Embase (Elsevier)

ORIGINAL ARTICLE

Association between Interleukin-6 (-174 G/C and -572 C/G) Promoter Gene Polymorphisms and Risk of Intracerebral Hemorrhage in North Indian Population: A Case Control Study

Pradeep Kumar[1], Amit Kumar[1], Ram Sagar[1], Shubham Misra[1], Mohammad Farooq[2], Varun Suroliya[1], Subiah Vivekanandhan[3], Achal Kumar Srivastava[1], Kameshwar Prasad[1]

[1]Department of Neurology, All India Institute of Medical Sciences, New Delhi, [2]Institutes of Genomics and Integrative Biology, New Delhi, [3] Department of Neurobiochemistry, All India Institute of Medical Sciences, New Delhi

Article Information

Received: 30 Sep 2015
Accepted: 15 Nov 2015
Plagiarism software: Turnitin

Keywords:
Intracerebral hemorrhage,
Stroke,
Inflammatory gene,
Single nucleotide polymorphisms,
Interleukin-6,
Cytokine

Pradeep Kumar

ABSTRACT

Background: Interleukin-6 (IL-6), a pro-inflammatory cytokine is involved in various vascular pathologies including stroke. Till date, no studies have been reported for the association between IL-6 gene polymorphisms with the risk of Intracerebral hemorrhage (ICH). **Objective:** The aim of this present case-control study was to investigate the association between IL-6 (-174 G/C and -572 C/G) gene polymorphisms and risk of ICH in North Indian population. **Methods:** Genotyping was carried out by using SNaPshot method for ICH patients and 100 age-sex matched ICH free controls. Conditional logistic regression analysis with adjusting multiple demographic and risk factor variables was used to calculate the strength of association between IL-6 (-174 G/C and -572 C/G) polymorphisms and risk of ICH. **Results:** Hypertension, diabetes, dyslipidemia, smoking and low socioeconomic status were found to be associated with the risk of ICH. The distribution of -174 G/C and -572 C/G genotypes was consistent with Hardy Weinberg Equilibrium (HWE) in the ICH and control subjects. Conditional logistic regression analysis showed a significant association between IL-6 -572 C/G gene polymorphism and the risk of ICH under dominant model (OR=3.7; 95%CI 1.05 to 13.1; p=0.004) and allelic model (OR=2.6; 95%CI 1.1 to 6.2; p=0.01). No significant association was observed for the association between IL-6 -174 G/C gene polymorphism and risk of ICH. **Conclusion:** Our results suggest that IL-6 (-572 C/G) polymorphism is significantly associated with the risk of ICH in North Indian population. Further prospective studies with large sample size are needed for independent validation.

INTRODUCTION

Stroke is the major leading cause of morbidity and mortality worldwide.[1] The estimated prevalence of stroke in India ranges from 44 to 843 per 100,000 populations.[2] Intracerebral haemorrhage (ICH) constitutes about 10–15% of all strokes. The incidence of ICH is higher in Asian countries compared to western countries.[3] This may be due to the difference in the prevalence of the risk factors as well as lifestyle, environmental and unclear genetic risk factors.[4] Inflammation is an essential process in the pathogenesis of atherosclerosis followed by cerebrovascular disease (CVD).[5] Inflammation is influenced by various cytokines, such as Interleukin-6 (IL-6) which plays an important role in immune regulation and inflammatory inhibition.[6–9]

Human IL-6 gene is located at chromosome 7(p21) which consists of 5 exons and 4 introns and synthesizes a precursor protein of 232 amino acids.[10,11] Two functional promoter polymorphisms, -174 G/C (rs1800795) and -572 C/G (1800796) have been identified in the IL-6 promoter region and these two genetic variants may be associated with the increased level of IL-6.[12] Recently, its significant role has been demonstrated in the pathogenesis of development and rupture of aortic aneurysm, ischemic

Access this article online	
Website: www.actamedicainternational.com	Quick Response code
DOI: 10.5530ami.2016.1.28	

Corresponding Author:
Dr. Kameshwar Prasad, Department of Neurology, Neurosciences Centre, All India Institute of Medical Sciences, Room No. 11, 6th Floor, Ansari Nagar, New Delhi, India. Phone: +91-11-26593497, 26588979, Fax: +91-11-26588663, 26588979, E-mail: kp0704@gmail.com

stroke (IS) and subarachnoid hemorrhage (SAH).[13–16] To the best of our knowledge, no study has been conducted for the genetic association of IL-6 gene polymorphisms with the risk of ICH. The purpose of this case-control study was to investigate whether the genetic variations (-174 G/C and -572C/G) in the IL-6 promoter gene are associated with the risk of ICH or not.

MATERIALS AND METHODS

Subjects

The study was conducted in the Department of Neurology, All India Institute of Medical Sciences (AIIMS), New Delhi in collaboration with Institute of Genomics and Integrative Biology (IGIB), New Delhi. The study was a hospital based case-control study and was completed in one and a half years (October 2013 to April 2015). Patients with a history of fever, rheumatologic disease, transient ischemic attack, any acute or chronic infection,autoimmune disease and computed tomographic (CT) or magnetic resonance imaging (MRI) proven IS were excluded. A total of 100 patients were recruited for the study after radiologic confirmation of ICH by CT or MRI scans of the brain. All patients had clinical signs consistent with the World Health Organization (WHO) definition of stroke.

A control group comprising of 100 age-sex-matched ICH free individuals was recruited from volunteers and healthy peoples accompanying the patients in the general outpatient department (OPD) and was assessed by questionnaire for verifying stroke free status (QVFSS).[17] Written informed consent was obtained from all subjects before the collection of information and blood samples. The study was approved by the Local Institutional Ethics Committee.

Clinical Examination

A detailed history and clinical evaluation was carried out. The National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and Barthel Index (BI) scores were used for the determination of clinical severity and independency. At six months, disability and functional independence was assessed telephonically by mRS and BI.

Definition of Variables

Definition of variables were modified from the study[18] and are as follows: Hypertension: Subjects will be considered to have hypertension if they either have the diagnosis of hypertension or treated for hypertension before the stroke or reference date. Diabetes: If a subject will have the diagnosis documented by a physician in the medical record or if fasting blood sugar level will be >126 mg/dl, Dyslipidemia: If the patient either will have the diagnosis of dyslipidemia or treated for dyslipidemia. Smoker: Person will be defined as regular smoker if a person smoking ≥1 cigarettes daily, bidis, and cigar for > three months. Family history of Stroke: A positive family history of stroke will be considered if a subject's first-degree relative (parent or sibling) had a stroke. Socioeconomic Status: It was classified into two classes based on four items, mainly two wheeler, refrigerator, computer or car. Low – not possessing any of the four, High- possessing either two- wheeler or refrigerator or computer or car. Physical activity: Physical activity was defined if a person engaged in morning or evening walk/running/jogging/swimming/cycling at least half an hour in four days or more in a week.[19,20]

Dna Isolation and Genotyping

Single time one teaspoon (4ml) venous blood samples were taken from ICH patients and controls in a tube containing ethylene diamine tetra acetic acid (EDTA). Genomic DNA was isolated from whole blood through standard phenol-chloroform method. The primers were designed for the two Single Nucleotide Polymorphism (SNPs) using the Primer3 online tool, (http://bioinfo.ut.ee/primer3-0.4.0/). The IL-6 (-174 G/C and -572 C/G) regions were amplified in T-100 thermal cycler (Bio-Rad) using the primer sequences and conditions for Polymerase Chain Reaction (PCR) are listed in Table 1. Genotyping was performed on 3130xl automated DNA sequencer (Applied Biosystems) using the SNaPshot method.

Statistical Analysis

The chi-square test was used to determine whether the allelic frequencies were in accordance with Hardy-Weinberg equilibrium (HWE) or not. The conditional logistic regression analysis was used to estimate Odds Ratio (OR) and 95% confidence intervals (CIs) for the strength of association between IL-6 gene polymorphisms with risk of ICH. Multivariate logistic regression was used to control the confounding effects of demographic and risk factor variables. Tests were considered significant at $p < 0.05$. Data was analyzed using the STATA, version 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Haplotypes were reconstructed using PHASE 2.0 software. The threshold value of the frequencies of the haplotypes included in the analysis was set to 2%.

RESULTS

After screening 137 stroke cases, 100 ICH cases were included in the study. For the control group, 119 people were screened and 100 age-sex matched ICH free controls were recruited for the study. The mean age of ICH patients was 50.56 ± 11.58 years and control group was 50.50 ± 11.46 years and both groups consisted of 74 males and 26 females. The risk factor variables such as history of hypertension (cases 42.0% vs controls 18.0%), diabetes (cases 25.0% vs controls 9.0%), smoking (cases 20.0% vs controls 5.0%), alcohol

Table 1: List of primer sequences and PCR conditions used for IL-6 gene polymorphisms

SNPs	rsID	Primers	Annealing (°C)	Amplicon size (bp)
-174 G/C	1800795	F.P-TGACTTCAGCTTTACTCTTTGT R.P-CTGATTGGAAACCTTATTAAG S.P- TTCCCCCTAGTTGTGTCTTGC	55	198
-572 C/G	1800796	F.P-GGAGACGCCTTGAAGTAACTGC R.P-GAGTTTCCTCTGACTCCATCGCAG S.P- CCAGGCAGTTCTACAACAGCC	55	163

Abbreviations: FP: Forward primer; RP: Reverse primer; SP: SNaPshot primer; BP: Base pair

Table 2: Demographic and risk factor variables for ICH patients and control subjects

Characteristics	N=100 (n (%))		[95% CI], p value	
	Controls	ICH	Crude OR	*Adjusted OR
Age in years (mean+S.D)	50.50±11.46	50.56±11.58	Matched	
Male/Female, n	74/26	74/26		
Hypertension	18 (18)	42 (42)	4.4 (1.9 to 10.1), <0.001	3.4 (1.1-10.1), 0.02
Diabetes	9 (9)	25 (25)	3.2 (1.3 to 7.5), 0.007	1.02 (0.3-3.2), 0.97
Dyslipidemia	5 (5)	17 (17)	3.5 (1.2 to 9.5), 0.013	2.4 (0.6-9.5), 0.18
Smoking	5 (5)	20 (20)	6.4 (1.8 to 21.8), 0.003	7.3 (1.4-36.4), 0.01
Alcohol	14 (14)	19 (19)	1.3 (0.6 to 2.7), 0.40	0.5 (0.1-1.6), 0.26
Myocardial infarction	2 (2)	5 (5)	2 (0.3 to 10.9), 0.42	2.3 (0.1-30.5), 0.51
Migraine with aura	3 (3)	4 (4)	1.4 (0.3 to 6.6), 0.61	2.6 (0.3-17.9), 0.32
Migraine without aura	1 (1)	6 (6)	6.7 (0.8 to 56.8), 0.07	13.3 (0.5-335.8), 0.11
Low socioeconomic status	5 (5)	23 (23)	6.6 (1.9 to 22.4), 0.02	11.4 (1.8-71.2), 0.009
Sedentary life style	67 (67)	58 (58)	1.2 (0.7 to 1.8), 0.35	1.4 (0.8-2.6), 0.18
Physical activity	89 (89)	99 (99)	0.09 (0.01 to 0.70), 0.02	0.02 (0.001-0.4), 0.01
Family history of stroke	4 (4)	6 (6)	1.08 (0.2 to 4.3), 0.90	0.8 (0.09-7.8), 0.97
Family history of diabetes	5 (5)	10 (10)	1.9 (0.68 to 5.8), 0.20	16.8 (2.1-135.3), 0.008
Family history of hypertension	5 (5)	7 (7)	1.2 (0.36 to 3.9), 0.30	0.4 (0.09-2.5), 0.39
Family history of heart attack	5 (5)	5 (5)	1.0 (0.2 to 3.4), 1.00	1.7 (0.2-12.9), 0.5

Conditional logistic regression analysis. *Adjusted variables include hypertension, diabetes, dyslipidemia, low socioeconomic status, smoking, migraine without aura, physical activity variables. Abbreviations: OR: Odds ratio; CI: Confidence interval; SD: Standard deviation, ICH: Intracerebral hemorrhage

intake (cases 19.0% vs controls 14%), dyslipidemia (cases 17.0% vs controls 5.0%), low socioeconomic status (cases 23.0% vs controls 5.0%) and physical inactivity (cases 99.0% vs controls 89.0%) were found significantly more often in cases than in controls (p<.05) [Table 2]. Out of 100 cases, 34 (34.0%) cases were recruited from outpatient department (OPD) and 66 (66.0%) cases were recruited from inpatient department (IPD). 96 patients (96.0%) completed full six months telephonic follow-up, eight patients (8.0%) died and four patients (4.0%) were lost to follow-up. The mean and standard deviation (S.D.) was observed as 13.39 ± 9.0 for NIHSS at admission, 3.24 ± 1.13 for mRS and 57.15 ± 22.9 for BI at discharge. After telephonic follow up at six months, the mean and S.D. of 1.5 ± 1.7 for mRS and 78.5 ± 27.7 for BI was noted.

All the genotypes and allelic frequencies were in HWE in both ICH patients and controls. Genetic analysis for IL-6 (-174 G/C and -572 C/G) gene polymorphisms were conducted for all 100 ICH cases and 100 age-sex matched controls. Conditional logistic regression analysis showed a significant association between IL-6 -572C/G gene polymorphism and the risk of ICH under dominant model (OR=3.7; 95%CI 1.05 to 13.1; p=0.004) and allelic model (OR=2.6; 95%CI 1.1 to 6.2; p=0.01). However, no significant association between IL-6 -174 G/C gene polymorphism and the risk of ICH was observed (Table 3). Haplotype analysis revealed no significant association with the increased risk of ICH (Table 4).

DISCUSSION

Our present case-control study represents a significant association between IL-6 -572 C/G gene polymorphism and the risk of ICH, but failed to find any association between IL-6 -174 G/C gene polymorphism and the risk of ICH in North Indian population. IL-6 is a multifunctional proinflammatory cytokine produced by many tissues including endothelium and plays an important role as a mediator of inflammatory reactions associated with atherosclerotic disease including stroke. *In vitro* and *In vivo* studies have shown that the promoter construct containing IL-6 -174G and -572C alleles was associated with higher stimulation of IL-6.[12,21]

Few studies have reported the relationship between -174G allele and GG genotype a higher IL-6 expression level while the -174C allele and CC genotype and -174G allele and GG

Table 3: Genotype and allelic frequencies of IL-6 (–174 G/C and –572 C/G) gene polymorphisms in ICH patients and controls

Polymorphisms	N=100	
	ICH	Controls
−174 G/C		
Genotype		
GG, n (%)	76 (76)	79 (79)
GC, n (%)	20 (20)	19 (19)
CC, n (%)	4 (4)	2 (2)
Allele		
G, n (%)	172 (86)	177 (88.5)
C, n (%)	28 (14)	23 (11.5)
Dominant (CC+GC vs. GG)		
*Adjusted OR (95% CI), P value	1.1 (0.4-3.1), 0.78	
Unadjusted OR (95% CI), P value	1.2 (0.6-2.4), 0.52	
Recessive (CC vs. GG+GC)		
*Adjusted OR (95% CI), P value	1.7 (0.2-14.6), 0.58	
Unadjusted OR (95% CI), P value	2 (0.3-10.9), 0.42	
Allelic C vs. G		
OR (95% CI), P value	1.2 (0.69-2.2), 0.45	
−572 C/G		
Genotype		
CC, n (%)	82 (82)	93 (93)
CG, n (%)	16 (16)	6 (6)
GG, n (%)	2 (2)	1 (1)
Allele		
C, n (%)	180 (90)	192 (96)
G, n (%)	20 (10)	8 (4)
Dominant (GG+CG vs. CC)		
*Adjusted OR (95% CI), P value	3.7 (1.05-13.1), 0.04	
Unadjusted OR (95% CI), P value	2.86 (1.12-7.28), 0.02	
Recessive (GG vs. CC+CG)		
*Adjusted OR (95% CI), P value	NE	
Unadjusted OR (95% CI), P value	2 (0.18-22.05), 0.57	
Allelic G vs. C		
OR (95% CI), P value	2.6 (1.1-6.2), 0.01	

*Adjusted variables include hypertension, diabetes, dyslipidemia, low socioeconomic status, smoking, migraine without aura and physical activity variables

Table 4: Frequencies and association of IL-6 (–174 G/C and –572 C/G) haplotypes in ICH patients and controls

Haplotypes	n (%)		Odds ratio (95% CI)	P value
	HS cases	Controls		
G174-C572	158 (79)	169 (84.5)	Reference	
G174-C572	17 (8.5)	8 (4)	2.27 (0.95-5.41)	0.006
G174-G572	25 (12.5)	23 (11.5)	1.16 (0.63-2.13)	0.62
Total	200	200		

genotype were found to be more responsive to induce other cytokines such as IL-1.[12,22,23] However, other studies have reported conflicting results.[24,25] The -572 polymorphic site in the promoter region might affect the activity of the -174 position in the IL-6 gene.[21,26] A study has also reported the association of C allele of -572G/C with higher IL-6 concentrations.[27] The exact relationship between these two promoter gene polymorphisms and IL-6 production is still contradictory.

Previous studies have shown IL-6 -174C allele to be associated with susceptibility to myocardial infarction[28] and with impaired endothelial function.[29] Conversely, other studies found the IL-6 -174GG genotype to be associated with higher IL-6 level, increased intima-media thickness of the carotid arterial wall,[30] history of ischemic stroke and with peripheral artery occlusive disease.[31] Previous meta-analysis published by Pera J *et al.* (2011)[32] showed no association between IL-6 -174G/C polymorphism with the risk of aneurysmal SAH. A recent metaanalysis published by Kumar P *et al.* (2015)[15] also concluded no association between IL-6 -174G/C and -572C/G polymorphisms with the risk of IS. To the best of our knowledge, our study is the first study which investigated the association between IL-6 (-174G/C and -572C/G) polymorphism and the risk of ICH in North Indian population.

However, there were a few limitations in our study. Firstly, the study was conducted in a single hospital and the participants might not have been the representatives from other areas. Therefore, further large sample size and multicentric studies are needed to confirm our findings. Secondly, we investigated the role of two SNPs (rs1800795 and rs1800796) with the risk of ICH. It may be possible that other SNPs might be associated with the risk of ICH. Hence, to draw more profound conclusions more polymorphisms of IL-6 gene need to be investigated with the risk of stroke. Despite these limitations, our study provides strong evidence for the association between IL-6 -572C/G gene polymorphism and risk of ICH.

CONCLUSION

Our results suggest that IL-6 (-572 C/G) polymorphism is significantly associated with the risk of ICH in North Indian population. Further prospective studies with large sample size are needed for independent validation.

ACKNOWLEDGEMENT

We acknowledge the technical assistance of staff members of the Neurology Department of All India Institute of Medical Sciences, New Delhi. We also thank all patients and controls participants for providing blood samples.

REFERENCES

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383:245–54.
2. Prasad K, Vibha D. Meenakshi null. Cerebrovascular disease in South Asia - Part I: A burning problem. JRSM Cardiovasc Dis. 2012;1.
3. Das SK, Banerjee TK. Stroke: Indian scenario. Circulation. 2008;118:2719–24.

4. Bevan S, Markus HS. Genetics of common polygenic ischaemic stroke: current understanding and future challenges. Stroke Res Treat. 2011; 2011:179061.
5. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol. 2010; 87:779–89.
6. Seino Y, Ikeda U, Ikeda M, Yamamoto K, Misawa Y, Hasegawa T, et al. Interleukin 6 gene transcripts are expressed in human atherosclerotic lesions. Cytokine. 1994;6:87–91.
7. Castillo J, Rodríguez I. Biochemical changes and inflammatory response as markers for brain ischaemia: molecular markers of diagnostic utility and prognosis in human clinical practice. Cerebrovasc Dis Basel Switz. 2004;17 Suppl 1:7–18.
8. Tso AR, Merino JG, Warach S. Interleukin-6 174G/C polymorphism and ischemic stroke: a systematic review. Stroke J Cereb Circ. 2007;38:3070–5.
9. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. Circulation. 2000;101:1767–72.
10. Sehgal PB, Zilberstein A, Ruggieri RM, May LT, Ferguson-Smith A, Slate DL, et al. Human chromosome 7 carries the beta 2 interferon gene. Proc Natl Acad Sci U S A. 1986;83:5219–22.
11. Zilberstein A, Ruggieri R, Korn JH, Revel M. Structure and expression of cDNA and genes for human interferon-beta-2, a distinct species inducible by growth-stimulatory cytokines. EMBO J. 1986;5:2529–37.
12. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest. 1998;102:1369–76.
13. Pawlikowska L, Tran MN, Achrol AS, McCulloch CE, Ha C, Lind DL, et al. Polymorphisms in genes involved in inflammatory and angiogenic pathways and the risk of hemorrhagic presentation of brain arteriovenous malformations. Stroke J Cereb Circ. 2004;35:2294–300.
14. Yin Y-W, Li J-C, Zhang M, Wang J-Z, Li B-H, Liu Y, et al. Influence of interleukin-6 gene -174G>C polymorphism on development of atherosclerosis: a meta-analysis of 50 studies involving 33,514 subjects. Gene. 2013;529:94–103.
15. Kumar P, Yadav AK, Kumar A, Sagar R, Pandit AK, Prasad K. Association between Interleukin-6 (G174C and G572C) promoter gene polymorphisms and risk of ischaemic stroke: A meta-analysis. Ann Neurosci. 2015;22:61–9.
16. Smallwood L, Allcock R, van Bockxmeer F, Warrington N, Palmer LJ, Iacopetta B, et al. Polymorphisms of the interleukin-6 gene promoter and abdominal aortic aneurysm. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2008;35:31–6.
17. Jones WJ, Williams LS, Meschia JF. Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. Stroke J Cereb Circ. 2001;32:2232–6.
18. Feigin VL, Wiebers DO, Nikitin YP, O'Fallon WM, Whisnant JP. Risk factors for ischemic stroke in a Russian community: a population-based case-control study. Stroke J Cereb Circ. 1998;29:34–9.
19. Kumar A, Prasad M, Kathuria P. Sitting occupations are an independent risk factor for Ischemic stroke in North Indian population. Int J Neurosci. 2014;124:748–54.
20. Kumar A, Prasad M, Kathuria P, Nair P, Pandit AK, Sahu JK, et al. Low socioeconomic status is an independent risk factor for ischemic stroke: a case-control study in North Indian population. Neuroepidemiology. 2015;44:138–43.
21. Terry CF, Loukaci V, Green FR. Cooperative influence of genetic polymorphisms on interleukin 6 transcriptional regulation. J Biol Chem. 2000;275:18138–44.
22. Burzotta F, Iacoviello L, Di Castelnuovo A, Glieca F, Luciani N, Zamparelli R, et al. Relation of the -174 G/C polymorphism of interleukin-6 to interleukin-6 plasma levels and to length of hospitalization after surgical coronary revascularization. Am J Cardiol. 2001;88:1125–8.
23. Hulkkonen J, Pertovaara M, Antonen J, Pasternack A, Hurme M. Elevated interleukin-6 plasma levels are regulated by the promoter region polymorphism of the IL6 gene in primary Sjögren's syndrome and correlate with the clinical manifestations of the disease. Rheumatol Oxf Engl. 2001;40:656–61.
24. Jerrard-Dunne P, Sitzer M, Risley P, Steckel DA, Buehler A, von Kegler S, et al. Interleukin-6 promoter polymorphism modulates the effects of heavy alcohol consumption on early carotid artery atherosclerosis: the Carotid Atherosclerosis Progression Study (CAPS). Stroke J Cereb Circ. 2003;34:402–7.
25. Jones KG, Brull DJ, Brown LC, Sian M, Greenhalgh RM, Humphries SE, et al. Interleukin-6 (IL-6) and the prognosis of abdominal aortic aneurysms. Circulation. 2001;103:2260–5.
26. Yamada Y, Metoki N, Yoshida H, Satoh K, Ichihara S, Kato K, et al. Genetic risk for ischemic and hemorrhagic stroke. Arterioscler Thromb Vasc Biol. 2006;268:1920–5.
27. Mälarstig A, Wallentin L, Siegbahn A. Genetic variation in the interleukin-6 gene in relation to risk and outcomes in acute coronary syndrome. Thromb Res. 2007;119:467–73.
28. Georges JL, Loukaci V, Poirier O, Evans A, Luc G, Arveiler D, et al. Interleukin-6 gene polymorphisms and susceptibility to myocardial infarction: the ECTIM study. Etude Cas-Témoin de l'Infarctus du Myocarde. J Mol Med Berl Ger. 2001;79:300–5.
29. Brull DJ, Leeson CPM, Montgomery HE, Mullen M, deDivitiis M, Humphries SE, et al. The effect of the Interleukin-6-174G > C promoter gene polymorphism on endothelial function in healthy volunteers. Eur J Clin Invest. 2002;32:153–7.
30. Rundek T, Elkind MS, Pittman J, Boden-Albala B, Martin S, Humphries SE, et al. Carotid intima-media thickness is associated with allelic variants of stromelysin-1, interleukin-6, and hepatic lipase genes: the Northern Manhattan Prospective Cohort Study. Stroke J Cereb Circ. 2002;33:1420–3.
31. Pola R, Flex A, Gaetani E, Flore R, Serricchio M, Pola P. Synergistic effect of -174 G/C polymorphism of the interleukin-6 gene promoter and 469 E/K polymorphism of the intercellular adhesion molecule-1 gene in Italian patients with history of ischemic stroke. Stroke J Cereb Circ. 2003;34:881–5.
32. Pera J, Dziedzic T, Adamski M, Jagiella J, Krupa M, Moskala M, et al. Interleukin 6-174G>C polymorphism and risk of aneurysmal subarachnoid hemorrhage: case-control study and meta-analysis. Acta Neurol Scand. 2012;125:111–5.

How to cite this article: Kumar P, Kumar A, Sagar R, Misra S, Farooq M, Suroliya V, Vivekanandhan S, Srivastava AK, Prasad K. Association between Interleukin-6 (-174 G/C and -572 C/G) promoter gene polymorphisms and risk of intracerebral hemorrhage in North Indian population: A case control study. Acta Medica International. 2016;3(1):132-136.

Source of Support: Institute of Genomics and Integrative Biology, New Delhi, **Conflict of Interest:** None declared.