Association between polymorphism of ALK receptor tyrosine kinase(ALK) gene and risk of intracerebral hemorrhage

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ALK 유전자 다형성과 뇌출혈과의 상관성 연구

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Abstract I investigated that ALK receptor tyrosine kinase (*ALK*) gene polymorphisms were contributed to susceptibility to ICH in Korean population. I recruited 156 ICH patients and 425 healthy controls for this study, respectively. rs1881421, rs1881420, rs3795850, and rs2246745 single nucleotide polymorphisms (SNPs) were genotyped. The genotype and allele distributions of tested four SNPs was analyzed using the SNPStats, SPSS 22.0, and the Haploview v.4.2 software. The Odd's ratios (OR), 95% confidence intervals (CI), and P values were calculated in allele and genotype models. I found that rs1881421, rs1881420, rs3795850, and rs2246745 SNPs of *ALK* gene (rs1881421, OR=2.02, 95% CI=1.54-2.64, p<0.001; rs1881420, OR=0.53, 95% CI=1.16-2.01, p=0.003; rs3795850, OR=1.54, 95% CI=1.17-2.02, p=0.002; rs2246745, OR=1.95, 95% CI=1.46-2.60, p<0.001 in each allele analysis). And distributions of CC, GT, and GC haplotypes between the ICH group and the control group also showed significant association with ICH (CC haplotype, p<0.001; GT haplotype, p=0.006; GC haplotype, p<0.001). These minor alleles of tested four SNPs in *ALK* gene were contributed to increased risk of development for ICH. Our findings suggested that the *ALK* gene may be a risk factor for susceptibility to ICH.The Korea Internet of Things Society.

Key Words : case-control study, anaplastic lymphoma receptor tyrosine kinase, intracerebral hemorrhage, single nucleotide polymorphism

요 약 본 연구에서는 ALK receptor tyrosine kinase (ALK) 유전자의 단일염기다형성이 뇌출혈의 발병에 관여하는지를 연구하였다. 156명의 뇌출혈 환자와 425명의 정상인를 모집하였으며 네 개의 단일염기다형성에 대하여 상관성을 살펴보았다. 통계분석에서는 SNPstats, SPSS22.0, Haploview 프로그램을 활용하였다. Odd ratio, 95% 신뢰구간에서는 genotype 모델 및 allele 모델에서 계산하였다. 통계분석결과, rs1881421, rs1881420, rs3795850, rs2246745 의 단일염기다형성이 뇌출혈과 관련하여 유의성을 보였다. (rs1881421, OR=2.02, 95% CI=1.54-2.64, p<0.001; rs1881420, OR=0.53, 95% CI=1.16-2.01, p=0.003; rs3795850, OR=1.54, 95% CI=1.17-2.02, p=0.002; rs2246745, OR=1.95, 95% CI=1.46-2.60, p<0.001 in each allele analysis). CC, GT, and GC haplotypes 빈도 역시 유의성을 보였다. 네 개의 단일염기다형성의 minor allele 가 뇌출혈의 발병을 증가시키는데 기여하였다. 이러한 연구 결과는 ALK 유전자가 뇌출혈의 위험성과 관련 있음을 시사한다.

주제어 : 환자통제연구, 미분화 림프종 수용체 티로신 키나아제, 뇌출혈, 유전자다형성

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1. Introduction

Stroke is one of the severe cerebrovascular diseases. According to American Heart Association, it is the 5th cause of death and a leading cause of disability in the United States. Korea also reported that it is 2th cause of death in Korean population and accounts for 50.3 people per 100,000 in individuals 65 years and over in 2014.

Intracerebral hemorrhage (ICH) is the most common subtype of stroke [1] and represented the highest rate among stroke patients in Korea [2]. Previous study in America showed the different risk of development of ICH among the races [3]. Some other studies also reported the ethnic disparities in ICH incidence [4,5]. In addition to ethnic difference, the relation between genetic variations and the risk of ICH has been reported. Meta-analysis in 2014 showed that angiotensin converting enzyme gene insertion/deletion polymorphism might be a susceptible marker for ICH in Asian population [6].

ALK receptor tyrosine kinase (*ALK*) gene is located at 2p23 and expressed in the small intestine, testis, and brain. The sequence of *ALK* gene is similar to the insulin receptor subfamily of kinases. Abnormal expression of *ALK* gene is known to contribute to malignant transformation [7]. Thus, many previous studies focused the function of *ALK* gene on the cancer development. Mutations of *ALK* gene have been reported that it had a relation to non-small-cell lung cancer [8] and it was oncogenic in neuroblastoma [9]. In addition to oncogenic function, *ALK* gene is important in the development of the brain and the nervous system [10]. Previous study has shown that genetic polymorphisms of *ALK* gene might be associated with schizophrenia susceptibility [11].

Many previous studies showed the relation of *ALK* gene to various cancer or brain. But there have been no report for the association between *ALK* gene polymorphisms and ICH. In present study, I investigated the association between the *ALK* gene polymorphisms and ICH in Korean population.

2. Methods and Material

2.1 Subjects and Clinical Phenotypes

Table 1 shows clinical information in the control group and the ICH group. I recruited the ICH patients who visited the emergency room of K Medical Center and the Stroke Center of the East-West Neo-Medical Center in Seoul, Republic of Korea, between October 2007 and September 2014 and control subjects from individuals for a general health checkup. Selection criteria of ICH subjects are as following; 1) the patients with ICH, 2) the patients do not have other causes of cerebrovascular events including stroke from trauma, vascular malformation, brain tumors, and congenital brain disorders. And selection criteria of control subjects are as following; 1) observed any clinical symptoms such as neurological diseases, ischemic heart diseases, immunological disease, or any other severe diseases. Total of one hundred fifty-six Korean ICH patients (mean age ± standard deviation, 57.1 ± 13.3 years; male/female=90/66) and four hundred twenty-five healthy control (mean age ± standard deviation, 55.8 ± 13.3 years; male/female = 210/215) were participated in this study. ICH patient were diagnosis using computed tomography (CT) and magnetic resonance imaging (MRI) to confirm ICH. The severity of neurologic symptoms by the National Institutes of Health Stroke Survey (NIHSS) to investigate the neurological functional levels and the Modified Barthel Index (MBI) to investigate the quality of patients' daily life was measured in each subjects. This study was approved by the ethics review committee of the Medical Research Institute, K University School of Medicine (KMC-0806-01). Informed consent of each patient or guardian was obtained.

〈Table 1〉 Clinical characteristics in stroke patients and control subjects

	ICH	Control
Male/female (n)	90/ 66	210/215
Age (mean±SD)	57.2±13.3	55.8±13.3
Smoking (−/+)	112/ 41	
Hypertension (−/+)	41/114	
Diabetes Mellitus	124/ 31	
NIHSS score (mean±SD)	9.9±6.7	
MBI score (mean±SD)	29.8±26.9	

ICH, intracerebral hemorrhage; NIHSS, national institutes of health stroke survey; MBI, modified Barthel index.

2.2 SNP selection and gentoyping

Selected SNPs in *ALK* genes were from the National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/SNP).

Total of four tagging SNPs (rs1881421, rs1881420, rs3795850, and rs2246745) were selected. Genomic DNAs were extracted from the whole blood of each subject and genotypes were analyzed using direct sequencing after polymerase chain reaction (PCR). For PCR, the primer sequences of tested four polymorphisms were showed in table 2.

〈Table 2〉 Primer sequences for tested four polymorphism.

SNPs	Sense primer (5'−3')	Antisense primer (5'−3')
rs1881421	GGTTCCTCCTCTCCTGGTCT	GGAAGTGACGTAGCCTGAACA
rs1881420	GGTTCCTCCTCTCCTGGTCT	GGAAGTGACGTAGCCTGAACA
rs3795850	CCCTGGTTGGAATCCTTCTT	GTGAGCTGAGAACTGCAGCCT
rs2246745	CAGGGTCCTGAGGTCAACTC	TGGCTCCCACCAGGATACAG

2.3 Statistical Analysis

The codominant1, codominant2, dominant, recessive, log-additive models and the Hardy-Weinberg equilibrium (HWE) test were analyzed using SNPStats (http://bioinfo.iconcologia.net/index.php) and SPSS 22.0 (SPSS Inc, Chicago, IL, USA). The logistic regression analyses were used to estimate odds ratios (ORs) and 95 % confidence intervals (CIs) for the relations between genotypes of *ALK* gene polymorphisms and ICH. Allele frequencies between different groups were assessed using chi-square test. The haplotype analysis in linkage disequilibrium (LD) among tested *ALK* polymorphisms between the ICH group and the control group were analyzed using Haploview version 4.2 (Broad Institute).

3. Result

The genotypic distributions of tested four SNPs in *ALK* genes were in the HWE ($p>0.05$; data not shown). The genotypic and allelic distributions of tested four SNPs are presented in Table 3. As shown in Table 3, genotypes and alleles of rs1881421, rs1881420, rs3795850, and rs2246745 SNPs of *ALK* gene were associated with ICH. All four SNPs showed significant associations with ICH. The rs1881421 showed the association with ICH in the codominant2, dominant, recessive, log-additive model, and allele model ($p<0.05$) except in codominant1 model. The allele frequencies of rs1881421 (C and G) were 0.583 and 0.417 in ICH patients and 0.738 and 0.262 in control subjects and the genotype frequencies (CC, CG, and GG) were 0.385, 0.397, and 0.218 in ICH patients and 0.556, 0.364, and 0.080 in control subjects, respectively. The frequencies of G allele were significantly increased in ICH patients compared to control subjects. The rs1881420 showed the association with ICH in the codominant2, dominant, log-additive model, and allele model ($p<0.05$) except for codominant1 and recessive model. The allele frequencies of rs1881420 (C and T) were 0.652 and 0.348 in ICH patients and 0.741 and 0.259 in control subjects and the genotype frequencies (CC, CT, and TT) were 0.439, 0.426, and 0.136 in ICH patients and 0.560, 0.360, and 0.079 in control subjects, respectively. The frequencies of T allele were significantly increased in ICH patients compared to control subjects. The rs3795850 showed the association with ICH in the codominant1, codominant2, dominant, log-additive model, and allele model ($p<0.05$) except for recessive model (OR=1.58, 95%CI=0.91-2.76, p=0.110).

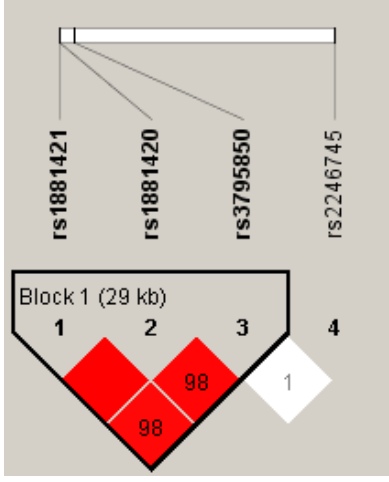
The allele frequencies of rs3795850 (T and G) were

〈Table 3〉 Logistic regression analysis of *ALK* gene polymorphisms between control subjects and ICH patients.

SNPs	Genotype Allele	Control n (%)	ICH n (%)	Models	OR (95% CI)	p
ALK rs1881421	C/C	252 (55.6)	60 (38.5)	Codominant1	1.51 (1.00-2.27)	0.060
	C/G	165 (36.4)	62 (39.7)	Codominant2	3.81 (2.19-6.60)	**0.000**
	G/G	36 (8.0)	34 (21.8)	Dominant	1.92 (1.32-2.80)	**0.001**
				Recessive	3.16 (1.89-5.28)	**〈0.001**
				Log-additive	1.84 (1.42-2.40)	**〈0.001**
	C	669 (73.8)	182 (58.3)		1	
	G	237 (26.2)	130 (41.7)		2.02 (1.54-2.64)	**〈0.001**
ALK rs1881420	C/C	255 (56)	68 (43.9)	Codominant1	1.44 (0.97-2.14)	0.080
	C/T	164 (36)	66 (42.6)	Codominant2	2.07 (1.13-3.80)	**0.025**
	T/T	36 (7.9)	21 (13.6)	Dominant	1.56 (1.07-2.26)	**0.019**
				Recessive	1.76 (0.99-3.13)	0.061
				Log-additive	1.44 (1.10-1.89)	**0.009**
	C	674 (74.1)	202 (65.2)		1	
	T	236 (25.9)	108 (34.8)		1.53 (1.16-2.01)	**0.003**
ALK rs3795850	T/T	245 (54.0)	62 (40.0)	Codominant1	1.62 (1.09-2.41)	**0.017**
	T/G	166 (36.6)	71 (45.8)	Codominant2	1.99 (1.10-3.59)	**0.031**
	G/G	43 (9.5)	22 (14.2)	Dominant	1.70 (1.17-2.46)	**0.005**
				Recessive	1.58 (0.91-2.76)	0.110
				Log-additive	1.47 (1.12-1.92)	**0.005**
	T	656 (72.2)	195 (62.9)		1	
	G	252 (27.8)	115 (37.1)		1.54 (1.17-2.02)	**0.002**
ALK rs2246745	T/T	302 (66.5)	80 (51.3)	Codominant1	1.54 (1.03-2.31)	**0.044**
	T/A	131 (28.9)	54 (34.6)	Codominant2	3.98 (2.07-7.66)	**〈0.001**
	A/A	21 (4.6)	22 (14.1)	Dominant	1.87 (1.29-2.72)	**0.001**
				Recessive	3.42 (1.81-6.46)	**〈0.001**
				Log-additive	1.81 (1.37-2.41)	**〈0.001**
	T	735 (80.9)	214 (68.6)		1	
	A	173 (19.1)	98 (31.4)		1.95 (1.46-2.60)	**〈0.001**

ICH, intracerebral hemorrhage; OR, odd ratio; CI, confidence interval.

0.629 and 0.371 in ICH patients and 0.722 and 0.278 in control subjects and the genotype frequencies (TT, TG, and GG) were 0.400, 0.458, and 0.142 in ICH patients and 0.540, 0.366, and 0.095 in control subjects, respectively. The frequencies of G allele were significantly increased in ICH patients compared to control subjects. The rs2246745 showed the association with ICH in all model; codominant1 (OR=1.54, 95%CI=1.03-2.31, p=0.044), codominant2 (OR=3.98, 95%CI=2.07-7.66, p<0.001), dominant (OR=1.87, 95%CI=1.29-2.72, p=0.001), recessive (OR=3.42, 95%CI=1.81-6.46, p<0.001), log-additive (OR=1.81, 95%CI=1.37-2.41, p<0.001) model, and allele model (OR=1.95, 95%CI=1.46-2.60, p<0.001). The allele frequencies of rs2246745 (T and A) were 0.686 and 0.314 in ICH patients and 0.809 and 0.191 in control subjects and the genotype frequencies (TT, TA, and AA) were 0.513, 0.346, and 0.141 in ICH patients and 0.665, 0.289, and 0.046 in control subjects, respectively.



Block 1 consists of rs1881421, rs1881420, and rs3795850 in *ALK* gene.

[Fig. 1] LD blocks of *ALK* gene.

The frequencies of A allele were significantly increased in ICH patients compared to control subjects. The

rs1881421, rs1881420, and rs3795850 were in complete LD in our study (Fig. 1). As shown in table 4, I found that the CC, GT and GC haplotypes were associated with ICH in haplotype analysis using Haploview 4.2.

〈Table 4〉 Haplotype analysis of *ALK* gene polymorphisms in control subjects and ICH patients.

Haplo-type	Frequ-ency	Control		ICH		Chi Square	p
		+	−	+	−		
CC	0.693	622.9	227.1	181.0	129.0	23.696	〈0.001
GT	0.287	225.0	625.0	107.9	202.1	7.696	0.006
GC	0.020	2.1	847.9	21.1	288.9	50.011	〈0.001

ICH, intracerebral hemorrhage.

4. Discussion

Previous study suggested that genetic factor backgrounds were contributed to development of ICH [12]. Several genetic studies have investigated and reported the relationship between ICH and specific polymorphisms of candidate genes. However, the genetic markers for development of ICH is still poorly understood [13,14].

Our results have shown the significant association between *ALK* gene polymorphisms and ICH. Many previous studies reported the genetic effects on the development of ICH. The FGA Thr312Ala polymorphism can be a risk factor for ICH in the Polish [15]. In addition, genes such as MMP-9, TIMP-1 [16], Aquaporin 4 [17], NADPH [18], IL-1B, IL-1A, IL-1RN [19], APOE [20], COL3A1 [21], HindIII [22], and so on, are reported to be associated with a risk of ICH.

It is observed to have a role in cancer as part of the fusion gene nucleophosmin (NPM)-ALK in anaplastic large cell lymphomas *ALK* gene is located in 2p23. And *ALK* gene encodes a transmembrane tyrosine kinase receptor. It is important role in the development of nervous system during embryogenesis [10,23,24,25]. Several studies reported that the rearranged, mutation, and over expression of *ALK* gene showed in anaplastic large cell lymphomas, neuroblastoma, and non-small cell lung cancer [26].

In this study, I have investigated the rs1881421, rs1881420, rs3795850, and rs2246745 SNPs in *ALK* gene. In these SNPs, rs1881421 is a missense mutation and results in an amino acid change (Asp to Glu). It is reported to be associated with a low response to ethanol and might be involved in the development of alcohol use disorders [27]. And previous whole genome sequencing study showed that rs1881421 and rs1881420 SNPs might be cancer-susceptibility genes [28]. Some authors detected rs3795850 SNP in lung adenocarcinoma patient [29]. ALK was first described related to non-Hodgkin's lymphoma and the associations between *ALK* gene polymorphisms and cancer had been well reported as mentioned above. But in addition to that, previous study in mice showed the wide expression of ALK in central nervous systems and other parts of the brain [30]. And another study reported that ALK is specifically present during dorsal root ganglion development and play a role in the neurons-Schwann cells interaction [31]. In spite of role of ALK in nervous system, there have been no reports on the association between *ALK* gene polymorphisms and ICH. This paper might be the first article for the relation of *ALK* gene polymorphisms to ICH susceptibility.

5. Conclusions

In present case and control study, I evaluated the association between *ALK* gene polymorphisms and ICH susceptibility in Korean population. Our present results showed the significant association between *ALK* gene polymorphisms and ICH susceptibility in Korean population. To clarify this relation, more future works in larger study samples or different populations need to be performed to confirm our results. If more results in various populations would be accumulated in further studies, the relation between *ALK* gene polymorphisms and ICH would be clarified and that would help improving clinical prognosis.

REFERENCES

[1] "A classification and outline of cerebrovascular diseases II", *Stroke,* Vol.**6**, No.5, pp.564-616, 1975.

[2] S.R.Seo, S.Y.Kim, S.Y.Lee, T.H.Yoon, H.G.Park, S.E.Lee and C.W.Kim, "The incidence of stroke by socioeconomic status, age, sex, and stroke subtype: a nationwide study in Korea". *Journal of Preventive. Medicine and Public Health,* Vol.47, No.2, pp.104-112, 2014.

[3] A.L.Klatsky, G.D. Friedman S.Sidney, H.Kipp, A.Kubo and M.A.Armstrong, "Risk of hemorrhagic stroke in Asian American ethnic groups", *Neuroepidemiology,* Vol.**25**, No.1, pp.26-31, 2005.

[4] C.Agyemang, A.A. van Oeffelen, M.Norredam, L. J. Kappelle, C.J.Klijn, M.L.Bots, K.Stronks and I.Vaartjes, "Ethnic disparities in ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage incidence in the Netherlands", *Stroke,* Vol.45, No.11, pp.3236-3242, 2014.

[5] Y.Xian, R.G. Holloway, E.E.Smith, L.H. Schwamm, M.J.Reeves, D.L.Bhatt, P.J.Schulte, M. Cox, D.M.Olson, A.F.Hernandez, B.L.Lytle, K.J.Anstrom, G.C.Fonarow and E.D.Peterson, "Racial/Ethnic differences in process of care and outcomes among patients hospitalized with intracerebral hemorrhage", *Stroke,* Vol.45, No.11, pp.3243-3250, 2014.

[6] A.Kumar, K.Prasad, S.Vivekanandhan, A. Srivastava, S.Goswami, M.V.Srivastava and M. Tripathi, "Association between angiotensin converting enzyme gene insertion/deletion polymorphism and intracerebral haemorrhage in North Indian population: a case control study and meta-analysis", *Neurological Sciences,* Vol.35, No.12, pp.1983-1990, 2014.

[7] S. W. Morris, M. N. Kirstein, M. B. Valentine, K. G. Dittmer, D. N. Shapiro, D. L. Saltman and A. T. Look, " Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma" *Science,* Vol.263, No.5151 pp.1281-1284, 1994.

[8] M.Soda, Y.L.Choi, M.Enomoto, S.Takada, Y.Yamashita, S.Ishikawa, S.Fujiwara, H.Watanabe, K.Kurashina, H.Hatanaka, M.Bando, S.Ohno, Y.Ishikawa, H.Aburatani, T.Niki, Y.Sohara, Y.Sugiyama and H.Mano, "Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer", *Nature,* Vol.448, pp.561-566, 2007.

[9] Y.Chen, J.Takita, Y.L.Choi, M.Kato, M.Ohira, M. Sanada, L.Wang, M.Soda, A.Kikuchi, T.Igarashi, A.Nakagawara, Y.Hayashi, H.Mano and S.Ogawa, "Oncogenic mutations of ALK kinase in neuroblastoma", *Nature,* Vol.455, pp.971-974, 2008.

[10] T.Iwahara, J.Fujimoto, D.Wen, R.Cupples, N.Bucay, T.Arakawa, S.Mori, B.Ratzkin and T.Yamamoto, "Molecular characterization of ALK, a receptor tyrosine kinase expressed specifically in the nervous system", *Oncogene* Vol.14, No.4, pp.439-449, 1997.

[11] H.Kunugi, R.Hashimoto, T.Okada, H.Hori, T.Nakabayashi, A.Baba, K.Kudo, M.Omori, S.Takahashi, R.Tsukue, K.Anami, N.Kosuga, A.Hirabayashi, M.Tatsumi, K.Kamijima, T.Asada, S.Harada, K.Arima, and O.Saitoh, "Possible association between nonsynonymous polymorphisms of the anaplastic lymphoma kinase (ALK) gene and schizophrenia in a Japanese population", *Journal of Neuralal Transmission(Vienna),* Vol.113, No.10, pp.1569-1573, 2006.

[12] D.Woo, L.R.Sauerbeck, B.M.Kissela, J.C. Khoury, J.P.Szaflarski, J.Gebel, R.Shukla,, A.M. Pancioli, E.C.Jauch, A.G.Menon, R.Deka, J.A. Carrozzella, C.J.Moomaw, R.N.Fontaine and J.P. Broderick, "Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study", *Stroke,* Vol.33, No.5, pp.1190-1195, 2002.

[13] B. Liu, L. Zhang and Q. Yang, "Genetics of intracerebral hemorrhage: Insights from candidate gene approaches", *Neurology India* Vol. 60, Vo:. 1, pp.3-8 , 2012.

[14] N. S. Rost, S. M. Greenberg and J. Rosand, "The genetic architecture of intracerebral hemorrhage". *Stroke,* Vol. 39, No. 7, pp.2166-2173, 2008.

[15] J.Jagiella, E.Dardiotis, J.Gasowski, J.Pera, T.Dziedzic, A.Klimkowicz-Mrowiec, A.Golenia, M.Wnuk, K.Fountas, K.Paterakis, G.Hadjigeorgiou and A.Slowik, "The FGA Thr312Ala polymorphism and risk of intracerebral haemorrhage in Polish and Greek populations", *Neurologia i neurochirurgia polska,* Vol.48, No.2, pp.105-110, 2014.

[16] W.M.Ho, C.M.Chen, Y.S.Lee, K.H.Chang, H.W. Chen, S.T.Chen and Y.C.Chen, "Association of MMP-9 Haplotypes and TIMP-1 Polymorphism with Spontaneous Deep Intracerebral Hemorrhage in the Taiwan Population, *PloS one,* Vol,10, No.5, 2015.

[17] G.Appelboom, S.Bruce, A.Duren, M.Piazza, A.Monahan, B.Christophe, S. Zoller, M.LoPresti, and E.S.Connolly, "Aquaporin-4 gene variant independently associated with oedema after intracerebral haemorrhage", *Neurological*

research, Vol.37, No.8, pp.657-661, 2015.

[18] Y.Zhou and Y.C.Zhao, "Association between the nicotinamide adenine dinucleotide phosphate oxidase p22phox gene -A930G polymorphism and intracerebral hemorrhage", *Molecular medicine reports* Vol.11, No.5, pp.3511-3516, 2015.

[19] N. A.Rezk and H. S. Mohamad, "Influence of interleukin-1 gene cluster polymorphisms on the susceptibility and outcomes of acute stroke in Egyptian patients", *Cell biochemistry and biophysics,* Vol.71, No.2, pp.637-647, 2015.

[20] R.Zhang, X.Wang, Z.Tang, J.Liu, S.Yang, Y.Zhang, Y.Wei, W.Luo, J,Wang, J.Li, B.Chen and K.Zhang, "Apolipoprotein E gene polymorphism and the risk of intracerebral hemorrhage: a meta-analysis of epidemiologic studies". *Lipids in health and disease, Vol.*13, No.47, 2014.

[21] W. Lv, Y. Lin, W. Song, K. Sun, H. Yu, Y. Zhang, C. Zhang, L. Li, M. Suo, R. Hui, and J. Chen, "Variants of COL3A1 are associated with the risk of stroke recurrence and prognosis in the Chinese population: a prospective study", *Journal of molecular neuroscience :MN,* Vol.53, No.2, pp.196-203, 2014.

[22] B. Gu, Y. C. Zhao, Z. W. Yang, H. T. Li and F. P. Yu, "HindIII polymorphism in the lipoprotein lipase gene and hypertensive intracerebral hemorrhage in the Chinese Han population", *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association,* Vol.23 No.6, pp.1275-1281, 2014.

[23] R.Chiarle, C.Voena, C.Ambrogio, R.Piva and G. Inghirami, "The anaplastic lymphoma kinase in the pathogenesis of cancer", *Nature reviews. Cancer,* Vol.8, No.1, pp.11-23, 2008.

[24] J.S.,Ross, K.Wang, R.N.Al-Rohil, T. Nazeer, C.E.Sheehan, G.A.Otto, J.He,G.Palmer, R.Yelensky, D.Lipson, S.Ali, S.Balasubramanian, J.A.Curran, L.Garcia, K.Mahoney, S.R.Downing, M.Hawryluk, V.A.Miller and P.J.Stephens, "Advanced urothelial carcinoma: next-generation sequencing reveals diverse genomic alterations and targets of therapy", *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.,* Vol. 27, No.2, pp.271-280, 2014.

[25] E.L.Kwak, Y.J.Bang, D.R.Camidge, A.T. Shaw, B.Solomon, R.G.Maki, S.H.Ou, B.J. Dezube, P.A.Janne, D.B.Costa, M.Varella-Garcia, W.H.Kim, T.J.Lynch, P.Fidias, H.Stubbs, J.A. Engelman, L.V.Sequist, W.Tan, L.Gandhi, M. Mino-Kenudson, G.C.Wei, S.M.Shreeve, M.J. Ratain, J.Settleman,, J.G.Christensen, D.A.Haber, K.Wilner, R.Salgia, G.I.Shapiro, J.W.Clark and A. J.Iafrate, "Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer". *The New England journal of medicine,* Vol.363, No.18, pp.1693-1703, 2010.

[26] A.T. Shaw, B.Y.Yeap, M.Mino-Kenudson, S.R. Digumarthy, D.B.Costa, R. S.Heist,B.Solomon, H. Stubbs, S.Admane, U.McDermott, J.Settleman, S.Kobayashi, E.J.Mark, S.J.Rodig, L.R.Chirieac, E. L.Kwak, T.J.Lynch and A.J.Iafrate, "Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML*4*-ALK", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology, Vol.*27, No.26, pp. 247-4253, 2009.

[27] A.W.Lasek, J.Lim, C.L.Kliethermes, K.H. Berger, G.Joslyn, G.Brush, L.Xue, M.Robertson, M.S. Moore, K.Vranizan, S.W.Morris, M.A.Schuckit, R. L.White and U.Heberlein, "An evolutionary conserved role for anaplastic lymphoma kinase in behavioral responses to ethanol", *PloS one,* Vol. 6, No.7, e22636, 2011.

[28] D.L.Bodian, J.N. McCutcheon, P.Kothiyal, K.C. Huddleston, R.K.Iyer, J.G.Vockley and J.E. Niederhuber, "Germline variation in cancer-susceptibility genes in a healthy, ancestrally diverse cohort: implications for individual genome sequencing", *PloS one,* Vol.9, No.4, e94554, 2014.

[29] Y.L.Choi, M.Soda, Y.Yamashita, T.Ueno, J.Takashima, T.Nakajima, Y.Yatabe, K. Takeuchi, T.Hamada, H.Haruta, Y.Ishikawa, H.Kimura, T.Mitsudomi, Y.Tanio, H.Mano, and ALK Lung Cancer Study Group, "EML*4*-ALK mutations in lung cancer that confer resistance to ALK inhibitors", *The New England journal of medicine,* Vol.363, No.18, pp.1734-1739, 2010.

[30] E.Vernersson, N.K.Khoo, M.L.Henriksson, G.Roos, R.H.Palmer and B.Hallberg, "Characterization of the expression of the ALK receptor tyrosine kinase in mice". *Gene expression patterns : GEP,* Vol.6, No.5 pp.448-461, 2006.

[31] J.Degoutin, N.Brunet-de Carvalho, C.Cifuentes-Diaz and M. Vigny, "ALK (Anaplastic Lymphoma Kinase) expression in DRG neurons and its involvement in neuron-Schwann cells interaction". *The European journal of neuroscience,* Vol.29, No.2, pp.275-286, 2009.

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