

## Guillain-Barre syndrome outbreak in Peru: Association with polymorphisms in *IL-17*, *ICAM-1* and *CD1*

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### SUMMARY:

Guillain-Barre Syndrome (GBS) is considered a complex disorder with significant environmental effect and genetic susceptibility. Genetic polymorphisms in *CD1E*, *CD1A*, *IL-17* and/or *ICAM-1* genes had been proposed as susceptibility genetic variants for GBS mainly in Caucasian population. This study explores the association between selected polymorphisms in these genes and GBS susceptibility in confirmed GBS cases reported in mestizo population from northern Peru during the most recent GBS outbreak of May 2018. A total of 9 non-related cases and 11 controls were sequenced for the polymorphic regions of *CD1A*, *CD1E*, *IL-17* and *ICAM-1* genes. We found a significant protective association between heterozygous GA genotype in *ICAM-1* gene (241Gly / Arg) and GBS ( $p < 0.047$ ). *IL-17* was monomorphic in both controls and patients. No significant differences were found in the frequency of SNPs in *CD1A* and *CD1E* between the group with GBS patients and healthy controls. Further studies with larger sample size will be required to validate these findings.

KEYWORDS: Guillain-Barre syndrome, genetic polymorphism, *CD1*, *IL-17*, *ICAM-1*

### INTRODUCTION

Guillain-Barre syndrome (GBS) is an acute inflammatory polyradiculoneuropathy with ascending weakness starting in lower limbs, extension to the upper limbs and face, as well as complete loss of deep tendon reflexes (1- 4). The annual incidence of GBS is 0.5-2 cases per 100,000 people, which increases with age (3,4). GBS is rare in children under two years (5); males are 1.5 times more likely to suffer GBS than women (4-6). The exact cause of GBS has not been defined yet; however, 50-70% of the cases appear 1-2 weeks after an infection (bacterial or viral) inducing an aberrant autoimmune response directed to the peripheral nerves and their spinal roots (4,7,8). GBS is known to occur in several forms including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), Miller Fisher syndrome (MFS), acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAN).

The interaction between microbial and host factors has been poorly studied in GBS, as well as the genetic susceptibility of an individual to develop this syndrome. Possible markers of genetic

susceptibility to GBS have been reported, including *CD1E* (OMIM #188411), *CD1A* (OMIM #188370), *IL-17* (OMIM #606496) and *ICAM-1* (OMIM #147840) (9,10). The *CD1E* and *CD1A* genes are glycoproteins of Major Histocompatibility Complex (MHC) specialized in capturing and presenting glycolipids to T cells (10,11). In a research study conducted by Caporale et al, it was reported that individuals with the genotype *CD1E*\*01/01 were 2.5 times more susceptible to develop GBS, while individuals with the genotypes *CD1A*\*01/02 or *CD1E*\*01/02 had a risk of 3.6 and 2.3 times lower, respectively (10). Likewise, there has also been an association of GBS with polymorphisms *IL-17* (Glu126Gly) and *ICAM-1* (Gly241Arg) (9). *IL-17* regulates the expression of inflammatory genes, including proinflammatory chemokines, hematopoietic cytokines, acute phase response genes and antimicrobials (12) in neutrophils, macrophages and endothelial cells (13). On the other hand, previous studies show that *ICAM-1* plays a central role in the development of demyelinating disease (14).

GBS and its association with a variety of infectious agents have been reported in Peruvian population. By 2014, case series of 32 GBS cases followed in Lima (capital city) found that AIDP was the most common form (75%) followed by AMAN and MFS with frequencies of 18.8% and 6.3%, respectively (15). By contrast, series from northern Peru (2017) found 16 Peruvian cases where AMSAN was the most common form (37.5%) followed by AMAN (25%) and AIDP (12.5%) (16). In 1987, five GBS cases were associated with a viral infection caused by a rabies vaccine prepared with the brain of a lactating mouse (17). In 2010, a GBS case was reported associated to Brucellosis, an infectious disease caused by *Brucella* bacteria genus (18).

In Peru, 15 cases of GBS were reported between April and May of 2018 in Trujillo, northern Peru, during summer time, activating a national epidemiological alert declared by the Ministry of Health. All cases were put on immunoglobulin G and managed in the intensive care unit at a regional Hospital. Blood samples were taken in all cases for both environmental exposure and DNA extraction for further genetic analysis.

This study determines the occurrence of polymorphisms in *IL-17*, *ICAM-1* and *CD1* genes in GBS cases with a medical history of enteric respiratory and / or gastrointestinal infection and controls.

## PATIENTS AND METHODS:

### *Ethical approval*

This study was approved by the ethics and research committee of Belen Hospital of Trujillo, northern Peru. A written informed consent was obtained from all subjects prior to recruitment for the study.

### *Cases and controls*

Nine patients with GBS (7 men and 2 women, age: 52 to 65 years) followed at a regional hospital in northern Peru were enrolled in the study during the outbreak of GBS occurred in May, 2018. Eleven healthy subjects (7 women and 4 men, age: 27 to 74 years) were randomly selected as controls from the same geographical area of residence. A total of 3mL of blood was obtained from peripheral veins in all subjects.

### *Isolation of DNA and genotyping of IL-17, ICAM-1 and CD1 genes*

100 microliters of peripheral blood were used to extract DNA using QIAamp DNA Blood Kit Mini (Qiagen, CA, USA) and INBIOMag Genomic DNA Kit (INBIOMEDIC, Peru). According to the literature and genotypes location reported, the following fragments were selected: *IL-17*, *ICAM-1* and *CD1* (2 fragments, found in exon 2). Specific primers were designed for each DNA

fragment (Table 1) and the fragments were PCR amplified using Taq PCR Master Mix Kit (Qiagen, CA, USA). PCR products were purified and sequenced by Sanger technique in Macrogen (Soul Korea).

#### *Genetic analysis*

The DNA sequence data was processed using Geneious R11 software (Biomatters Ltd.). The polymorphisms *IL-17* (Glu126Gly), *ICAM-1* (Gly241Arg) and *CDIA* and *CDIE* genotypes were evaluated. The sequences obtained from *IL-17*, *ICAM-1* and *CDI* were compared with sequences reported in previous research and/or global database.

#### *Statistical analysis*

Polimorfisms of *IL-17*, *ICAM-1* and *CDI* were listed by frequency and percentage. Exploratory analysis comparing frequency of polymorphisms between cases and controls were performed by the chi square test and logistic regression models. Results were considered significant if  $p < 0.05$ . Statistical analysis were performed by SATA version 15.0 (Illinois, USA).

## RESULTS

A total of 9 cases (7 males, 77.8%) analyzed (Table 2) were diagnosed as SGB of atypical presentation. Eight patients reported some type of symptomatology 8 weeks before the onset of paralysis such as respiratory, gastrointestinal infections, non-purulent conjunctivitis, joint and head pain. Only one reported a trip to Virú province days before the paralysis.

All 9 cases experienced muscle weakness, 6 of them also complained of pain, 3 cases presented ataxia, 2 cases had cranial nerves compromise and 3 cases presented symmetric paralysis. Autonomic disturbances, urinary dysfunction, sinus tachycardia and arrhythmia, were each one demonstrated in one case.

Among controls and GBS cases, *IL-17* gene is monomorphic in 01/01 genotype. Table 3 shows the frequencies of *CDIA*, *CDIE* and *ICAM-1* alleles and genotypes in controls and patients with GBS. *CDIA* gene is biallelic. Allele 01 is more frequent in both controls and patients with GBS. *CDIA*\*02/02 genotype is not represented in controls and is present in only one of 9 patients with GBS. *CDIA*\*01/01 genotype is slightly more frequent in control patients compared with GBS.

*CDIE* gene has two alleles with approximately the same frequency in controls and patients. (Table 3). *CDIE*\*01/02 genotype is more frequent in both controls and patients with GBS. *ICAM-1* gene is biallelic (Table 3). Allele 01 is more frequent in patients with GBS than in controls. *ICAM-1*\*01/01 genotype is not represented in controls and is present in 6 of 9 patients with GBS. *ICAM-1*\*02/02 genotype is not represented in GBS patients and is present in 9 of 11 control patients.

According to a first bivariate analysis (Table 2), the risk of being diagnosed with SGB in people with *ICAM-1* GA genotype is lower compared to people with *ICAM-1* GG genotype and this difference is statistically significant ( $p: 0.040$ ). No statistically significant differences were found between groups of patients studied according to GBS diagnosis and other covariates analyzed: sex, age, genotypes *CDIA*, *CDIE*, *IL-17* ( $p > 0.05$ ).

According to regression analysis, *ICAM-1* genotype and BMI variables contribute statistically to association under study (Table 4); Thus, the risk (OR) of being diagnosed with GBS in people with *ICAM-1* GA genotype is about one third (33%) compared with people with *ICAM-1* GG

genotype (95% CI: 0.11 – 0.99; p: 0.047). The rest of covariates with exception of BMI do not contribute statistically significant to the association under study.

## DISCUSSION

This is the first analysis of *IL-17*, *ICAM-1* and *CD1* genes polymorphisms in Peruvian patients with GBS and healthy controls. Significant differences in the frequency of *ICAM-1* SNPs were observed between patients with GBS and healthy controls, implying *ICAM-1* polymorphisms do influence susceptibility to GBS in the Peruvian population. Additionally, no genetic associations were observed between *IL-17* and *CD1* polymorphisms and GBS susceptibility.

Members of the CD1 family are key players in the immune response to glycolipids and may be involved in the GBS pathogenesis, especially in patients with history of *C. jejuni* infections and anti-ganglioside antibodies (10,19). SNPs in *CD1B* (OMIM #188360), *CD1C* (OMIM #188340), and *CD1D* (OMIM #188410) genes were not determined in the current study because these are very rare and/or silent (21).

*CD1A* and *CD1E* are biallelic in exon 2 (20). *CD1E* is the most polymorphic gene and reports variants in exon 3 also (20, 21). In our study, no significant differences were found in the SNPs frequency of *CD1A* and *CD1E* between GBS patients and healthy controls, which indicates that these genetic polymorphisms do not influence the susceptibility to GBS development in the population studied. (Table 3). In addition, there was no genetic association with clinical outcome in GBS patients. These results do not support the hypothesis that *CD1A* and *CD1E* influence GBS risk as it was raised in a previous study that was based on an Italian cohort of GBS patients (10). It is likely that this discrepancy is caused by differences in patient populations, although both had an ethnic origin, with a similar distribution of polymorphic frequencies in *CD1E* gene, but different in *CD1A* gene. On the other hand, it should be noted that the absence of association with polymorphisms of *CD1* gene does not exclude the possibility that *CD1* molecules play an important role in GBS pathogenesis. More research is needed to determine if it is *CD1* molecules or pathways subsequent to *CD1*, those that participate in process of glycolipids antigenic presentation in GBS.

Many association studies have reported that *IL-17* polymorphisms predispose to autoimmune and inflammatory diseases (22,23,24,25). However, some *IL-17F* polymorphisms (Glu126Gly and His161Arg) may not be significantly associated with autoimmune diseases (26). There are no data reported in the context of *IL-17F* polymorphism with GBS. The importance of *IL-17F* polymorphism in GBS is still largely unknown. In our study, it was observed that *IL-17* gene is monomorphic in 01/01 genotype for patients with GBS and controls.

Increased expression of *ICAM-1* gene has been demonstrated in endothelial cells, microglia and astrocytes in patients with multiple sclerosis (27, 28). We have observed significant protection association with GBS in people with heterozygous GA genotype in *ICAM-1* gene (241Gly / Arg) (p <0.047). These results do not support the association hypothesis of significant risk of heterozygous *ICAM-1* genotype (241Gly / Arg) in GBS as it was raised in a previous control case study in India with GBS (Table 5). Here, we can see other associated diseases for *ICAM-1* G241R polymorphisms studies. Differences can also be explained in part by statistical analysis methods (10,35).

The study number and sample size were limited, which may affect the reliability of the results. As well as, the differences may be explained by genetic diversities, different risk factors in life

styles, and the exposure to different environmental factors. In conclusion, *ICAM-1* polymorphisms might be considered as potential genetic markers of GBS susceptibility after studies with larger sample size and further validation in ethnically different populations.

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#### REFERENCES:

1. Rodríguez Y, Rojas M, Pacheco Y, Acosta-Ampudia Y, Ramírez-Santana C, Monsalve DM, et al. Guillain-Barré syndrome, transverse myelitis and infectious diseases. *Cell Mol Immunol* [Internet]. 2018; Available from: <http://www.nature.com/doi/10.1038/cmi.2017.142>
2. Eelco FM, Wijdicks EFM KC. Síndrome de Guillain Barré. *Mayo Clin Proceedings*. 2006;22(2):1-9.
3. Winner SJ, Evans JG. Age-specific incidence of Guillain-Barré syndrome in Oxfordshire. *Q J Med* [Internet]. 1990;77(284):1297-304. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2290923>
4. Esposito S, Longo MR. Guillain-Barré syndrome. *Autoimmun Rev*. 2016;1-6.
5. Rosen B a. Guillain-Barré syndrome. *Pediatr Rev* [Internet]. 2012;33(4):164-70; quiz 170-1. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22474113>
6. Hughes R, Cornblath D. Guillain-Barré syndrome. *Lancet*. 2005;366(9497):1653-66.
7. Ropper AH. The Guillain-Barré syndrome. *N Engl J Med* [Internet]. 1992;326(17):1130-6. Available from: [papers2://publication/uuid/FB22A687-EFE7-4401-9F7D-A86DDB0FE6D7](https://pubmed.ncbi.nlm.nih.gov/14888888/)
8. Walgaard C, Lingsma HF, Ruts L, van Doorn PA, Steyerberg EW, Jacobs BC. Early recognition of poor prognosis in Guillain-Barre syndrome. *Neurology* [Internet]. 2011;76(11):968-75. Available from: <http://www.neurology.org/cgi/doi/10.1212/WNL.0b013e3182104407>
9. Kharwar NK, Prasad KN, Singh K, Paliwal VK, Modi DR. Polymorphisms of IL-17 and ICAM-1 and their expression in Guillain-Barré syndrome. *Int J Neurosci*. 2017;127(8):680-7.
10. Caporale CM, Papola F, Fioroni MA, Aureli A, Giovannini A, Notturmo F, et al. Susceptibility to Guillain-Barré syndrome is associated to polymorphisms of CD1 genes. *J Neuroimmunol*. 2006;177(1-2):112-8.
11. Porcelli SA, Modlin RL. THE CD1 SYSTEM: Antigen-Presenting Molecules for T Cell Recognition of Lipids and Glycolipids. *Annu Rev Immunol* [Internet]. 1999;17(1):297-329. Available from: <http://www.annualreviews.org/doi/10.1146/annurev.immunol.17.1.297>
12. Shen F, Gaffen SL. Structure-function relationships in the IL-17 receptor: implications for signal transduction and therapy. *Cytokine*. 2008;41:92-104. Epub 2008/01/08.
13. Zepp J, Wu L, Li X. IL-17 receptor signaling and T helper 17-mediated autoimmune demyelinating disease. *Trends Immunol*. 2011;32:232-9. Epub 2011/04/16

14. Musso AM, Zanusso GL, Bonazzi ML, Tomelleri G, Bonetti B, Moretto G, Vio M, Monaco S. Increased serum levels of ICAM-1, ELAM-1 and TNF-alpha in inflammatory disorders of the peripheral nervous system. *Ital J Neurol Sci.* 1994;15:267-71. Epub 1994/09/01
15. Apaza N, Litman E. Características clínicas y electrofisiológicas del Síndrome de Guillain-Barré en el Instituto de Ciencias Neurológicas 2008-2012 Lima. Universidad Nacional Mayor de San Marcos; 2014.
16. Ballón-Manrique B, Campos-Ramos N. Características clínicas y paraclínicas del Síndrome de Guillain-Barré en el Hospital Regional Lambayeque. *Rev Neuropsiquiatría.* 2017;80(1).
17. Cabrera J, Griffin DE, Johnson RT. Unusual features of the Guillain-Barre syndrome after rabies vaccine prepared in suckling mouse brain. *J Neurol Sci.* 1987;81(2-3):239-45.
18. Montalvo R, García Y, Ñavincopa M, Ticona E, Chávez G, Moore DA. Guillain barré syndrome in association with brucellosis. *Rev Peru Med Exp y Salud Publica.* 2010;27(2):292-5.
19. De Libero, G., Moran, A.P., Gober, H.J., Rossy, E., Shamshiev, A., Chelnokova, O., Mazorra, Z., Vendetti, S., Sacchi, A., Prendergast, M.M., Sansano, S., Tonevitsky, A., Landmann, R., Mori, L., 2005. Bacterial infections promote T cell recognition of self-glycolipids. *Immunity* 22, 763-772.
20. Han, M., Hannick, L.I., DiBrino, M., Robinson, M.A., 1999. Polymorphism of human CD1 genes. *Tissue Antigens* 54, 122-127.
21. Mirones, I., Oteo, M., Parra-Cuadrado, J.F., Martinez-naves, E., 2000. Identification of two novel human CD1E alleles. *Tissue Antigens* 56, 159-161.
22. Kawaguchi M, Takahashi D, Hizawa N, Suzuki S, Matsukura S, Kokubu F, Maeda Y, Fukui Y, Konno S, Huang SK, Nishimura M, Adachi M. IL-17F sequence variant (His161Arg) is associated with protection against asthma and antagonizes wild-type IL-17F activity. *J Allergy Clin Immunol.* 2006;117:795-801. Epub 2006/04/25.
23. Arisawa T, Tahara T, Shibata T, Nagasaka M, Nakamura M, Kamiya Y, Fujita H, Yoshioka D, Arima Y, Okubo M, Hirata I, Nakano H. The influence of polymorphisms of interleukin-17A and interleukin-17F genes on the susceptibility to ulcerative colitis. *J Clin Immunol.* 2008;28:44-9. Epub 2007/09/11.
24. Jang WC, Nam YH, Ahn YC, Lee SH, Park SH, Choe JY, Lee SS, Kim SK. Interleukin-17F gene polymorphisms in Korean patients with Behcet's disease. *Rheumatol Int.* 2008;29:173-8. Epub 2008/09/05.
25. Seiderer J, Elben I, Diegelmann J, Glas J, Stallhofer J, Tillack C, Pfennig S, Jurgens M, Schmechel S, Konrad A, Goke B, Ochsenkuhn T, Muller-Myhsok B, Lohse P, Brand S. Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn's disease and analysis of the IL17F p.His161Arg polymorphism in IBD. *Inflamm Bowel Dis.* 2008;14:437-45. Epub 2007/12/20
26. Paradowska-Gorycka A, Wojtecka-Lukasik E, Trefler J, Wojciechowska B, Lacki JK, Maslinski S. Association between IL-17F gene polymorphisms and susceptibility to and severity of rheumatoid arthritis (RA). *Scand J Immunol.* 2010;72:134-41. Epub 2010/07/14.

27. Carrithers MD, Visintin I, Kang SJ, Janeway CA, Jr. Differential adhesion molecule requirements for immune surveillance and inflammatory recruitment. *Brain*. 2000;123 ( Pt 6):1092-101. Epub 2000/05/29.
28. Mycko MP, Kwinkowski M, Tronczynska E, Szymanska B, Selmaj KW. Multiple sclerosis: the increased frequency of the ICAM-1 exon 6 gene point mutation genetic type K469. *Ann Neurol*. 1998;44:70-5. Epub 1998/07/17.
29. Kharwar, N. K., Prasad, K. N., Singh, K., Paliwal, V. K., & Modi, D. R. (2016). Polymorphisms of IL-17 and ICAM-1 and their expression in Guillain-Barré syndrome. *International Journal of Neuroscience*, 127(8), 680–687. doi:10.1080/00207454.2016.1231186
30. Mycko MP, Kwinkowski M, Tronczynska E, Szymanska B, Selmaj KW (1998). Multiple sclerosis: the increased frequency of the ICAM-1 exon 6 gene point mutation genetic type K469. *Ann. Neurol.*, 44: 70-75
31. Cheng, D., & Liang, B. (2015). Intercellular Adhesion Molecule-1 (ICAM-1) Polymorphisms and Cancer Risk: A Meta-Analysis. *Iranian journal of public health*, 44(5), 615-24.
32. Luca Cimino, Luigi Boiardi, Raffaella Aldigeri, Bruno Casali, Davide Nicoli, Enrico Farnetti, Carlo Salvarani, Daniele Cirone, Liberatina De Martino, Alessandro Pupino, Luca Cappuccini (2010). G/R 241 Polymorphism of Intercellular Adhesion Molecule 1 (ICAM-1) Is Associated with Fuchs Uveitis. *Invest. Ophthalmol. Vis. Sci.*;51(9):4447-4450.
33. Riedel M, Krönig H, Schwarz MJ, Engel RR, Sikorski C, Kühn KU, Behrens S, Möller HJ, Ackenheil M, Müller N (2003). Investigation of the ICAM-1 G241A and A469G gene polymorphisms in schizophrenia. *Mol Psychiatry*; 8: 257–258.
34. Volcik KA, Ballantyne CM, Hoogeveen R, Folsom AR, Boerwinkle E (2010). Intercellular adhesion molecule-1 G241R polymorphism predicts risk of incident ischemic stroke: Atherosclerosis Risk in Communities study. *Stroke*. May;41(5):1038-40
35. Bang, H., Mazumdar, M., Zaykin, D., 2007. A letter to the editor in reply to “susceptibility to Guillain-Barré syndrome is associated to polymorphisms of CD1 genes” by Caporale et al. in the *J of Neuroimmunology* (2006), 177:112–118. *J. Neuroimmunol.* 186, 201–202.

TABLES

**Table 1.** Primers used in the genetic analysis of Guillain-Barre Syndrome

Gen	Primers (5'→3')
<i>CD1A</i>	AGACGGGCTCAAGGAGCCTC
	TTCAAAGTGAATTCATGGGC
<i>CD1E</i>	GAGGAGCAGCTGTCCTCCG
	ATTGACCAGCAGAAGCTTGC
<i>IL-17</i>	GTTGTACAGGCCAGTGTAG
	GGATATGCACCTCTTACTGC
<i>ICAM-1</i>	CCGTGGTCTGTTCCCTGTAC
	GAAGGAGTCGTTGCCATAGG

**Table 2.** Bivariate analysis of factors associated with the diagnosis of Guillain-Barre Syndrome

Variables	Guillain-Barre Syndrome		p
	Yes (n=9) n(%)	No (n=11) n(%)	
<b>Sex</b>			0.080 <sup>a</sup>
Male	7 (63.6)	4 (36.4)	
Women	2 (22.2)	7 (77.8)	
<b>Age</b>	55 (52 – 65)*	44 (34 – 63)*	0.087 <sup>b</sup>
<b>BMI</b>			0.013 <sup>a</sup>
Malnourished (<18)	1 (100.0)	0 (0.0)	
Normal (18-25)	2 (16.7)	10 (83.3)	
Overweight (>25)	4 (80.0)	1 (20.0)	
<b>rs2269715 (CD1A)</b>			0.361 <sup>a</sup>
01/01 (CC)	6 (37.5)	10 (62.5)	
01/02 (GC)	2 (66.7)	1 (33.3)	
02/02 (GG)	1 (100.0)	0 (0.0)	
<b>rs2269714 (CD1A)</b>			0.421 <sup>a</sup>
01/01 (CC)	6 (37.5)	10 (62.5)	
01/02 (CT)	2 (100.0)	0 (0.00)	
02/02 (TT)	1 (50.0)	1 (50.0)	
<b>rs1065457 (CD1E)</b>			0.816 <sup>a</sup>
01/01 (AA)	1 (33.3)	2 (66.7)	
01/02 (AG)	6 (42.9)	8 (57.1)	



02/02 (GG)	2 (66.7)	1 (33.3)	0.040 <sup>a</sup>
<b><i>rs1799969 (ICAM-1)</i></b>			
01/01 (GG)	6 (71.4)	2 (28.6)	
01/02 (GA)	3 (25.0)	9 (75.0)	
02/02 (AA)	0 (0.0)	0 (0.0)	

\*Median (Q1 – Q3)

p value from statistical test: Fisher's exact. b:Mann-Whitney

BMI: Body Mass Index

**Table 3:** Genotype and frequency of alleles for *CDIA*, *CDIE*, *IL-17* and *ICAM-1* in GBS patients and controls

	Genotype			% of allele		% of persons	
	Persons number (%)			Frequency		Positive for alleles	
	01/01	01/02	02/02	01	02	01	02
<b><i>CDIA</i></b>							
<i>rs2269715</i>							
GBS	6 (67%)	2 (22%)	1 (11%)	82	18	89	33
Control	10 (91%)	1 (9%)	0 (0%)	95	5	100	9
<i>rs2269714</i>							
GBS	6 (67%)	2 (22%)	1 (11%)	82	18	89	33
Control	10 (91%)	0 (0%)	1 (9%)	91	9	91	9
<b><i>CDIE</i></b>							
GBS	1 (11%)	6 (67%)	2 (22%)	44	56	78	89
Control	2 (18%)	8 (73%)	1 (9%)	55	45	91	82
<b><i>IL-17</i></b>							
GBS	9 (100%)	-	-	100	-	100	-
Control	11 (100%)	-	-	100	-	100	-
<b><i>ICAM-1</i></b>							
GBS	6 (67%)	3 (33%)	0 (00%)	83	17	100	33
Control	0 (0%)	2 (18%)	9 (82%)	9	91	18	100

**Table 4.** Regression analysis of factors associated with diagnosis of Guillain-Barre Syndrome

Features	Bivariate analysis		
	OR	CI 95%	p
<b>Sex</b>			
Women	Ref.		
Male	2.86	0.75 – 9.17	0.122
<b>Age (years)</b>	1.03	0.99 – 1.07	0.136
<b>BMI</b>			
Normal	Ref.		
Malnourished	6.0	1.63 - 22.06	0.007
Overweight	4.8	1.21 – 19.04	0.026
<b>rs2269715 (CD1A)</b>			
01/01 (CC)	Ref.		
01/02 (CG)	1.78	0.62 – 5.06	0.281
02/02 (GG)	2.67	1.39 - 5.10	0.003
<b>rs2269714 (CD1A)</b>			
01/01 (CC)	Ref.		
01/02 (CT)	2.67	1.39 – 5.10	0.003
02/02 (TT)	1.33	0.28 – 6.36	0.718
<b>rs1065457 (CD1E)</b>			
01/01 (AA)	Ref.		
01/02 (AG)	1.29	0.22 – 7.44	0.779
02/02 (GG)	2	0.32 – 12.54	0.459
<b>rs179969 (ICAM)</b>			
01/01 (GG)	Ref.		
01/02 (GA)	0.33	0.11 – 0.99	0.047

p value from statistical test: Logistic regression  
 BMI: Body Mass Index

**Table 5.** Associated diseases of 8 eligible studies for *ICAM-1* G241R polymorphisms analysis

Diseases	Genotype	OR	p value	Population	Reference
Guillain-Barre Syndrome	241Gly / Arg (GA)	4.14	<0.001	Indian	(29)
Multiple Sclerosis	241Gly / Arg (GA)	0.64	<0.200	Polish Caucasian	(30)

Cancer	241Gly / Arg (GA)	2.03	<0.010	Asian-European-American	(31)
Cancer	241Gly / Arg (GA)	1.95	<0.010	European	(31)
Fuchs Uveitis	241Gly / Arg (GA)	3.3	0.012	Italian	(32)
Schizophrenia	241Gly / Arg (GA)	1.14	0.771	German Caucasian	(33)
Ischemic Stroke	241Gly / Arg (GA)	1.82	0.001	ARIC Study (white)	(34)
Ischemic Stroke	241Gly / Arg (GA)	1.49	0.300	ARIC Study (black)	(34)
Guillain-Barre Syndrome	241Gly / Arg (GA)	0.33	0.047	Our study	

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ARIC: Atherosclerosis Risk in Communities