ISFAHAN UNIVERSITY OF MEDICAL SCIENCES
SCHOOL OF MEDICINE

Thesis for obtaining the M.D. degree

Title:

Association between promoter region of the uPAR (rs344781) gene polymorphism in genetic susceptibility to migraine without aura in three Iranian hospitals

NUMBER: 191006

Author:

Samira Soleimani

Supervisor:
Dr. Shaghayegh Haghjooy Javanmard
(Assistant Professor of Isfahan Faculty of medicine)

Aug 2015

Clinical Neurology and Neurosurgery 120 (2014) 45–48

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Association between promoter region of the uPAR (rs344781) gene polymorphism in genetic susceptibility to migraine without aura in three Iranian hospitals

Alireza Zandifar[a,b], Samira Soleimani[a,b], Niloufar Iraji[a,b], Faraidoon Haghdoost[a,b], Mohamadhasan Tajaddini[a,c], Shaghayegh Haghjooy Javanmard[a,*]

[a] Physiology Research Center, Department of Physiology, Isfahan University of Medical Sciences, Isfahan, Iran
[b] Medical Student Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[c] School of Pharmacy and Isfahan Pharmaceutical Sciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

A B S T R A C T

Introduction: Migraine is a chronic neurological disorder. Inflammation has a key role in migraine pathophysiology. Urokinase plasminogen activator receptor (uPAR) directly involves in inflammatory conditions by facilitating migration of inflammatory cells to different tissues. The aim of this study was to investigate whether uPAR rs344781, common genetic polymorphism in the uPAR promoter region, might be associated with migraine without aura susceptibility in an Iranian population.

Methods: We enrolled 103 newly diagnosed patients with migraine and 100 healthy controls. Peripheral blood sample was used for DNA extraction and uPAR rs344781 gene polymorphism was determined. Patients filled HIT-6 as a tool to evaluate headache severity.

Results: The genotype frequency of uPAR is significantly different between migraine patients and control subjects. Heterozygote genotype (AG) was statistically more frequent in the patients than the controls ($P = 0.001$; OR = 2.67, 95% CI = 1.51–4.7). Also G allele was more frequent in the patients. Total HIT-6 score was not significantly different between heterozygote and homozygote patients (55.50 ± 2.22 vs. 49.60 ± 3.68 respectively, $P = 0.075$).

Conclusion: In conclusion, our study showed a significant association between uPAR rs344781 gene promoter polymorphism and migraine without aura susceptibility but not with headache severity.

References

[1] Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343–9.

[2] Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. JAMA: The Journal of the AMERICAN Medical Association 2003;290:2443–54.

[3] Bigal ME, Ferrari M, Silberstein SD, Lipton RB, Goadsby PJ. Migraine in the triptan era: lessons from epidemiology, pathophysiology, and clinical science. Headache 2009;49(Suppl. 1):S21–33.

[4] Bernstein C, Burstein R. Sensitization of the trigeminovascular pathway: perspective and implications to migraine pathophysiology. Journal of Clinical Neurology (Seoul, Korea) 2012;8:89–99.

[5] Moulton EA, Burstein R, Tully S, Hargreaves R, Becerra L, Borsook D. Interictal dysfunction of a brainstem descending modulatory center in migraine patients. PLoS ONE 2008;3:e3799.

[6] Richter F, Lehmenkuhler A. Cortical spreading depression (CSD): a neurophysiological correlate of migraine aura. Schmerz 2008;22:544–6, 548–550.

[7] Ngo JC, Jiang L, Lin Z, Yuan C, Chen Z, Zhang X, et al. Structural basis for therapeutic intervention of uPA/uPAR system. Current Drug Targets 2011;12:1729–43.

[8] Manetti M, Allanore Y, Revillod L, Fatini C, Guiducci S, Cuomo G, et al. A genetic variation located in the promoter region of the UPAR (CD87) gene is associated with the vascular complications of systemic sclerosis. Arthritis and Rheumatism 2011;63:247–56.

[9] Thuno M, Macho B, Eugen-Olsen J. suPAR: the molecular crystal ball. Disease Markers 2009;27:157–72.

[10] The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24(Suppl. 1):9–160.

[11] Kosinski M, Bayliss MS, Bjorner JB, Ware Jr JE, Garber WH, Batenhorst A, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Quality of Life Research 2003;12:963–74.

[12] Zandifar A, Banihashemi M, Haghdoost F, Masjedi SS, Manouchehri N, Asgari F, et al. Reliability and Validity of the Persian HIT-6 Questionnaire in Migraine and Tension-type Headache. Pain Practice: The Official Journal of World Institute of Pain 2013, in press.

[13] Blasi F, Carmeliet P. uPAR: a versatile signalling orchestrator. Nature Reviews: Molecular Cell Biology 2002;3:932–43.

[14] Yilmaz IA, Ozge A, Erdal ME, Edgunlu TG, Cakmak SE, Yalin OO. Cytokine polymorphism in patients with migraine: some suggestive clues of migraine and inflammation. Pain Medicine 2010;11:492–7.

[15] Kuzuya M, Iguchi A. Role of matrix metalloproteinases in vascular remodeling. Journal of Atherosclerosis and Thrombosis 2003;10:275–82.

[16] Tkachuk VA, Plekhanova OS, Parfyonova YV. Regulation of arterial remodeling and angiogenesis by urokinase-type plasminogen activator. Canadian Journal of Physiology and Pharmacology 2009;87:231–51.

[17] Imamura K, Takeshima T, Fusayasu E, Nakashima K. Increased plasma matrix metalloproteinase-9 levels in migraineurs. Headache 2008;48:135–9.

[18] Ishizaki K, Takeshima T, Fukuhara Y, Araki H, Nakaso K, Kusumi M, et al. Increased plasma transforming growth factor-beta1 in migraine. Headache 2005;45:1224–8.

[19] Napoli R, Guardasole V, Zarra E, Matarazzo M, D'Anna C, Sacca F, et al. Vascular smooth muscle cell dysfunction in patients with migraine. Neurology 2009;72:2111–4.

[20] Lee ST, Chu K, Jung KH, Kim DH, Kim EH, Choe VN, et al. Decreased number and function of endothelial progenitor cells in patients with migraine. Neurology 2008;70:1510–7.

[21] Milhaud D, Bogousslavsky J, van Melle G, Liot P. Ischemic stroke and active migraine. Neurology 2001;57:1805–11.

[22] Nicholl SM, Roztocil E, Davies MG. Plasminogen activator system and vascular disease. Current Vascular Pharmacology 2006;4:101–16.

[23] Albers GW. Management of acute ischemic stroke. An update for primary care physicians. Western Journal of Medicine 1997;166:253–62.

[24] Wang YF, Tsirka SE, Strickland S, Stieg PE, Soriano SG, Lipton SA. Tissue plasminogen activator (tPA) increases neuronal damage after focal cerebral ischemia in wild-type and tPA-deficient mice. Nature Medicine 1998;4:228–31.

[25] Nagai N, De Mol M, Lijnen HR, Carmeliet P, Collen D. Role of plasminogen system components in focal cerebral ischemic infarction: a gene targeting and gene transfer study in mice. Circulation 1999;99:2440–4.

[26] Lindgren A, Lindoff C, Norrving B, Astedt B, Johansson BB. Tissue plasminogen activator and plasminogen activator inhibitor-1 in stroke patients. Stroke 1996;27:1066–71.

[27] Bruneau N, Szepetowski P. The role of the urokinase receptor in epilepsy, in disorders of language, cognition, communication and behavior, and in the central nervous system. Current Pharmaceutical Design 2011;17:1914–23.

[28] Bhaskar S, Abdullah JM, Ghazali MM. Coexistence of CACNA1A, ATP1A2, and KCNN3 gene mutation in migraine patients with human platelet polymorphism. Neurosciences (Riyadh, Saudi Arabia) 2008;13:356–8.

[29] Bhaskar S, Abdullah JM. Platelet alloantigen polymorphism and migraine headaches. Neurosciences (Riyadh, Saudi Arabia) 2013;18:185–6.

[30] Shih CM, Kuo WH, Lin CW, Chen W, Cheng WE, Chen SC, et al. Association of polymorphisms in the genes of the urokinase plasminogen activation system with susceptibility to and severity of non-small cell lung cancer. Clinica Chimica Acta; International Journal of Clinical Chemistry 2011;412:194–8.

[31] Weng CJ, Tsai CM, Chen YC, Hsieh YH, Lin CW, Liu YF, et al. Evaluation of the association of urokinase plasminogen activator system gene polymorphisms with susceptibility and pathological development of hepatocellular carcinoma. Annals of Surgical Oncology 2010;17:3394–401.