Association between Interleukin-10 -1082G/A Gene Polymorphism and Risk of Stroke in the North Indian Population: A Case–Control Study

Pradeep Kumar, PhD,* Amit Kumar, PhD,* Ram Sagar, MSc,* Shubham Misra, M.Tech,* Mohammad Faruq, PhD,† Varun Suroliya, MSc,* Subiah Vivekanandhan, PhD,‡ Achal Kumar Srivastava, DM,* and Kameshwar Prasad, DM*

Background: Anti-inflammatory interleukin-10 (IL-10) cytokine and its genetic variations may play an important role in the pathogenesis of various human diseases including stroke. *Objective:* The aim of this present case–control study was to determine the association between IL-10 -1082G/A (rs1800896) gene polymorphism and risk of stroke in the North Indian population. *Methods:* Genotyping was carried out by using SNaPshot method (Applied Biosystems, Foster City, California, United States) for 250 ischemic stroke (IS) patients, 250 age- and sex-matched IS free controls, 100 intracerebral hemorrhage (ICH) patients, and 100 age- and sex-matched ICH free controls. IS was classified using the Trial of Org 10172 in Acute Stroke Treatment classification. Conditional logistic regression analysis with adjustment for multiple demographic and risk factor variables was used to calculate the strength of association between IL-10 (-1082G/A) polymorphism and risk of stroke. *Results:* Conditional logistic regression analysis showed an independent association between IL-10 -1082G/A and risk of IS under a dominant model (odds ratio [OR] = 2.39, 95% confidence interval [CI] = 1.34-4.27, $P = .003$) and an allelic model (OR = 2.49, 95% CI 1.71-3.63, $P < .001$). An independent association between IL-10 -1082G/A, under the dominant model (OR = 6.8, 95% CI 2.2-20.7, $P < .001$) and the allelic model (OR = 3.4, 95% CI 1.8-6.3, $P < .001$), and the risk of ICH was also observed. *Conclusion:* Our results suggest that IL-10 -1082G/A gene polymorphism is an independent risk factor for the risk of IS and ICH in the North Indian population. Our findings indicate that IL-10 -1082G/A polymorphism may be used as a genetic marker for identifying individuals at increased risk of developing stroke. **Key Words:** Ischemic stroke—intracerebral hemorrhage—cerebrovascular disease—single-nucleotide polymorphism—promoter—interleukin-10—anti-inflammatory cytokine.

From the *Department of Neurology, All India Institute of Medical Sciences, New Delhi, India; †Department of Functional Genomics, Institute of Genomics and Integrative Biology, New Delhi, India; and ‡Department of Neurobiochemistry, All India Institute of Medical Sciences, New Delhi, India.

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Address correspondence to Kameshwar Prasad, Department of Neurology, Neurosciences Centre, All India Institute of Medical Sciences, Room No. 11, 6th Floor, Ansari Nagar, New Delhi 110029, India. E-mail: kp0704@gmail.com.

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Introduction

Stroke, a heterogeneous multifactorial disorder, is known to be a major cause of death and adult disability within both developed and developing countries. About 85% of stroke cases are ischemic, whereas 15% are hemorrhagic.[1] The incidence of stroke in South Asian countries has increased by more than 100%, while this is decreased by 42% in developed European countries in the last 4 decades.[2] Previous studies have indicated that anti-inflammatory cytokine interleukin-10 (IL-10) and its genetic variations may play an important role in the pathogenesis of various human diseases including stroke.[3-7]

IL-10 is a multifunctional anti-inflammatory cytokine, mainly secreted by lymphocytes and monocytes. The human IL-10 gene is located on chromosome 1, at q31-32, and is highly polymorphic, containing 6 different polymorphisms at -1082, -819, -652, -127 and -41 positions.[8-10] Studies have claimed that G/A substitution at -1082 position in the promoter region of IL-10 gene is related to high/low IL-10 production.[11-13] A transient increase in IL-10 concentration in plasma, cerebrospinal fluid, and blood mononuclear cells has been detected in patients suffering from acute stroke.[7-14] IL-10 counterbalances the potentially harmful effects of tumor necrosis factor-α and other proinflammatory molecules.[12]

Several emerging studies have reported the association between -1082G/A polymorphism in the IL-10 gene and risk of stroke, but the results are inconclusive.[15-18] To draw a more profound conclusion, this present case–control study was undertaken to determine the association between IL-10 -1082G/A (rs1800896) gene polymorphism and risk of stroke in the North Indian population.

Methods

Subjects

The study was conducted in the Department of Neurology, All India Institute of Medical Sciences (AIIMS), New Delhi, in collaboration with the Institute of Genomics and Integrative Biology (IGIB), New Delhi. The study was a hospital-based case–control study and was completed in 1.5 years (from October 2013 to April 2015). Patients with a history of transient ischemic attack, fever, rheumatologic disease, autoimmune disease, any acute or chronic infection, and a history of regular immunosuppressive or analgesic therapies were excluded. A total of 250 ischemic stroke (IS) and 100 intracerebral hemorrhage (ICH) patients were recruited for the study after radiologic confirmation of stroke by computed tomography or magnetic resonance imaging scans of the brain.

All patients had clinical signs consistent with the World Health Organization definition of stroke. A control group composed of 250 age- and sex-matched individuals for IS and 100 age- and sex-matched individuals for ICH was recruited from volunteers and healthy people accompanying the patients in the general outpatient department (OPD) and was assessed by the Questionnaire for Verifying Stroke-Free Status.[19] 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. IS was classified using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[20] 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 6 months, disability and functional independence were assessed telephonically by mRS and BI.

Definition of Variables

Definitions of variables were modified from the study[21] and are as follows: Hypertension: patients are considered to have hypertension if they either have the diagnosis of hypertension or have been treated for hypertension before the stroke or reference date. In addition, if a control has no recorded blood pressure before the reference date but has a diastolic pressure of 90 mm Hg or more, or a systolic pressure of 140 mm Hg or more on 2 or more occasions during the study evaluation, he/she is considered to have hypertension. Diabetes: a patient is considered to have diabetes if he/she has the diagnosis documented by a physician on the medical record or if fasting blood sugar level is higher than 126 mg/dL. Dyslipidemia: a patient is considered to have dyslipidemia if he/she has the diagnosis of dyslipidemia or has been treated for dyslipidemia. Smoker: a person is defined as a regular smoker if he/she smokes 1 or more cigarettes, bidis, or cigars daily, for more than 3 months. Body mass index: the body mass index is calculated by weight in kilograms divided by the square of height in meters. Family history of stroke: a positive family history of stroke is considered if the patient's first-degree relative (parent or sibling) has had a stroke. Socioeconomic status: this is classified into 2 classes based on 4 items, mainly 2-wheeler, refrigerator, computer, or car: low—not possessing any of the four, and high—possessing either 2-wheeler, refrigerator, computer, or car. Occupational behavior: this comprises sedentary or sitting occupations (mostly sitting, e.g., shopkeeper or clerk), moderate physical work (involves walking, e.g., salesman, nurse, or housework), and heavy physical work (carrying and lifting, e.g., laborer or coolie).

Laboratory Investigations

Single time 1 teaspoon (4 mL) venous blood samples were taken in an ethylenediaminetetraacetic acid (EDTA)