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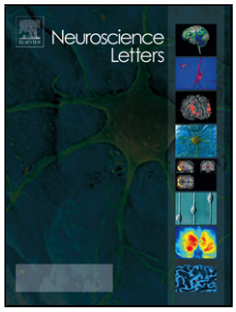

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Title

Minor allele C of rs12807809 polymorphism in *NRGN* contributes to the severity of psychosis in patients with Schizophrenia in South Indian population

Authors

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Highlights

- The SNP rs12807809 in *NRGN* is a promising risk variant identified for schizophrenia by genome-wide association studies.
- We investigated the association of *NRGN* rs12807809 in 1005 Schizophrenia patients and 1069 controls in South Indian population.
- The rs12807809 in NRGN showed a significant difference between cases and controls and is associated with Schizophrenia.
- The minor non-risk allele 'C' contributes to the severity of psychosis in this study population.

Abstract

Schizophrenia (SCZ) as a severe and complex neuropsychiatric disorder and is characterized by positive symptoms, negative symptoms and cognitive dysfunctions. Genome-wide association studies (GWAS) have identified a strong association between the single nucleotide polymorphism (SNP) rs12807809 upstream of Neurogranin (*NRGN)* in a European population. This evidence prompted us to conduct an association study among 1,005 schizophrenia cases and 1,069 controls in a South Indian Population using TaqMan Allelic discrimination method. We observed an association of rs12807809 with SCZ in this study population. Allele frequencies and genotype frequencies of rs12807809 showed significant differences between cases and control subjects [**p=0.0019**; OR = 0.69; 95% CI = (0.55 – 0.87)] and **(p=0.0062).** Further Genotype-Phenotype correlation revealed a moderate association of rs12807809 with flat affect (**p=0.039**) and Hallucinations (**p=0.012**). The ancestral non-risk C allele contributes to the severity of psychosis (**p=0.039**) in this population.

Keywords: *NRGN* genotype, rs12807809, Cases Control study, GWAS Replication, Schizophrenia.

Introduction

Schizophrenia (SCZ) a severe and complex neuropsychiatric disorder, has a lifetime prevalence of ~1% which constituting ~ 1% of the global burden of disease (GBD) [1]. SCZ is characterized by positive symptoms (hallucinations, delusions), negative symptoms (avolition, social withdrawal, reduced affective expression) and cognitive dysfunctions (attention, memory, executive functions, etc.). Genetic epidemiology of SCZ has documented

a heritability of ~ 80%, highlighting a major role for inherited genetic variants in the etiology of schizophrenia. Family, twin and adoption studies have consistently demonstrated genetic component to schizophrenia, together with developmental and environmental influences. The onset of large-scale genome-wide association and copy number variation (CNV) studies has led to rapid advances in our understanding of the genetic architecture of schizophrenia. A growing number of common SNPs and rare CNVs have now been replicated, including some that hint at possible novel aetiological mechanisms [2]. A combined GWAS analysis in European populations reported seven significant SNPs associated with SCZ [3], including rs12807809, located 3,457 bases upstream from the Neurogranin (*NRGN)* gene at 11q24.2. While the latest SCZ GWAS study by the Psychiatric Genomics Consortium (PGC) did not observe genome-wide significance for rs12807809, it did report strong support (p=4.114E-7) for this SNP [4]. Other studies in Han Chinese and Japanese populations have, however, failed to observe an association of this SNP with SCZ [5,6].

The Neurogranin (*NRGN*) gene on chromosome 11q24.2 spans 7.3 kb of genomic DNA and contains four exons. A genome-wide linkage study demonstrated that 11q23.3-24, wherein *NRGN* is located, was linked to SCZ (p=0.0003) [7]. *NRGN* regulates the release of CaM and the activities of downstream CaM-Ca2+-dependent enzymes that play an important role in the neuroplasticity mechanisms of learning and memory [8]. It has been shown to play a role in dendritic spine formation, synaptic plasticity, long-term potentiation and spatial learning, and is abundantly expressed in areas of the brain that are important for learning, memory and cognitive processing, particularly CA1 pyramidal neurons in the hippocampus [9]. Altering *NRGN* activity could mimic the effects of *NMDA* receptor hypofunction suggesting implication in the pathophysiology of SCZ [10]. Based on the above reports *NRGN* appears to be a key candidate gene for schizophrenia by its function and position. To the best of our knowledge this is the first report of this important polymorphism in an Indian population.

Materials and Methods

Subject selection:

In this case-control study a total of 1005 SCZ patients were recruited from the Schizophrenia Research Foundation (SCARF), Chennai. Inclusion criteria were: (1) Consensus diagnosis of Schizophrenia/Schizoaffective disorder based on the Diagnostic and Statistical Manual of

Mental Disorders, fourth edition (DSM-IV-TR) by experienced psychiatrists; (2) Tamil Indian ethnicity with biological parents and grandparents having the same ethnic background. Exclusion criteria for individuals were: (1) age less than 18 years; (2) inability to give informed consent; (3) psychosis judged to be secondary to substance use or a known neurological disorder such as epilepsy; and (4) severe mental retardation [11,12]. Healthy controls (N=1069) from similar ethnic groups were recruited for this study. Subjects having a first degree relative with severe mental illness and/or Mental retardation were excluded. Written informed consent was obtained from all the participants and the study was carried out with prior approval from the Institutional Ethics Committee of SCARF, Chennai.

Clinical Diagnosis

All patients were assessed using the Diagnostic Interview for Genetic Studies (DIGS) [13] and Family Interview for Genetic Studies (FIGS) [14] instruments. DIGS is a structured interview for studies of psychiatric disorders and covers relevant history including age of onset of illness, duration of untreated psychoses, and symptom history, both medical and psychiatric. The psychosis section of DIGS covers positive and negative symptoms with the severity of the symptoms rated using the Schedule for Assessment of Positive (SAPS) and Negative (SANS) [15,16] . Symptoms are rated on a six point scale with scores ranging from “0” (none) to “5” (severe). Positive symptoms (SAPS) include Hallucinations, Delusions, Bizzare Behaviour and Thought disorder while Negative Symptoms (SANS) include Affective flattening, Alogia, Avolition/Apathy, Anhedonia/Asociality and Attention. The DIGS also includes longitudinal assessment of course and pattern of illness as well as severity in functional deterioration that is rated on a five-point scale from ‘episodic shift’ (1) to ‘relatively stable’ (5) with the higher score denoting worse outcome.

The FIGS is a structured interview conducted with a family informant to identify and collect history of the illness about their ill relatives as well as constructing a pedigree chart with information regarding the presence of family history of mental illness (in up to three generations) and consanguinity in marriages (up to 3rd degree). All the data from the DIGS and FIGS were collated into a clinical summary which was reviewed by independently by two experienced psychiatrists who together subsequently arrived at a consensus diagnosis of the case according to DSM-IV-TR criteria.

The controls were screened using the General Screening Questionnaire (GSQ) from the FIGS for screening out those with both a personal history of mental illness as well as a family history (first degree) of mental illness.

SNP genotyping

The peripheral venous blood samples were collected in EDTA tubes and genomic DNA was extracted from whole blood sample by the salting out method [17]. Genotyping of the rs12807809 polymorphism was conducted using high-throughput fluorescence-based TaqMan SNP Genotyping Assay (Assay ID: C_32029000_20, Applied Biosystems, Foster City, CA). The assay was performed in 384 well microtiter plates containing 10 ng DNA and TaqMan Mastermix (Applied Biosystems, USA) in a total 5 µl reaction. The reaction mixture was amplified with the following thermal cycling conditions: 2 min at 50°C, 10 min at 95°C followed by 40 cycles of 15 sec at 92°C and 60 sec at 60°C. Allelic discrimination with end point detection of fluorescence was performed using ABI 7900 real-time PCR system (Applied Biosystems, Foster City, CA). Genotypes were called using an automated allele scoring software SDS v 2.1 with confidence value of 95% and analysed with TaqMan SNP Genotyper Module v1.0.

Statistical analysis

Statistical analyses were performed with the R program (R Core Team, 2015). The data were analysed by χ^2 test for goodness-of-fit using the GENETICS package (Gregory Warnes, 2013) to know whether the samples were in Hardy-Weinberg equilibrium. Pearson's chi-square test and Fisher's exact test were used for association analysis of genotypes using EPITOOLS package (Tomas J. Aragon, 2012). Chi-Square Test of Independence by contingency table calculated in SPSS 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) were used to test association between the *NRGN* genotype and clinical characteristics. All P-values were two-tailed, and P-value less than 0.05 was considered as statistically significant.

Results

Genotyping analysis of the *NRGN* SNP rs12807809 was conducted in 1005 SCZ patients (Male=501; Female=504) and 1069 controls (Male=721; Female=348). Bio-Demographic details of patients and controls are listed in Table 1. The mean age did not differ significantly between cases and controls (p =0.3785); however, the male female ratio of the controls was higher than that of patients. The genotype frequencies of the rs12807809 in the patients and controls with the Odds ratio and p-value are shown in Table 2. The $\chi 2$ goodness-of-fit test demonstrated that the distributions of the *NRGN* SNP rs12807809 genotypes were consistent with Hardy-Weinberg equilibrium in controls (**p = 0.61**). In patients, there was an acceptable deviation in HWE (**p = 0.008**) providing additional support for an association of the marker locus with the disease.

The marker rs12807809 in *NRGN* shows an association with SCZ in this study population. Allele **(p=0.0019)** and genotypic frequencies **(p = 0.0062)** of rs12807809 showed significant differences between the cases and control. However, the SNP had the opposite direction of effect **(OR = 0.69, 95% CI = 0.55 – 0.87)** compared to previously reported GWAS.

Assessment of Clinical characteristics with genotype

Analysis of genotype and clinical characteristics were done by test of independence by cross tabulation. When the subjects were sub grouped by gender, there was no significant sex-specific associations for this marker. Further clinical details were analysed in 561 schizophrenia patients. Age of onset was grouped as early (<=14), common (15-45), late onset (>45) and no significant association was observed between genotype and age of onset (p=0.136). Moreover, no association was observed with family history and consanguinity. A moderate association was observed with the rs12807809 for flat affect (**p=0.039**), hallucinations (**p=0.012**) and pattern of disease severity (**p=0.039**) although after applying the Bonferroni correction (α=0.003) clinical association was no longer significant. Interestingly, the non-risk C allele of rs12807809 polymorphism seems to contributes to the severity of psychosis in this study population (Table 3).

Discussion

Schizophrenia as a severe mental disorder with a lifetime risk of approximately 1% and is characterized by positive symptoms, negative symptoms and cognitive dysfunctions. Genome-wide association and follow-up studies have reported an association between SCZ and rs12807809 of the *NRGN* gene on chromosome 11q24.2. The chromosomal region 11q23.3-24, including the *NRGN* gene, is linked to SCZ in British and Icelandic populations, confirmed by a genome-wide genetic linkage analysis [7]. The marker rs12807809 of *NRGN* gene attain genome wide significance ($p = 2.4 \times 10^{-9}$) when studied in 12,945 schizophrenia patients and 34,591 healthy control from eight European locations [3]. A recent Schizophrenia PGC study conducted a mega-analysis using 36,989 cases and 113,075 controls did not observe genome-wide significance but it did report strong support (p=4.114E-7) for this SNP [4] In contrast to genome-wide significance in Caucasian populations, replication studies in Han Chinese (p = 0.36, odds ratio = 1.04, 95% CI = (0.96, 1.12) [5] and Japanese populations (p = 0.25, odds ratio = 1.06 (0.96–1.16) [6] showed no association. Furthermore, a meta-analysis of rs12807809 in 4269 Han Chinese cases and 6962 controls also failed to show any association with the disease [18]. These contrasting results may be reflect ethnic differences.

In the present replication study a total 2074 cases and control subjects were analysed to validate the association between the marker rs12807809 and SCZ in a South Indian population. There was significant variation between patients and controls for allele and genotype distributions. Clinical correlations showed a moderate association of this SNP with hallucinations and flat affect. In this study population the non-risk C allele showed a moderate association with pattern of severity of disease. The opposite direction of effect of this SNP (OR = 0.69) suggests the risk of C allele in Indian population. Also difference may be due potential ethnic and environmental heterogeneity between Europeans and Indians, which is also reflected by the differences in allele frequencies of this SNP between populations (T allele, 0.83 in Europeans vs. 0.93 in Indian samples). Ohi *et al*., 2017 reported that 86 of 122 genetic variations detected by a previous GWAS (PGC-II), showed significant genetic heterogeneities between East Asian and European populations [19].

Varying results of T allele/C allele contribution to disease were evidenced by the association of the SNP rs12807809 with endophenotype and brain imaging studies. No significant difference between TT carriers and CT/CC carriers was observed in Irish samples on any neuropsychological measures assessed [20]. Similarly, Rose *et al*. investigated *NRGN* genotype effects on brain activity during a spatial working memory task in healthy controls. This study reported a failure to disengage ventromedial prefrontal areas in rs12807809 risk allele TT homozygotes but found no effect on grey or white matter volume [21]. The NRGN expression of high-risk TG of rs12807809–rs12278912 haplotype is lower than that of the protective TA haplotype in immortalized lymphoblasts in Japanese samples [22].

In another study, carriers of risk allele of rs12807809 (T) were observed to have a smaller grey matter volume in the left anterior cingulate cortex (Brodmann area 32) than carriers of the non-risk allele (C) in patients with SCZ [23]. The MRI study carried out in patients/controls to understand the impact of this polymorphism in brain morphology reported that TT genotype was associated with widespread cortical thinning involving frontal, parietal and temporal cortices compared with controls having same genotype. No volumetric difference in subcortical structures (hippocampus, thalamus, amygdala, basal ganglia) was observed between risk TT genotype in schizophrenia patients and controls [24]. In contrast, *NRGN* rs12807809 non-risk allele (C) carriers were reported to have reduced cortical grey matter thickness compared to risk allele homozygotes (TT) in an area comprising the right pericalcarine gyrus, the right cuneus, and the right lingual gyrus, suggesting the C allele as a potential risk allele [25]. In the Han population of south China, the C allele of rs12807809 was associated with a higher PANSS aggression subscale score, activation subscale score and higher scores of global symptoms than carriers of the T allele [26]. Similarly, in this study the non risk C allele contributes to the severity of psychosis in SCZ cases.

The discordant results associated with the SNP rs12807809 in replication studies cannot eliminate the importance of *NRGN* with reference to its strong role in neuronal development, synaptic signalling, plasticity, learning and memory which are probably underlying SCZ symptoms. To the best of our knowledge this is the first replication study of this important polymorphism in an Indian population. The results indicate that rs12807809 may play a significant role in conferring susceptibility to schizophrenia and the minor C allele is associated with severity of psychosis in patients with SCZ in Indian population.

This study contributes toward the establishment of *NRGN* as a susceptibility gene for schizophrenia South Indian Population. Further studies, including those using high density mapping and deep sequencing, are required to identify other common susceptibility variants within the *NRGN*. Considering that multiple SNPs within the same gene may be associated with SCZ and several other factors might interact with and/or regulate the NRGN, functional study dissecting the molecular basis of the schizophrenia pathogenesis is strongly warranted.

Conflict of Interest

The authors declare that they have no conflict of interests.

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References

R Core Team. 2015. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/

Tomas J. Aragon Developer. 2012. epitools: Epidemiology Tools. R package version 0.5-7. http://CRAN.R-project.org/package=epitools

Gregory Warnes, with contributions from Gregor Gorjanc, Friedrich Leisch and Michael Man. 2013. genetics: Population Genetics. R package version 1.3.8.1. http://CRAN.R-project.org/package=genetics

[1] A. Lora, R. Kohn, I. Levav, R. McBain, J. Morris, S. Saxena, Service availability and utilization and treatment gap for schizophrenic disorders: a survey in 50 low- and middle-income countries., Bulletin of the World Health Organization. 90 (2012) 47–54, 54A–54B.

[2] B.J. Mowry, J. Gratten, The emerging spectrum of allelic variation in schizophrenia: current evidence and strategies for the identification and functional characterization of common and rare variants., Molecular Psychiatry. 18 (2013) 38–52.

[3] H. Stefansson, R. Ophoff, S. Steinberg, O. Andreassen, S. Cichon, D. Rujescu, et al., Common variants conferring risk of schizophrenia, Nature. 460 (2009) 744–747.

[4] Unknown, Biological insights from 108 schizophrenia-associated genetic loci., Nature. 511 (2014) 421–7.

[5] T. Li, Z. Li, P. Chen, Q. Zhao, T. Wang, K. Huang, et al., Common variants in major histocompatibility complex region and TCF4 gene are significantly associated with schizophrenia in Han Chinese., Biological Psychiatry. 68 (2010) 671–3.

[6] K. Ohi, R. Hashimoto, Y. Yasuda, M. Fukumoto, H. Yamamori, S. Umeda-Yano, et al., Functional genetic variation at the NRGN gene and schizophrenia: evidence from a gene-based case-control study and gene expression analysis., American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics. 159B (2012) 405–13.

[7] H.M. Gurling, G. Kalsi, J. Brynjolfson, T. Sigmundsson, R. Sherrington, B.S. Mankoo, et al., Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q32.2, 5q33.2, and 8p21-22 and provides support for linkage to schizophrenia, on chromosomes 11q23.3-24 and 20q12.1-11.23., American Journal of Human Genetics. 68 (2001) 661–73.

[8] J.H. Pak, F.L. Huang, J. Li, D. Balschun, K.G. Reymann, C. Chiang, et al., Involvement of neurogranin in the modulation of calcium/calmodulin-dependent protein kinase II, synaptic plasticity, and spatial learning: a study with knockout mice., Proceedings of the National Academy of Sciences of the United States of America. 97 (2000) 11232–7.

[9] F.L. Huang, K.-P.P. Huang, C. Boucheron, Long-term enrichment enhances the cognitive behavior of the aging neurogranin null mice without affecting their hippocampal LTP., Learning & Memory (Cold Spring Harbor, N.Y.). 14 (2007) 512–9.

[10] G. Tsai, J.T. Coyle, Glutamatergic mechanisms in schizophrenia., Annual Review of Pharmacology and Toxicology. 42 (2002) 165–79.

[11] E.G. Holliday, D.R. Nyholt, S. Tirupati, S. John, P. Ramachandran, M. Ramamurti, et al., Strong evidence for a novel schizophrenia risk locus on chromosome 1p31.1 in homogeneous pedigrees from Tamil Nadu, India., The American Journal of Psychiatry. 166 (2009) 206–15.

[12] R. Thara, T. Srinivasan, S. John, D. Nancarrow, D. Chant, E. Holliday, et al., Design and clinical characteristics of a homogeneous schizophrenia pedigree sample from Tamil Nadu, India., The Australian and New Zealand Journal of Psychiatry. 43 (2009) 561–70.
[13] J.I. Nurnberger, M.C. Blehar, C.A. Kaufmann, C. York-Cooler, S.G. Simpson, J. Harkavy-Friedman, et al., Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative., Archives of General Psychiatry. 51 (1994) 849–59; discussion 863–4.
[14] E.M. Maxwell, Manual for the FIGS, Bethesda (MD): Clinical Neurogenetics Branch, National Institute of Mental Health. (1992).
[15] N.C. Andreasen, Scale for the assessment of negative symptoms (SANS), Department of Psychiatry, College of Medicine, The University of Iowa, 1984.
[16] N.C. Andreasen, Scale for the assessment of positive symptoms (SAPS), University of Iowa Iowa City, 1984.
[17] S.A. Miller, D.D. Dykes, H.F. Polesky, A simple salting out procedure for extracting DNA from human nucleated cells., Nucleic Acids Research. 16 (1988) 1215.
[18] Z. Wen, J. Chen, R.A. Khan, M. Wang, Z. Song, Z. Li, et al., Polymorphisms in NRGN are associated with schizophrenia, major depressive disorder and bipolar disorder in the Han Chinese population., Journal of Affective Disorders. 194 (2016) 180–7.
[19] K. Ohi, T. Shimada, T. Yasuyama, T. Uehara, Y. Kawasaki, Variability of 128 schizophrenia-associated gene variants across distinct ethnic populations., Transl Psychiatry. 7 (2017) e988.
[20] G. Donohoe, J. Walters, D. Morris, A. Costa, E. Rose, A. Hargreaves, et al., A neuropsychological investigation of the genome wide associated schizophrenia risk variant NRGN rs12807809, Schizophrenia Research. 125 (2011) 304–306.
[21] E. Rose, D. Morris, C. Fahey, I. Robertson, C. Greene, J. O'Doherty, et al., The effect of the neurogranin schizophrenia risk variant rs12807809 on brain structure and function., Twin Research and Human Genetics : The Official Journal of the International Society for Twin Studies. 15 (2012) 296–303.
[22] K. Ohi, R. Hashimoto, Y. Yasuda, K. Nemoto, T. Ohnishi, M. Fukumoto, et al., Impact of the Genome Wide Supported NRGN Gene on Anterior Cingulate Morphology in Schizophrenia, PLoS ONE. 7 (2012).
[23] K. Ohi, R. Hashimoto, Y. Yasuda, M. Fukumoto, H. Yamamori, S. Umeda-Yano, et al., Influence of the NRGN gene on intellectual ability in schizophrenia, Journal of Human Genetics. 58 (2013) 700–705.
[24] J. Thong, A. Qiu, M. Sum, C. Kuswanto, T. Tuan, G. Donohoe, et al., Effects of the Neurogranin Variant rs12807809 on Thalamocortical Morphology in Schizophrenia, PLoS ONE. 8 (2013).
[25] E. Walton, D. Geisler, J. Hass, J. Liu, J. Turner, A. Yendiki, et al., The Impact of Genome-Wide Supported Schizophrenia Risk Variants in the Neurogranin Gene on Brain Structure and Function, PLoS ONE. 8 (2013).
[26] L. Su, J. Long, R. Pan, X. Xie, X. Mao, Y. Zhou, et al., Influence of NRGN rs12807809 polymorphism on symptom severity in individuals with schizophrenia in the Han population but not the Zhuang population of south China., Acta Neuropsychiatrica. 27 (2015) 221–7

Table 1. Demographic variables of Patients and Control Subjects

	Schizophrenia (n=1005) Mean ± SD	**Controls (n=1069) Mean ± SD**
SOCIO-DEMOGRAPHIC		
Sex– Male/Female (%)	49.85/50.14	67.44/32.55
Age (Years)	41.11 ± 11.71	38.73 ± 12.17
Education (in Years)	9.18 ± 4.60	
Marital Status(Married/Never Married/Married but Single)%	46.1/37.7/16.2	
CLINICAL		
Age of onset (Years)	26.59 ± 9.10	
Duration of Illness (Years)	13.25 ± 8.72	
FAMILY HISTORY		
Consanguinity (Yes/No) (%)	25.2/74.6	
Family History (Yes/No) (%)	32.4/66.7	

Table 2.Allele and genotype frequencies of rs12807809 and its association with Schizophrenia

	Genotype Distribution (%)			**Allelic Distribution (%)**		**HWE p - Value**
	CC	**CT**	**TT**	**C**	**T**	
SCZ Cases (n=1005)	1.7	15.8	82.5	9.61	90.4	0.008
Controls (n=1069)	0.6	12.4	86.9	6.8	93.2	0.6164
Genetic Model		**Odds Ratio**		**(95% CI)**	**Chi-square**	**p value**
Genotypic Association	CC vs CT vs TT				10.159	**0.0062**
Allelic Model	C vs T	0.69		(0.55 – 0.87)	9.964	**0.0019**

Table 3. Association of rs12807809 with Pattern of severity

***NRGN* rs12807809 Vs Pattern of severity**								
		Pattern of severity N (%)						**p-value**
		Episodic shift	**Mild Deterioration**	**Moderate deterioration**	**Severe Deterioration**	**Relatively stable**	**Total**	
NRGN rs12807809	CC	3 (5)	4 (3.5)	9 (5)	14 (9.1)	6 (13)	36 (6.5)	
	CT	5 (8.3)	15 (13)	30 (16.8)	27 (17.5)	12 (26.1)	89 (16.1)	**0.039**
	TT	52 (86.7)	96 (83.5)	140 (78.2)	113 (73.4)	28 (60.9)	429 (77.4)	
Total		60 (100)	115 (100)	179 (100)	154 (100)	46 (100)	554 (100)	