Neurology Asia 2013; 18(1) : 123 – 125

CORRESPONDENCE

Evidence for association of a polymorphism in the 3´-UTR of IL-1R-Associated Kinase (IRAK1) with ischemic stroke

Ischemic stroke is a complex disorder with both genetic and environmental factors contributing to disease predisposition and prevalence. Taking into account that stroke is the third cause of death in Western countries, it is of great importance to identify the molecular pathways involved in disease susceptibility.[1]

IRAK1 gene polymorphism rs3027898 (located in the 3'-untranslated region) has been associated previously with atherothrombotic celebral infarction in Japanese patients.[2] The present study addresses, for first time, the role of IRAK1 polymorphism rs3027898 in Caucasian ischemic stroke (IS) patients. IRAK1 gene is located on chromosome X (Xq28) and according to a recent study, the genotype-based analysis of X-linked polymorphisms should be performed in females[3], which is the case of the present study. On the other hand, stroke tends to be more severe in women than in males.[4] Therefore, if this polymorphism is confirmed to be associated with disease severity, this could strengthen further the association with IS.

The female stroke patients were diagnosed according to the WHO definition. The demographic data, laboratory findings and the established risk factors for stroke are summarized in Table 1. The stroke severity was categorized using the Modified Rankin Scale (MRS). The control group included 136 female subjects. They were matched to the patient group for age and the known risk factors of stroke (hypertension, smoking, diabetes mellitus, dyslipidemia) (Table 1). The genotypic analysis of rs3027898 in IS patients and controls was performed as previously described.[5]

The distribution of IRAK1 rs3027898 genotypes was in Hardy-Weinberg equilibrium in control subjects (p= 0.937), while the Hardy-Weinberg equilibrium was marginal in IS patients (p= 0.046), which may be explained by the rs3027898 association with IS as it was revealed by our analysis. Statistically significant difference was observed in IRAK1 rs3027898 genotypes' distribution between IS patients and controls (p=0.049) (Table 2). When we grouped AC and CC genotypes vs AA genotypes, the statistical significant difference was higher (p=0.038, OR=2.03, CI: 1.08-3.81). No association was observed between IRAK1 rs3027898 genotypes and patients' age, stroke type, or the known risk factors of stroke. However, significant difference was observed in IRAK1 rs3027898 genotypes distribution and stroke severity (p=0.006, OR=0.11, CI: 0.02-0.58) (Table 2). Specifically, the 15 and

Table 1: Demographic and clinical features of ischemic stroke (IS) patients and control subjects

	IS Patients n=56	Controls n=136
Age (years) (mean ± SD)	61.04±8.47	58.68 ± 6.73
Smoking (%)	6 (11)	16 (12)
Hypertension (%)	47 (84)	110 (81)
Diabetes mellitus (%)	14 (25)	29 (21)
Dyslipidemia (%)	37 (66)	86 (63)
Large artery atherosclerosis (%)	22 (39)	
Lacunars (%)	34 (61)	
Stroke severity		
Patients (MRS:1,2,3) (%)	45 (80)	
Patients (MRS:4,5,6) (%)	11 (20)	

MRS, Modified Ranking Scale

Table 2. The distribution of IL-1R-associated kinase (IRAK1) rs3027898 polymorphism in ischemic stroke patients and control subjects. Additionally, rs3027898 polymorphism' distribution in ischemic stroke patients with data for their disease severity are presented.

		IRAK1 rs3027898	
Genotypes	**AA**	**AC**	**CC**
IS Patients n=56 (%)	24 (43)	30 (54)	2 (4)
Controls n=136 (%)	82 (60)	47 (35)	7 (5)
Stroke severity			
Patients (MRS:1,2,3) n=45 (%)	15 (33)	28 (62)	2 (4)
Patients (MRS:4,5,6) n=11 (%)	9 (82)	2 (18)	0 (0)

the 30 patients with MRS 1,2,3 had the genotype AA and AC/CC; respectively, vs. the 9 and the 2 patients with MRS 4,5,6 who had the genotype AA and AC/CC; respectively.

Previously the IRAK1 polymorphism rs3027898 has been associated with the atherothrombotic celebral infarction in Japanese individuals and with the widely used biomarker of inflammatory conditions C-reactive protein (CRP).[2,6] IRAK1 plays significant role in TLR/IL-1 receptor (TIR) activation of NF-κB. IRAK1 is considered as a linker of the TLR with the TRAF6 intra-cytoplasmic activator of the transcription factor NF-κB which subsequently increases the expression of many genes such as TNF-α and IL-8 related to immunological functions.[7,8] Among the most studied cytokines related to atherosclerosis or inflammation in ischemic stroke are TNF-a, IL-8 and IL-1β, while TNF-a was also reported to predispose brain endothelium to a subsequent brain injury.[9-11] Thus, the association of IRAK1 rs3027898 C variant with IS seems to be of great importance if we take into account a potential effect of this polymorphism to the above mentioned IS related molecules.

Furthermore, it is worth mentioning that IRAK1 gene polymorphisms have been associated with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in female patients of Asian origin.[12,13] The present study in female patients with IS seems to confirm the association of IRAK1 gene with inflammatory conditions. The higher prevalence of the effect of IRAK1 gene polymorphisms in females may be due to its mapping on X-chromosome. Additionally, given that SLE and RA predispose to vasculitis, vascular dysfunction and subsequently stroke, the revealed positive association of IRAK1 gene with all the above diseases may point out the critical role of IRAK1 in their pathogenesis. As a result, further functional studies are needed to reveal if IRAK1 molecule is associated with all these disorders with common or distinct molecular pathways.

To conclude, the expansion of this study to other larger ethnic groups of IS patients is of great importance so as to increase the power of the identified genetic association. In addition, functional studies of the role of rs3027898 polymorphism in the expression of inflammation related molecules could elucidate its mode of function and its association with inflammatory conditions.

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