomarkers are powerful criteria for patient selection. The results of imaging can be used to precisely target the key population for a novel treatment, reducing the sample size and saving costs. Trial imaging selection criteria may also be successful in reducing the heterogeneity in stroke mechanisms (104). Recently, endovascular therapy trials used various imaging paradigms to achieve positive findings with only a fraction of the expected sample sizes (108, 109).

Despite the emphasis on its importance, several national precision initiatives are not collecting imaging data. Although stroke is included in the “Million Hearts” Initiative for precision medicine, brain imaging data cannot be collected. Liebeskind *et al.* strongly recommended that brain imaging become an integral part of stroke precision medicine, which should be rooted in data closely relevant to clinical practice (104, 110). Thus, there now exists a substantial opportunity to establish an individualized approach to stroke management, but it must include leveraging big data found within imaging studies.

9. BIG DATA AND PRECISION MEDICINE IN STROKE

The implementation of precision medicine produces massive data, such as genomics, proteomics, metablolomics, and diverse cellular assays, which together comprise the most important components of big data (1). Access to large amounts of clinical health information provides a potentially powerful complement to genome-based precision medicine (111). Big data have emerged at the forefront of biomedical research and is refining precision medicine. The American Heart Association has recommended the formation of a science advisory committee to evaluate the move towards merging of electronic health record data, genomics and cardiovascular research (112).

Phenotype-based precision medicine is used to determine individually targeted interventions from large data sets such as electronic hospital records (EHRs) and administrative claims. Combined data from multiple sources can reduce biases that are intrinsic in homogeneous source data. Standardizing data elements is also essential to controlling these biases. The National Institute of Neurological Disorders and Stroke launched the stroke-specific Common Data Elements (CDEs) project, which proposes standardization of data elements in clinical and population translational research in stroke. CDEs are able to decrease the study time necessary to process data, expedite data sharing, and promote well-informed clinical practice guidelines, creating a robust foundation for using big data from multiple sources (113). The number of patients with consistent data could create an immense network for examining subgroups that would not be possible in individual trials.

EHRs have played a vital role in medical practice, especially in developed countries (114). EHRs include massive medical data such as laboratory data, images, vital signs, and other clinical information. These elements compose a major part of the data for phenotypic precision medicine. With the application of genetic and genomic data in clinical practice, EHRs also allow this information to be recorded with efficiency equivalent to that of clinical laboratory data. EHR-coupled biobanks, which contain biological specimens linked to data in the EHR, are experiencing increasingly widespread usage. In comparison to conventional cohort studies or clinical trials, the link between EHRs and genomic data generates large data sets more rapidly and inexpensively (115). The National Human Genome Research Institute launched the Electronic Medical Records and Genomics (eMERGE) Network, including 10 EHR-based DNA repositories and >350 000 subjects (116). The eMERGE initiative has had a tremendous impact on the domains of genomics and informatics. The EMR is regarded as a powerful and cost-effective tool for precision medicine. Based on its success, eMERGE, through the EMRs, is poised to lead the way in implementing genomic medicine in clinical care (116). These findings from precision medicine and “real world” data of EMRs will be translated quickly into clinical practice, and thus lead to improvements in health care through safer and

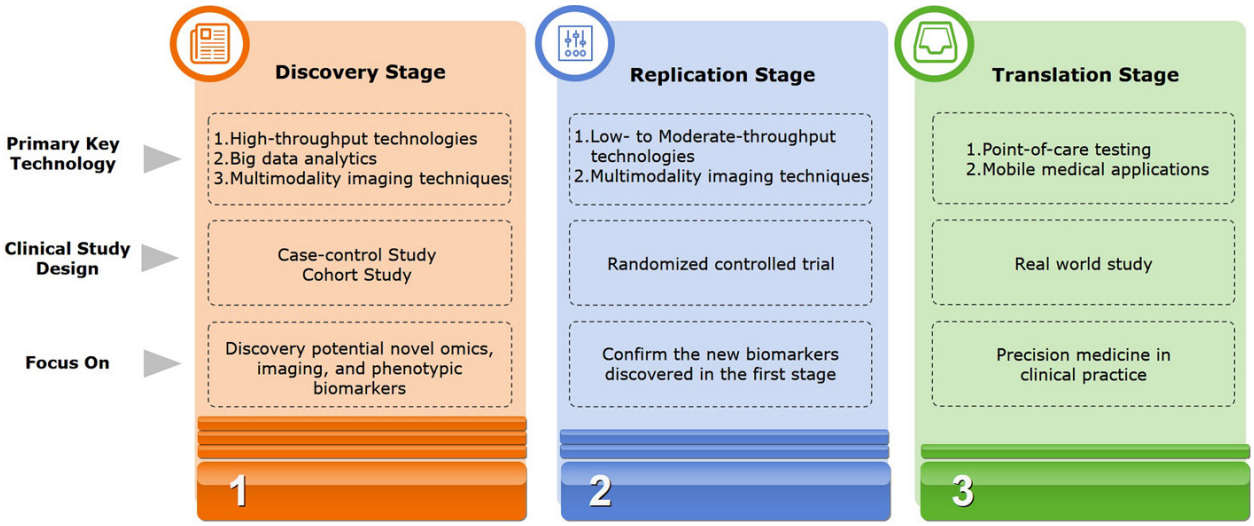

Figure 1. The three-stage progress of precision medicine for ischemic stroke or transient ischemic attack. (1) In the first stage, high-throughput omics' technologies, big data analyses and multidality imaging techniques have been combined in case-control studies and cohort studies, which would explore potential novel biomarkers for ischemic stroke or TIA. (2) And then, these novel potential biomarkers should be confirmed in pre-set randomized controlled trials. And the low-to-moderate-throughput omics' technologies would be predominance in the second stage. (3) With the improvements of point-of-care testing approaches and mobile medical devices, the confirmed biomarkers could be translated into clinical practice in the real world.

more effective prescription guidelines, augmentation of primary and secondary prevention strategies, and enhanced understanding of disease biology.

In addition, EHRs provide a large number of patients with longitudinal data that may improve the ability to separate true-positive from false-positive associations. Stroke outcomes can be ascertained by linking multiple sources of coded data in the UK Biobank through stroke-specific codes (117). Claim data can provide data about rare diseases that are difficult to obtain from a single site. For example, the incidence, mortality, and risk factors for pregnancy-related stroke in the United States from 2000-2001 were estimated through the Nationwide Inpatient Sample (118). In addition, the J-ASPECT study demonstrated the impact of CSC capacity on in-hospital mortality in stroke (119). EHR-derived data have helped identify single-nucleotide polymorphisms in 9p21 that are noted to be associated with cardiovascular disease (120). Via advanced machine-learning techniques, a stroke prediction model was established from aggregated health records in patients with atrial fibrillation.

10. SUMMARY AND PERSPECTIVE

Ischemic stroke is a complex disease with heterogeneity in etiology, disease pathophysiology, clinical presentation, and response to treatment. A one-size-fits-all approach would not be suitable for all patients. Precision medicine provides a novel strategy for specialists to establish a treatment plan for one patient that is distinct from that of another, with the goal of improving population health and clinical management of IS. The entire implementation of precision medicine in ischemic stroke or TIA should be a three-stage progress (Figure 1). The first stage is the "discovery" stage. In this stage, the associations between potential novel omics, imaging, and phenotypic biomarkers with ischemic stroke or TIA should be documented in case-control or in cohort studies. The "replication" stage is the second stage. The biomarkers identified in the first stage should be replicated in a biomarker-tailored randomized controlled trial. Lastly, the "translation" stage serves to translate these practices to clinical practice by using point-of-care testing approaches or mobile medical devices. To date, most of studies for precision medicine in ischemic stroke or TIA were in the first stage.

Precision medicine would distinguish patients with ischemic stroke primarily based on genetics and imaging information, while considering other phenotypic and psychosocial characteristics. Studies of other "omics" have explored several potential novel biomarkers, which might provide critical mechanistic insights into key biologic processes of ischemic stroke or TIA. These biomarkers might be put forward to a new clinical subtype as substitute or modification for TOAST/OCSP classification in ischemic stroke. The system integration of the omics' data, phenotypes, exposome and microbiome would give us comprehensive insight into the development of ischemic stroke or TIA and the response variability to drugs, to which further study and analysis is needed in the future.

11. ACKNOWLEDGEMENT

Yi Lin, Zixiao Li contributed equally to this work. The authors have no disclosure. This study was supported by grants from the Ministry of Science

and Technology of the People's Republic of China (2006BA101A11, 2008ZX09312-008, 2011BAI08B01, 2011BAI08B02, 2012ZX09303, 2013BAI09B14, 2013BAI09B03, 2015BAI12B02, and 2015BAI12B04), grants from Beijing Municipal Science and Technology Commission (D15110700200000, D151100002015001, D151100002015002, Z161100000516223 and Z141107002514125), a grant from National Natural Science Foundation of China (81322019), a grant from China Postdoctoral Science Foundation Grant (2014T70093), a grant from Fujian Provincial Natural Science Foundation (2015J01394), and a grant from Beijing Biobank of Cerebral Vascular Disease (D131100005313003).

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Key Words: Ischemic Stroke, Transient Ischemic Stroke, Precision Medicine, Review

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