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SNP8NRG433E1006 NEUREGULIN-1 GENETIC VARIATION IN BATAKS ETHNIC WITH SCHIZOPHRENIA PARANOID AND HEALTHY CONTROL

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Background: The neuregulin 1 (NRG1) gene which influences the development of white matter connectivity has been associated with schizophrenia. It influences neuronal migration, synaptogenesis, gliogenesis, neuron-glia communication, myelination, and neurotransmission in the brain and others. NRG1 is located in 8p13, and it is frequently replicated in schizphrenia. SNP8NRG433E1006 gene NRG1 is one of core at risk haplotype of schizphrenia. This study looked forward differences SNP8NRG433E1006 neuregulin 1 between Bataks ethnic with schizophrenia paranoid and Bataks ethnic healthy control. **Methods:** Batak ethnic with schizophrenia paranoid were recruited and interviewed with semi-structured MINI ICD-X to establish the diagnosis. All the eligible subjects were requested their permission for blood sampling. Healthy Batak ethnic were also recruited by mathcing the age and gender. The blood samples went through DNA isolation, Nested PCR, and DNA sequencing. **Results:** Ninety three subjects were recruited, but only 74 blood samples were succesfully sequenced. We found three types of polymorphisms, i.e. G/A allele at base pair (bp) 76, G/T allele at bp 112, and deletion at bp 110 in Batak ethnic with schizophrenia. There were two kind sequences at bp 113-116 in Batak ethnics, and Batak ethnics with ATCG were at higher risk for having schizophrenia. This study support that *NRG1* is a schizophrenia-susceptibility gene.

Keywords: Schizophrenia paranoid, Single Nucleotide Polymorphism, NRG1 gene

INTRODUCTION

Schizophrenia is a complex genetic disorder affecting approximately 1% of the population worldwide.1-5 The molecular lesions in schizophrenia are very highly biologically determined.3,4 Using a positional cloning approach, identification of a core risk haplotype in the 5'region of NRG1 on 8p12 which was associated with schizophrenia, was initially reported by Stefansson and colleagues.[1,6,7] Then, association between NRG1 and schizophrenia has been most replicated associations in the schizophrenia genetics literature.[8-11]

NRG1 belongs to a family of neuregulins that consists of four growth factor genes that are structurally related to the epidermal growth factor genus of cell-to-cell signalling molecules.[12-14] NRG1 is localized to widespread areas of the brain, including frontal cortex, hippocampus, midbrain, and cerebellum. NRG1 has a broad range of bioactivities in the CNS, including synapse formation, regulation of N-methyl-D-aspartate and gamma-aminobutyric acid-A receptor subunit expression, as well as neuron differentiation, proliferation, and migration.[2,15] These activities are partly developmental, but NRG1 continues to be expressed in the adult brain.[2] Leading theories about the pathogenesis of schizophrenia suggest a neurodevelopmental origin of the disease or aberrant signalling in glutamatergic and dopaminergic pathways.[12,13] This makes NRG1as an interesting candidate in the etiopathogenesis of schizophrenia. The NRG1 gene localizes to chromosome 8p22.[2] Genetic variation in NRG1 is associated with schizophrenia, but exactly how genetic variation in NRG1 impacts on disease susceptibility remains uncertain.[3,4,16] SNP8NRG433E1006 is one of five core at risk

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haplotype which Stefansson and colleagues has been identified.[17]

Bataks are one of Indonesian ethnicities, found mainly in North Sumatera. Their physical appearances can be easily differentiated with the Caucasians and Negroes. They are also very committed to their own traditional cultures. Besides their regular prevalence visits to the hospital, the Bataks are especially selected in this project because their race is the purest among others,to maintain their race purity, they usually marry within their own race.[18]

PATIENTS AND METHOD

Subjects Sampling

This study was approved by the Research Ethics Committee of Medical Faculty University of Sumatera Utara. All participants were Bataks ethnic which have first and second degree Bataks ethnic families. Fifty-five Bataks ethnic patients with schizophrenia paranoid which cooperative and age between 15 and 55 years old at Pemprovsu mental hospital and thirty-eight Bataks ethnic as healthy control were recruited as participants. All subjects were Batak ethnic with schizophrenia paranoid, cooperative, age between 15 and 55 years old. Exclusion criteria for all subjects were having severe medical illness: especially heart disease, having other psychiatric disorder and pregnant. Written informed consent was obtained from all participants after giving a full explanation of the study protocol. Semi-structured interviews using MINI-ICD X were carried out for all participants. Diagnoses of schizophrenia paranoid were made based on ICD X criteria. Control subjects were recruited primarily from the staff of participating hospitals and associated laboratories. We matched the ages and genders of the control healthy volunteers to those of the patients examined.

SNP Genotyping

From each subject, 3 ml of venous blood was drawn into EDTA vacuum tubes, and genomic DNA was extracted using standards protocols and coded to create and preserve anonimity. Genotyping was performed by persons who were blind to diagnostic status of the samples. SNP8NRG433E1006 was scored by sequencing bp 163 of the exon. Nested PCR was performed to obtain product for direct sequencing. The first amplification reaction was done using primers CCTACCCCTGCACCCCCAATAAATAAA and CTTCCTGTCGAGTGCCCCCTGCT.

The reaction volume was 10 ml, and, for each PCR, 30 ng of genomic DNA was amplified in the presence of 3.5 pmol of each primer, 0.25 U Ampli *Taq* Gold, 0.2 mM dNTPs, 10% dimethyl sulfoxide, and 2.5 mM MgCl-2 (buffer was supplied by the manufacturer). Cycling conditions were 95^0 C for 10 minutes, followed by 40 cycles at 94^0 C for 15 seconds, annealing at 68^0C for 30 seconds, and extension at 72^0C for 1 minute. The second reaction was performed using the same concentration of inner primers, TGCCACTACTGCTGCTGCT and ACCTTT CCCTCGATCACCAC. Except for the addition of 1 ml of the first amplification reaction, as a template, to 9 ml of the mixture, conditions were the same as in the first amplification reaction described above. Cycling conditions for the second amplification step were 95^0C for 10 minutes, followed by 35 cycles at 94^0C for 15 seconds, annealing at 58^0C for 30 seconds, and extension at 72^0C for 1 minute. The PCR product was sequenced by direct sequencing after cleaning the PCR product by use of a BigDye Terminator Cycle Sequencing kit (PE Biosystems). The inner primers were used for the cycle-sequencing reaction, and fragments were separated by electrophoresis on ABI 3700 instruments (Applied Biosystems).

DNA Sequencing

We used sequence scanner version 1.0 to extract the forward-and-reverse sequences from the PCR products. The complete sequence was obtained by uploading the forward and reverse sequences to http://blast.ncbi.nlm.nih.gov/, which was an online DNA sequence software called NCBI's BLAST (Basic Local Allignment Search Tool). NCBI's BLAST was used to prevent the subjectivity in sequence reading.

Statistical analysis

Univariat analysis in frequency table was performed to describe all sequences reading which was classified by base pair was used each variable and was described by frequency table. The putative confounding factors included age and gender was analyzed between the batak ethnics with schizophrenia and healthy by using nonparametric test. The next step was identifing polymorphisms in all sequences.

Bivariat analysis was performed to analyze whether there are correlation between the evidence of polymorphisms in Batak ethnic with schizophrenia and healthy control. The hypothesis was tested by nonparametric test. Statistical analysis was performed using SPSS software. The probability level of $p < 0.05$ and confidence interval 95% was considered to be statistically significant.

RESULTS

Ninety three subjects were recruited, and all blood sampling from those subjects were processed but only 80 subject samples were sequenced because 13 of the samples were identified with multiple close bands in their nested-PCR products.

From 80 samples which went trough the DNA sequencing, only 74 samples were successfully sequenced due to technical problem (Table 1).

Complete sequence showed that in bp 117 – 141, there was a lot of "N" notation. "N" refers to undetectable peak of nucleotida, which means in that bp, the nucleotida could not be read. Only from first bp to bp 116, the seqence could be interpreted. The Batak ethnic with schizophrenia consisted of 45 patients (20 males, 25 females); the mean 38.16±7.17 years old; age of onset 30.42±3.75 years old; the mean duration of schizophrenia paranoid was 7.73 ±3.75 years.

Table 1
Characteristic of study participants

Variable	Batak Ethnic		*p*
	Schizophrenia paranoid N = 45	Healthy control N = 29	
Age (years)	38.16 ± 7.17	37.03 ± 7.20	0.51
Duration of illness	7.73 ± 3.75		
Age at onset	30.42 ± 3.75		
Dose of antipsychotics medication*	1071.11±656.31		
Antipsychotic medication	21		
Haloperidol (3-15mg/day) and Chlorpromazine(300-1000mg/hari)			
Risperidone (2-6mg/day)	24		
Endogen factor			
positive	18 (40.00%)	14 (48.28%)	0.48
negative	27 (60.00%)	15 (51.72%)	
Sex			
Male	20 (44.44%)	21 (72.41%)	0.02
Female	25 (55.56%)	8 (27.59%)	
Psychosocial stresor			
positive	17 (37.78%)	17 (58.62%)	0.08
negative	28 (62.22%)	12 (41.38%)	

*Chlorpromazine-equivalent dose (mg/day)
**Some patients took multiple antipsychotics

The control group consisted of 29 healthy persons (21 males and 8 females). There was no significant differentiation ($p > 0.05$) of age, endogen factor, and psychosocial factors between groups. There was a significant differentiation ($p < 0.05$) in sex between groups, which the Batak ethnic with schizophrenia group consisted of more female then healthy control.

Some polymorphism could be identified in Batak ethnic with schizophrenia, i.e. i) deletion in one subject (bp 110); ii) Alelle G/A in 4 subjects (bp 76); iii) Alelle G/T in 1 subjects (bp 112); and iv) sequence differentiation ATCG/GATC in 6

subjects (bp 113-116). In healthy control, there was only sequence differentation ATCG /GATC in 16 subjects (bp 113-116) see Table 2 and 3. Correlation between these polymorphisms and schizophrenia were tested with nonparametric test, and there was a significant correlation (p=0.001, OR: 0.125, CI 95%: 0.04-0.39).

DISCUSSION

Many studies have indicated a genetic linkage between human chromosome and schizophrenia.[5] Stefansson et al[1] reported that the NRG1 gene, resides in this genomic locus is associated to the vulnerability to schizophrenia. Subsequent studies have confirmed the genetic association to NRG1 throughout different countries and populations. [19-21] NRG1 gene implicates in neuropathology of schizophrenia, although its biological contribution to this illness is not fully understood.[3,4,16]

Table 2
Nucleotid Frequency Distribution of SNP8NRG433E1006 NRG1 Gene Sequences in Batak Ethnic with Schizophrenia Paranoid

Bp	G	C	A	T	Bp	G	C	A	T	Bp	G	C	A	T
1	0	0	0	45	40	0	45	0	0	79	45	0	0	0
2	0	0	0	45	41	0	45	0	0	80	0	45	0	0
3	45	0	0	0	42	45	0	0	0	81	0	45	0	0
4	0	45	0	0	43	45	0	0	0	82	0	0	0	45
5	0	45	0	0	44	45	0	0	0	83	0	45	0	0
6	0	0	45	0	45	45	0	0	0	84	45	0	0	0
7	0	45	0	0	46	45	0	0	0	85	45	0	0	0
8	0	0	0	45	47	0	45	0	0	86	0	0	0	45
9	0	0	45	0	48	45	0	0	0	87	45	0	0	0
10	0	45	0	0	49	45	0	0	0	88	0	0	0	45
11	0	0	0	45	50	0	45	0	0	89	45	0	0	0
12	45	0	0	0	51	45	0	0	0	90	0	45	0	0
13	0	45	0	0	52	45	0	0	0	91	0	0	0	45
14	0	0	0	45	53	0	45	0	0	92	0	0	45	0
15	45	0	0	0	54	0	45	0	0	93	0	45	0	0
16	0	45	0	0	55	45	0	0	0	94	0	0	0	45
17	0	0	0	45	56	45	0	0	0	95	0	45	0	0
18	45	0	0	0	57	0	45	0	0	96	45	0	0	0
19	0	45	0	0	58	0	0	45	0	97	0	0	0	45
20	0	0	0	45	59	0	0	45	0	98	0	45	0	0
21	45	0	0	0	60	0	45	0	0	99	0	45	0	0
22	45	0	0	0	61	45	0	0	0	100	0	45	0	0
23	45	0	0	0	62	0	0	45	0	101	0	45	0	0
24	45	0	0	0	63	45	0	0	0	102	45	0	0	0
25	0	0	45	0	64	45	0	0	0	103	0	45	0	0
26	0	45	0	0	65	0	45	0	0	104	0	45	0	0
27	0	45	0	0	66	45	0	0	0	105	0	45	0	0
28	45	0	0	0	67	45	0	0	0	106	0	0	45	0
29	0	45	0	0	68	0	45	0	0	107	45	0	0	0
30	45	0	0	0	69	0	0	0	45	108	0	45	0	0
31	45	0	0	0	70	0	45	0	0	109	45	0	0	0
32	0	45	0	0	71	0	45	0	0	110	0	0	0	44
33	0	45	0	0	72	0	45	0	0	111	45	0	0	0
34	0	45	0	0	73	45	0	0	0	112	44	0	0	1
35	0	0	0	45	74	0	45	0	0	113	6	0	39	0
36	45	0	0	0	75	45	0	0	0	114	0	0	6	39
37	45	0	0	0	76	41	0	4	0	115	0	39	0	6
38	0	45	0	0	77	45	0	0	0	116	39	6	0	0
39	45	0	0	0	78	45	0	0	0					

Table 3
Nucleotid Frequency Distribution of SNP8NRG433E1006 NRG1 Gene Sequences in Batak Ethnic Healthy Control

BP	G	C	A	T	BP	G	C	A	T	BP	G	C	A	T
1	0	0	0	29	40	0	29	0	0	79	29	0	0	0
2	0	0	0	29	41	0	29	0	0	80	0	29	0	0
3	29	0	0	0	42	29	0	0	0	81	0	29	0	0
4	0	29	0	0	43	29	0	0	0	82	0	0	0	29
5	0	29	0	0	44	29	0	0	0	83	0	29	0	0
6	0	0	29	0	45	29	0	0	0	84	29	0	0	0
7	0	29	0	0	46	29	0	0	0	85	29	0	0	0
8	0	0	0	29	47	0	29	0	0	86	0	0	0	29
9	0	0	29	0	48	29	0	0	0	87	29	0	0	0
10	0	29	0	0	49	29	0	0	0	88	0	0	0	29
11	0	0	0	29	50	0	29	0	0	89	29	0	0	0
12	29	0	0	0	51	29	0	0	0	90	0	29	0	0
13	0	29	0	0	52	29	0	0	0	91	0	0	0	29
14	0	0	0	29	53	0	29	0	0	92	0	0	29	0
15	29	0	0	0	54	0	29	0	0	93	0	29	0	0
16	0	29	0	0	55	29	0	0	0	94	0	0	0	29
17	0	0	0	29	56	29	0	0	0	95	0	29	0	0
18	29	0	0	0	57	0	29	0	0	96	29	0	0	0
19	0	29	0	0	58	0	0	29	0	97	0	0	0	29
20	0	0	0	29	59	0	0	29	0	98	0	29	0	0
21	29	0	0	0	60	0	29	0	0	99	0	29	0	0
22	29	0	0	0	61	29	0	0	0	100	0	29	0	0
23	29	0	0	0	62	0	0	29	0	101	0	29	0	0
24	29	0	0	0	63	29	0	0	0	102	29	0	0	0
25	0	0	29	0	64	29	0	0	0	103	0	29	0	0
26	0	29	0	0	65	0	29	0	0	104	0	29	0	0
27	0	29	0	0	66	29	0	0	0	105	0	29	0	0
28	29	0	0	0	67	29	0	0	0	106	0	0	29	0
29	0	29	0	0	68	0	29	0	0	107	29	0	0	0
30	29	0	0	0	69	0	0	0	29	108	0	29	0	0
31	29	0	0	0	70	0	29	0	0	109	29	0	0	0
32	0	29	0	0	71	0	29	0	0	110	0	0	0	29
33	0	29	0	0	72	0	29	0	0	111	29	0	0	0
34	0	29	0	0	73	29	0	0	0	112	29	0	0	0
35	0	0	0	29	74	0	29	0	0	113	16	0	13	0
36	29	0	0	0	75	29	0	0	0	114	0	0	16	13
37	29	0	0	0	76	29	0	0	0	115	0	13	0	16
38	0	29	0	0	77	29	0	0	0	116	13	16	0	0
39	29	0	0	0	78	29	0	0	0					

In the original report of association with schizophrenia in an Icelandic population, Stefansson and colleagues 1,6,7 identified a "core at-risk haplotype" consisting of five SNPs (SNP8NRG221132, SNP8NRG221533, SNP8NRG 241930, SNP8NRG243177, and SNP8NRG433E 1006 and two microsatellites covering the 5' end of the NRG1 gene and extending into the second intron (hereafter referred to as the ''deCODE haplotype''). Separate follow-up studies in Scottish, Irish, mixed United Kingdom, and Dutch populations confirmed the genetic association between schizophrenia and NRG1 by using markers within the same core haplotype or with overlapping markers in the 5'region.[7,22] Studies in four Asian populations also showed a strong association between schizophrenia and NRG1 polymorphisms at the 5' and 3' end of the gene.[9] Together these results, not withstanding two negative studies, provide strong evidence that NRG1 is a schizophrenia-susceptibility gene.[11] Additional support for NRG1's role in schizophrenia comes from the phenotype of NRG1 and ErbB4 mutant mice, which exhibit behaviors similar to those of established rodent models of schizophrenia.23 In present study we found that batak ethnic with scizophrenia has polymorphism. This finding support previous studies that SNP8NRG433E1006 was one of the core at-risk halpotype.

Interestingly in this study, there were 2 types sequence of Batak ethnics especially in bp 113-116 were observed. Previous, it was expected that Batak ethnicity that had a tradition to keep their ethnicity purity by marring their relative would show a similar sequence, but there was no similirity. The explanation of these phenomena could because some Batak ethnic married with other race, but they adopt their wife or husband into Batak ethnic by adding a Batak's surename. Interestingly, batak ethnic with ATCG sequences were at higher risk for having schizophrenia.[18]

Strength and Limitation

This study is the first study to investigate SNP NRG1 gene in Bataks Ethnic and in Indonesia. This study includes confounding factors such as age, gender and psychososial stressor which in previous study these factors had influenced the result.[1] In this study, duration of medication and severity of illness were not evaluated. Theoretically, the course of schizophrenia is influenced by those factors. Furthemore, it could modulate the pharmacotherapy, at the end it was possible to influence expression of the protein.[23]

CONCLUSION

This study supported that NRG1 gene was one of core at risk haplotype susceptible gene for schizophrenia.

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