A Genome-wide Quantitative Linkage Scan of Niacin Skin Flush Response in Families With Schizophrenia

Yin-Ju Lien¹,², Sih-Syuan Huang¹, Chih-Min Liu³, Hai-Gwo Hwu¹,³, Stephen V. Faraone⁵,⁶, Ming T. Tsuang⁷,⁹, and Wei J. Chen*¹,²,¹⁰

¹Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, 17 Xu-Zhou Road, Taipei 100, Taiwan; ²Department of Public Health, College of Public Health, National Taiwan University, Taipei, Taiwan; ³Department of Psychiatry, National Taiwan University Hospital, and College of Medicine, Taipei, Taiwan; ⁴Neurobiology and Cognitive Center, National Taiwan University, Taipei, Taiwan; ⁵Department of Psychiatry, SUNY Upstate Medical University, Syracuse, NY; ⁶Department of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY; ⁷Department of Psychiatry, Center for Behavioral Genomics, University of California, San Diego, CA; ⁸Harvard Department of Epidemiology, Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA; ⁹Harvard Department of Psychiatry, Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, MA; ¹⁰Genetic Epidemiology Core Laboratory, Center of Genomic Medicine, National Taiwan University, Taipei, Taiwan

*To whom correspondence should be addressed; tel: 886-2-33668010, fax: 886-2-33668004, e-mail: wjchen@ntu.edu.tw

Schizophrenia patients frequently display reduced niacin flush responses, and similar characteristics are also observed in their nonpsychotic relatives. This study aimed to identify loci influencing flush response to niacin in schizophrenia using genome-wide quantitative linkage scan. In a nationwide sample of families with at least 2 siblings affected with schizophrenia in each family, 115 families that had at least 2 affected siblings with information on the niacin skin test were subjected to quantitative trait loci linkage analysis, either involving affected individuals only or the whole family. Nonparametric linkage \( Z \) scores were calculated for each of 386 microsatellite markers spaced at an average of 9-cM intervals. Niacin patches of 3 concentrations (0.001M, 0.01, and 0.1M) were applied to forearm skin, and the flush response was rated at 5, 10, and 15 minutes, respectively, with a 4-point scale. Determination of genome-wide empirical significance was implemented using 1000 simulated genome scans. One linkage peak attaining genome-wide significance was identified at chromosomal region 14q32.12 for 0.01M concentration at 5 minutes (NPL-\( Z \) scores = 5.287) for the analyses of the whole family. This locus is distinct from the chromosomal region identified in the previous genome-wide scan for the diagnosis of schizophrenia, and the signal was higher than the peak linkage signal in that study. These findings indicate that there might be modifier or susceptibilitymodifier genes at 14q32.12 for schizophrenia-related attenuation of flush response to niacin.

Key words: endophenotype/relative pair/identical by descent/nonparametric linkage \( Z \) score/modifier gene/susceptibility-modifier gene

Introduction

Schizophrenia is a common and often disabling mental illness, and its etiology remains unresolved.¹,² Evidence for a substantial genetic contribution to schizophrenia has been drawn mainly from family, twin, and adoption studies.³ Many genome-wide scans have been conducted in a variety of populations with varying degrees of evidence for linkage to schizophrenia across the genome.⁴,⁵ One reason for the inconsistency in findings is that etiological heterogeneity may reduce the power to detect linkage. Under these circumstances, searching for quantitative trait loci (QTL) influencing schizophrenia-related trait-bearing endophenotypic characteristics may be an attractive alternative strategy. Compared with disease per se, endophenotypes seem to have greater power to harbor a subset of genes that influence a disorder, which are more proximal to the biological etiology. Theoretically, the strategy can increase power due to potential partition of heterogeneous pathophysiology.

Among many potential schizophrenia-related quantitative traits, impaired niacin flush response is one of emerging interest as a candidate endophenotype for schizophrenia. Niacin (nicotinic acid) can induce a visible skin flush response that is mediated by the release of vasodilatory prostaglandins from the skin.⁶,⁷ Studies consistently found lowered incidence or intensity of flush response to niacin in many individuals with schizophrenia.⁸
One possible mechanism of impaired flush response to niacin is membrane phospholipid alterations that might be related to underlying susceptibility to schizophrenia. Depending on the criteria to define nonresponse, the prevalence estimates of impaired flush response to the niacin skin patch in schizophrenia patients ranged from 49% to 90%, whereas those in healthy controls ranged from 8% to 64%. The impaired niacin flush response was specific to schizophrenia and not observed in depression, bipolar disorder, or autism. One study in healthy subjects showed that age and gender might be associated with the niacin flush response. The impaired niacin flush response in schizophrenia patients was not influenced by medication status, antipsychotic drug doses, or substance use such as tobacco smoking, coffee drinking, or alcohol consumption. Attenuated niacin flush response has also been demonstrated in nonpsychotic first-degree relatives of patients with schizophrenia, with a heritability of 47% to 54%. Greater familial loading for schizophrenia was associated with more impairment in flush response to niacin. Those clues implied that the niacin flush response may be a useful trait for QTL genome-wide linkage scans for schizophrenia.

This study aimed to evaluate the linkage signal for niacin flush response in schizophrenia by applying a genome-wide quantitative linkage scan. Building upon a large sample of families of siblings co-affected with schizophrenia, which consisted mainly of a single ethnic group and reported a maximum nonparametric linkage $z$ (NPL-Z) score of 2.88 on chromosome 10q22.3, we expected that a greater linkage signal and additional regions that were blurred in the original genome scan might be obtained and hence lead to identification of new schizophrenia susceptibility loci that bear relations to underlying niacin flush response.

Methods

Participants

Subjects of this study were part of the participants of the Taiwan Schizophrenia Linkage Study (TSLS), which collected a nationwide family sample with at least 2 affected siblings fulfilling the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia or schizoaffective disorder, depressive type from 1998 to 2002. In a total of 606 families recruited, 557 of them had both affected siblings having genotyped data and were included in the original genome scan, comprising 1207 affected individuals and 1035 unaffected individuals. Written informed consent was obtained from all subjects after complete description of the study. The study was approved by both the US Department of Health and Human Services and the National Taiwan University Hospital’s Internal Review Board of Human Studies.

Starting from 2002 to 2005, a second study entitled Positional Cloning Study on the Vulnerability Genes of Schizophrenia administered niacin skin patch test to part of the participants of the TSLS, especially those in northern Taiwan. The study was approved by the National Taiwan University Hospital’s Internal Review Board of Human Studies. Among the families of the TSLS, 115 families had at least 2 affected siblings with information on the niacin skin test, consisting of 226 affected individuals (215 siblings and 11 parents) and 137 unaffected individuals (27 siblings and 110 parents), were included for this study.

In addition, 94 healthy controls (45 males and 49 females) were recruited from members of the hospital staff of National Taiwan University Hospital who reported a negative history of any psychiatric disorder. This sample was used as the normal comparison group for the evaluation of the degree of attenuated niacin flush response for schizophrenia patients and their relatives.

Interview Instruments and Diagnosis

All the schizophrenia patients and their first-degree relatives were interviewed with the Diagnostic Interview for Genetic Studies (DIGS). The Chinese version of DIGS (DIGS-C) was translated by 2 psychiatrists and 1 psychiatric epidemiologist, and a standardized procedure in using the DIGS-C was reported elsewhere. Interviews with the DIGS-C were conducted by research assistants who had received strict psychiatric interviewing training. In addition to the DIGS, interviewers used the Chinese version of the Family Interview for Genetic Studies (FIGS) to collect relevant information on relatives. Best estimate psychiatric diagnosis according to the DSM-IV was made independently by 2 psychiatrists using all available information, including the DIGS-C, FIGS, the hospital record, and the interview notes. When the 2 psychiatrists disagreed on the diagnosis, a third one would be sought, and a consensus was reached after discussion.

Niacin Skin Patch Test

Participants had to meet the following criteria before undertaking niacin skin patch test: no pregnancy, no history of alcohol and drug abuse, no major systemic illness (especially heart disease, allergic skin illness, and asthma), and no usage of anti-inflammatory drugs (eg, aspirin, nonsteroidal anti-inflammatory drugs, and steroids) within 3 days before the niacin skin patch test. The protocol for the niacin skin patch test has been described in detail elsewhere. In brief, patches of absorbent paper were used to apply niacin in the form of aqueous methyl nicotinate (AMN). Equal volumes of 3 different concentrations (0.1M, 0.01M, and 0.001M) of AMN, as well as
a blank negative control, were applied topically to each subject’s forearm skin for 5 minutes and then removed. After the niacin patches were removed, the skin flush response was rated at 5, 10, and 15 minutes with a 4-point scale, in which 0, no erythema, 1, incomplete erythema, 2, complete erythema within the define area of the patch, and 3, erythema plus edema beyond the definite area of the patch (illustrated in Supplementary figure S1).

In a preliminary study of 50 subjects (34 schizophrenia patients, 4 bipolar affective patients, and 12 healthy controls), the interrater reliability for the flush scoring by 2 psychiatrists was demonstrated to be excellent with the intraclass correlation coefficient ranging from 0.85 to 0.94 at 3 different concentrations of AMN. The flush responses of all the participants in this study were rated by 1 of the 5 research assistants who were trained by the 2 psychiatrists. When research assistants rated the flush response, they were required to take a photo of each response, and a random sample of the photos was periodically checked by a psychiatrist to guarantee the quality of the data. In another sample of 50 subjects (25 schizophrenia patients and 25 controls), the interrater reliability of the 5 research assistants was good with the intraclass correlation coefficient for 3 different concentrations of AMN being 0.69, 0.74, and 0.76, respectively.

**Data Analyses**

**QTL Linkage Analyses**

The original genotyping was conducted by the Center for the Inherited Disease Research following the center’s standard genotyping procedures (http://www.cidr.jhmi.edu/protocol.html), with 386 microsatellite markers spaced at an average of 9-cM intervals, and has been described in more detail elsewhere. The discordancy for duplicate genotypes assayed on the same plates as the study genotypes was 0.06%. The overall rate of genotype and family errors was 0.39%. The call rate of the microsatellite markers was 96%, and all of them were in Hardy-Weinberg equilibrium. Non-Mendelian inheritance and excessive recombination events were checked, and erroneous genotypes were removed accordingly. Map distances were based on the Marshfield genetic map. The data included for this study were collected through National Institute of Mental Health’s genetic initiative for schizophrenia, and details about how to access these data can be found at the following website: http://zork.wustl.edu/nimh.

Two separate genome-wide linkage analyses were conducted. Initially, only affected individuals’ scores on the niacin flush response were subject to genome-wide QTL linkage analyses using Merlin, ie, any subject without a diagnosis of schizophrenia was coded as “missing” in phenotype. The second genome-wide scan was conducted using all available individuals (including both affected individuals and their unaffected relatives).

NPL-Z scores were calculated at all available markers throughout the genome using a nonparametric method to test for allele sharing identical by decent among individuals with similar traits. This method makes no assumption of trait distribution, and we thus used scores without transformation in this study. The statistic \( S_{\text{att}} \) that incorporates information from all relative pairs was then calculated. According to Lander-Kruglyak criteria, suggestive linkage results are defined as LOD scores of \( \geq 2.2 \), which corresponds to a \( P \) value of \( 7.4 \times 10^{-4} \). An NPL-Z score of 3.18 would be equivalent in \( P \) value to the LOD threshold of 2.2 of Lander and Kruglyak.

**Genome-wide Significance Level**

The genome-wide significance level was calculated from 1000 simulations using simulated genomes generated by the gene-dropping algorithm in Merlin. Simulated data were based on our original family structure, marker informativeness, spacing, and missing data, with phenotypic measurement and affection status being preserved. The genome-wide significance level, represented by the \( P \) value, was computed using the conservative \( P = r/1001 \), where \( r \) is the number of times an NPL-Z score greater than or equal to the observed maximum NPL-Z noted in a simulated sample.

**Results**

**Sample Characteristics**

Table 1 summarizes the demographic characteristics and niacin flush response scores in 115 families of patients with schizophrenia (226 affected individuals and 137 unaffected relatives) and the healthy controls (94 individuals). Compared with healthy controls, affected individuals had a higher proportion of males, while both affected individuals and their unaffected relatives had an older mean age. There were no differences among the 3 groups in terms of allergy history. Meanwhile, both affected individuals and their unaffected relatives had lower niacin flush scores than healthy controls for the moderate (0.01M) and high concentrations (0.1M) at each rating time, whereas the contrast was much less for the low concentration (0.001M). The effect sizes at the concentration of 0.01 or 0.1M for affected individuals were in general equivalent to those of unaffected relatives, with the size being large (>0.8) for the rating time at 10 or 15 minutes and medium (around 0.5) for the rating time at 5 minutes.

In addition, possible influences of sex and age on niacin skin flush responses were evaluated. First, comparing the flush response scores between males and females, there were no differences in the mean values for each AMN concentration-time lag combination as well as a summation of all 9 flush response scores rated for 3 concentrations at 3 time points in both affected individuals and their unaffected relatives. Second, age was not associated with any niacin score in affected individuals, and only a modest association of borderline significance...
was observed in 4 out of 10 flush scores in unaffected relatives, including $0.01M$ at $10$ minutes ($\beta = 0.01, P = 0.04$), $0.01M$ at $15$ minutes ($\beta = 0.01, P = 0.01$), $0.001M$ at $15$ minutes ($\beta = 0.01, P = 0.04$), and the summation of all $9$ flush response scores ($\beta = 0.01, P = 0.02$). Hence, we did not make adjustment in niacin flush scores for these $2$ demographic features.

### Results of QTL Linkage Analyses

Table $2$ summarizes the genomic regions where an NPL-Z score of $\geq 3.0$, which corresponds to a nominal $P$ value of $<0.002$ in our data in at least one sample, for the analyses conducted either in affected individuals only or the whole family. Five regions (ie, $14q31.3$, $14q32.12$, $16q22.3$, $22q12.3$, and $22q13.2$) were observed in the linkage scan.

### Table $2$. Peak nonparametric linkage z (NPL-Z) Scores at Each Chromosome for a Variety of Niacin Flush Responses in Families With Schizophrenia

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>cM</th>
<th>Markers</th>
<th>Cytogenetic Location</th>
<th>Affected Individuals (N = 226)</th>
<th>Affected Individuals and Their Relatives (N = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.1M at 15 min</td>
<td>0.01M at 5 min</td>
</tr>
<tr>
<td>$14$</td>
<td>96</td>
<td>C14S1937</td>
<td>$14q31.3$</td>
<td>$3.06^a$</td>
<td>$2.49^a$</td>
</tr>
<tr>
<td>$14$</td>
<td>106</td>
<td>D14S617</td>
<td>$14q32.12$</td>
<td>$3.39^a$</td>
<td>$2.87^a$</td>
</tr>
<tr>
<td>$16$</td>
<td>99</td>
<td>D16S3096</td>
<td>$16q22.3$</td>
<td>$2.69$</td>
<td>$3.04$</td>
</tr>
<tr>
<td>$22$</td>
<td>36</td>
<td>D22S683</td>
<td>$22q12.3$</td>
<td>$3.01$</td>
<td>$3.19^b$</td>
</tr>
<tr>
<td>$22$</td>
<td>46</td>
<td>D22S445</td>
<td>$22q13.2$</td>
<td>$2.39$</td>
<td>$3.09$</td>
</tr>
</tbody>
</table>

Note: Linkage regions achieving NPL-Z scores $\geq 3.0$, which is denoted in bold face, in at least one sample.

$^a$Reaching genome-wide significance derived from simulations (empirical $P$ value $< 0.05$).

$^b$Reaching the criterion of suggestive linkage (NPL-Z score $\geq 3.18$).
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22q12.3, and 22q13.2) achieving such signal were obtained for the moderate (0.01M) and high concentrations (0.1M) of niacin flush scores. It is worthwhile to note that none of the linkage results of using the summation score were above 3 (a maximum NPL-Z scores of 2.69 at 3p24.3). For the analyses conducted in affected individuals only, there were 3 regions with an NPL-Z score of $\geq 3.0$. The region with the highest signal (3.39 at 14q32.12) and the region with the second highest one (3.06 at 14q31.3), both for 0.01M at 5 minutes, were adjacent to each other, whereas the region with the third highest signal (3.01) was at 22q12.3. When unaffected relatives were incorporated in the analyses, the signals observed in affected samples were reduced to below 3.0 for 2 of the regions (14q31.3 and 14q32.12) but increased to 3.19 for the region 22q12.3, which reached the criterion of suggestive linkage (NPL-Z score $\geq 3.18$). Furthermore, 2 more chromosomal regions with an NPL-Z score of $\geq 3.0$ were obtained, including 22q13.2 (3.09 for 0.1M at 15 min and 3.06 for 0.01M at 15 min) and 16q22.3 (3.04 for 0.01M at 5 min). Among the regions summarized in table 2, only the NPL-Z scores of 3.39 at 14q32.12 for 0.01M at 5 minutes for the analyses conducted in affected individuals only reached genome-wide significance (genome-wide empirical $P = 0.03$).

Despite the differences in peak NPL-Z scores between the 2 types of analyses, the corresponding values were in general in close range. To illustrate this, the genome-wide NPL-Z scores for the niacin response to 0.01M at 5 minutes are depicted for both the analyses conducted in affected individuals only and the whole family in figure 1. The peak NPL-Z scores for this niacin response (0.01M at 5 min) in individuals with schizophrenia on chromosome 14 do not coincide with the original signals based on the dichotomous diagnosis (figure 2).

Discussion

To our knowledge, this is the first genome-wide linkage analyses to search for QTL influencing niacin flush responses in schizophrenia. Our results revealed a new linkage region with a greater signal reaching genome-wide significance (NPL-Z scores of 3.39 on 14q32.12) as compared with that in the original linkage study using a dichotomous disease phenotype (NPL-Z scores of 2.88 on 10q22.3). The finding indicates a promising chromosomal region harboring loci that bear relations to the underlying aberration in flush response to niacin in schizophrenia.

Our strategy used a series of genome-wide linkage analyses on a variety of concentration-time scores as well as a summation of the 9 concentration-time scores on niacin flush responses and assessed the genome-wide significance by means of simulations. We found that the response scores to 0.01M concentration at 5 minutes rather than the summation score exhibited the strongest linkage signal, which is in line with our previous findings that greater familial aggregation was obtained for the flush response to moderate or high concentrations (0.01 or 0.1M) at 5 minutes. On one hand, this strategy invokes the issues with regard to multiple comparisons. On the other hand, the highly correlated nature between each concentration-time flush response score rendered the Bonferroni correction inappropriately conservative. Nevertheless, the significant linkage signals reported here have adjusted for multiple markers based on simulated genome-wide scans, and readers may weigh the results for the multiple niacin scores used in the analysis.

Unlike differential degrees of deficits being found on the sustained attention between patients with schizophrenia and their nonpsychotic relatives in our previous studies, this study showed that niacin skin response scores were similar between affected and unaffected individuals.
in the families. These findings indicate that the attenuated flush response to niacin is a stable characteristic present in unaffected relatives that may reflect an endophenotype of genetic susceptibility to schizophrenia,9,21,32 which renders the incorporation of unaffected relatives with affected individuals in the QTL linkage scan plausible and may help increase the power to detect such genetic susceptibility loci for schizophrenia. Nevertheless, this does not imply that niacin flush response only reflects susceptibility to schizophrenia and hence excludes the possibility that it might still be related to clinical manifestation of schizophrenia, eg, modifier genes. It depends on whether the analyses of affected individuals only reveal any signals different from the whole-family approach, as illustrated in this study.

Our QTL linkage scans were conducted in 2 types of data structure, either in affected individuals only or the whole family, with each detecting linkage signals on distinct chromosomal regions. In particular, the linkage signal with genome-wide significance was obtained for the analyses in affected individuals only, rather than the analyses involving the whole family. If niacin flush response represented a novel endophenotype for schizophrenia,9,21,32 including unaffected individuals in the linkage scans was supposed to help increase the power because unaffected individuals with attenuated flush response presumably carry the same genetic susceptibility. A possible explanation for this seemingly paradoxical finding is that the QTL with greater linkage signals in affected individuals may contain genes that influence the expression of symptoms following the onset of the disease, so-called modifier genes.33,34 Because the affected individuals only approach and the whole-family approach provided different linkage peaks for potential regions. This possibility of modifier genes is supported by several empirical studies. A genome-wide linkage scan using affected-only design found several modifier loci that might influence the symptoms and courses of schizophrenia.35 Several genetic association studies also implied the existence of modifier genes of schizophrenia, showing association with more severe clinical features36 or working memory.37

Another possibility is that the locus with linkage signal revealed in the analyses of the affected individuals might contain genes that influence both the susceptibility and the clinical features of schizophrenia, hence termed susceptibility-modifier genes.33 For example, an NPL-Z score of reaching genome-wide significance was found for the analyses of niacin flush responses using the affected individuals only (ie, modifier) at loci 14q32.12, whereas the corresponding linkage signals remained strong, with an NPL-Z score of 2.87, for the analyses incorporating the niacin responses of unaffected individuals as well (ie, susceptibility).

The locus with the strongest linkage signal found in this study, 14q32.12, had little support in the original diagnosis-based linkage scan.23 Intriguingly, 2 genes located in 14q32.12 may be related to schizophrenia’s clinical feature or susceptibility. First, the ataxin 3 gene, also known as AT3, JOS, MJD, ATX3, MJDI, SCA3, or ATXN3, is a cause of Machado-Joseph disease, an autosomal dominant neurological disorder.38 To date, there has been only one study of small sample size demonstrating that the genetic variants of ataxin 3 exhibited a weak association with schizophrenia.39 Second, chromogranin A (parathyroid secretory protein 1) gene, also known as CGA or CHGA,40 encodes a precursor to peptides that act as autocrine or paracrine negative modulators of the neuroendocrine system. An acute increase in the level of chromogranin A–derived peptides was postulated to reflect an active disease process for schizophrenia.41,42 The expression level of the
chromogranin A was reduced in the prefrontal cortex and the cerebrospinal fluid of patients with schizophrenia. Hence, future genetic fine mapping on the region in search of potential modifier or susceptibility-modifier genes for schizophrenia is warranted.

It is important to note that both ataxin 3 and chromogranin A are not related to phospholipase A2, a class of enzyme that catalyzes the release of fatty acids from phospholipids and constitutes the prostaglandin signaling pathway that is responsible for the visible skin flush response to niacin. PL2G6 gene that encodes phospholipase A2 is located in 22q13.1, a region nearby 22q13.2, which exhibited an NPL-Z score of >3.0 for the analyses involving the whole family but failed to attain genome-wide significance in this study. This line of prostaglandin signaling pathway is compatible with the proposition that schizophrenia may be a genetically mediated central nervous system microvascular inflammation disease. However, there has been limited research on the genetic variants underlying the prostaglandin signaling pathway and their relations to the niacin responses in schizophrenia. More investigation is needed to clarify the role of PL2G6 gene in the schizophrenia-related attenuation of flush response to niacin.

There are limitations in this study. First, a 4-point scale for rating the flush responses to niacin was used to accommodate a nationwide study of large sample size. Nevertheless, more elaborate measurements, such as laser Doppler flowmeter or optical reflection spectroscopy, may be needed for studying the relationship between the flush response and the underlying biochemical markers. Second, flush responses to niacin were unavailable from some family members of schizophrenia patients. This would introduce noise into the QTL linkage analysis and tend to bias the results toward the null. Third, antipsychotic treatment might influence the niacin flush response in patients with schizophrenia, and we did not control this covariate in our analysis. However, most studies suggested that medication status did not influence the flush response to niacin.

In summary, this study applied genome-wide quantitative linkage scan for the flush response to niacin in 115 families with at least 2 siblings affected with schizophrenia. The results revealed a chromosomal region, 14q32.12, attaining genome-wide significance for the analyses involving affected individuals only, and the corresponding linkage signal remained strong for the analyses of the whole family. These findings indicate that there might be modifier or susceptibility-modifier genes at 14q32.12 for schizophrenia-related attenuation of flush response to niacin.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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