

Commentary on “Inherited Neurovascular Diseases Affecting Cerebral Blood Vessels and Smooth Muscle”

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Neurovascular diseases are a group of highly detrimental human disorders. The diseases are among the leading causes of mortality and long-term disability due to aneurysm, stroke and other cardiovascular complications in both children and adults, becoming a serious hazard to human health, and bringing heavy burden to community and the patients' family [1]. In most cases, neurovascular diseases have complex genetic traits [2]. The pathogenesis of the disease is sophisticated. For example, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is due to the co-effects of genetic and environmental factors [3]. So far, advances in human genomics have provided tools for identification of genetic variants underlying complex traits, and have been applied to neurovascular diseases studies. The main task of present studies is to identify the genetic defects involved in the pathogenesis of neurovascular diseases.

So far, although many works has been carried on mapping mutations in neurovascular diseases and many studies in genetic mechanisms of inherited neurovascular diseases have obtained remarkable results, those studies are only at early stage, so those diseases are still not fully understood, and the much deeper mechanisms are still largely unknown.

In the recent paper “Inherited neurovascular diseases affecting cerebral blood vessels and smooth muscle”, we briefly reviewed and summarized the latest findings of six neurovascular disease, containing CADASIL, Marfan syndrome, Moyamoya disease, hereditary hemorrhagic telangiectasia (HHT), microcephalic osteodysplastic primordial dwarfism type II (MOPD II), and Fabry's disease. We introduced these diseases mainly in seven aspects, including epidemiology, pathogenesis, genetics, onset age, classification, clinical characteristics, and treatment methods. Those diseases mainly have two pathogenic features, such as the CADASIL and Marfan syndrome are neurovascular diseases that affect vascular smooth muscle (VSM), while the Moyamoya disease, HHT, MOPD II, and Fabry's disease

that affect endothelial cells of blood vessels [4]. Motor impairment, hemorrhage, and stroke are common symptoms yielded by these diseases in spite of their differences in pathogenesis and onset. Table 1 shows the resumptively listed information of the six diseases. The writer systematically listed the information of the diseases that may help develop better diagnosis and treatment.

Just like works of other inherited diseases, the studies of the aforementioned six diseases also come to a choke point. For Moyamoya disease, most disease genes are still unknown. Moreover, there are often multitudinous mutations in different genes and even in one single gene. To date, mutations in a large number of genes have been reported in these diseases, such as *Notch3*, *FBNI*, *ENG*, *PNCT*, and *GALA* [5-8], however, we still have difficulty in determining which of the hundreds of different mutations in these genes are associated with the diseases or whether they have diagnostic values. Despite extensive mapping and mutational analyses have been used to determine the mechanisms of those diseases at present, there is still no uniform and standard genetic diagnoses for those diseases. At the same time, environmental factors also seemed to play an important role in the occurrences and development of those diseases. Such as for CADASIL, Some carriers who were not exposed to risk factors, did not show any clinical feature of the disease [9]. Nonetheless, more works still need to be done to discover mutations responsible for pathogenesis of those diseases.

It is worth mentioning that our team has also made some contributions to the study of genetic defects of inherited neurovascular diseases-CADASIL and MOPDII.

In the article “Identification of a known Mutation in Notch 3 in Familiar CADASIL in China”, we reported a p.R133C mutation on exon 4 of *Notch3* gene in members of a 5-generational Han Chinese family in which clinical manifestations of the disease are unusual. Many mutations in the 23 exon of the *NOTCH3* gene have been identified to

Granule and osmiophilic materials (GOM)

Table1: The resumtively listed information of the six neurovascular diseases

Disease	Property	Pathogenesis	Gene(s)	Onset age	Common symptoms	Treatment
CADASIL	hereditary small cerebral artery disease	Aggregation of Notch3 and GOM →degeneration of VSM cells	<i>Notch3</i> on chromosome 19p13	late	Ischemic attack, depressive or maniac episodes, migraine, Cognitive and motor impairment	Antiepileptic drugs, β blockers, exercise restriction
Marfan syndrome	connective tissue disorder	Defective connections between smooth muscle cells and elastic fibers	<i>FBNI</i> on chromosome 15q21	variable	Loose joints , Ectopia lentis, myopia	β blockers aortic root surgery
Moyamoya disease	Cerebral vasculopathic disease	Occlusion of supraclinoid internal carotid arteries→arterial collaterals	3p24.2- p26, 6q25, 8q23, 12p12,17q25	childhood	Ischemic attack, headache, Intracerebral hemorrhage,	direct or indirect bypass surgery
HHT	Dominant vascular disorder	Telangiectasias result in frail blood vessel walls	<i>ENG, ACVRL1, MADH4.</i>	early	motor impairment Hemorrhage, anemia	More iron intake, Surgery to remove the arteriovenous malformations
MOPD II	autosomal recessive disease	Abnormity in mitotic spindle organization in centrosomes	<i>PCNT</i> on 21q22.3	childhood	growth retardation, microcephaly hemorrhage, aneurysms	hormone therapy
Fabry disease	X-linked Lysosome storage disorder	lipid accumulation in the lysosome of cells in organs and vascular endothelium	<i>GALA</i> on chromosome Xq22	Late Male earlier than female	Stroke, cataracts, painful neuropathy	enzyme replacement therapy—α-galactosidase A

be associated with the CADASIL disease [10], and the main clinical features of the disease are recurrent ischemic stroke and vascular dementia [5]. At present, the full spectrum of genetic changes in the disease is unknown, and this disease is rare to be reported in Asian populations. We identified the p.R133C mutation in the *Notch3* gene in a 5-generational Han Chinese family with CADASIL. However, only individuals exposed to vascular risk factors show clinical feature of CADASIL, suggesting the significance of environmental factors in the development of the disease [9].

Also, we did research on mutations in PCNT gene resulting in MOPD II and reported the findings in the article “Identification of two novel critical mutations in PCNT gene resulting in microcephalic osteodysplastic primordial dwarfism type II associated with multiple intracranial aneurysms”. We identified three novel mutations in the PCNT gene. They are two deletions (Del-C in exon 30 and Del-16 in exon 41) and one single base alteration (9842A>C in exon 45) [11]. The deletions were co-segregated with the affected individual in the family and were not shown in the control population, however the single base alteration was not co-segregated and showed in the control population. Computer modeling demonstrated that the deletions may alter the secondary and

tertiary structures, affect the stability and anchoring functions of the mutant proteins and make an influence on the protein interactions with the γ-tubulin [11].

Future direction

Although some neurovascular diseases are orphan diseases (such as Fabry’s disease, CADASIL [12] and MOPDII), they still harm human health seriously and are worth emphasis. Those challenges will be translated into discoveries of causative genetic variations of the neurovascular diseases and feasible clinical therapeutic approaches. In order to achieve this, doctors and patient communities should promote the search for carriers of the mutation in families, and suspected and non-suspected cases. It is hard to develop an appropriate therapy against the diseases when the pathogenic mechanisms are yet to be known. Consequently, nowadays there is not an actionable treatment to cure neurovascular diseases and the only way is to use drugs to relieve the symptoms. While it is very hard for the technical nature of such studies to be used in large population studies, the progression in technology will widely improve the feasibility of wide scale measurement. It requires the elucidation of pathogeneses to find strategies that reduce the incidence of inherited neurovascular diseases. Moreover, we need to be careful with the balance between

potential benefits and adverse effects. Also, we should use our knowledge of the existing mutations to work on developing methods to easily make a diagnosis. We believe that the effective treatment and the way to prevent inherited neurovascular diseases will be finally found.

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Competing Interests

The authors have declared that no competing interests exist.

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