Association of a Novel KIF26B Gene Polymorphism with Susceptibility to Schizophrenia and Breast Cancer: A Case-Control Study

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(Received 15 Apr 2020; accepted 21 Jul 2020)

Abstract

Background: KIF26B gene is found to play essential roles in regulating different aspects of cell proliferation and development of the nervous system. We aimed to determine if rs12407427 T/C polymorphism could affect susceptibility to schizophrenia (SZN) and breast cancer (BC), the two genetically correlated diseases.

Methods: The current case-control study was performed from Aug 2018 to Dec 2018. Briefly, 159 female pathologically confirmed BC cases referring to Alzahra Hospital, Isfahan, Iran, and 102 psychologically confirmed SZN patients (60 males and 42 females) admitted to Baharan Hospital, Zahedan, Iran, were enrolled. Using the salting-out method, genomic DNA was extracted, and variants were genotyped using allele-specific amplification refractory mutation system polymerase chain reaction (ARMS-PCR) method.

Results: The results revealed a significant association between the KIF26B rs12407427 codominant CT (P=0.001), CC (P=0.0001), dominant CT+CC, and recessive CC (P=0.001) genotypes with the risk of developing SZN. Significant correlations were also found regarding rs12407427 and BC susceptibility in different inheritance models, including over-dominant CT (P=0.026), dominant CT+CC (P=0.001), recessive CC (P=0.009), and codominant CT and CC (P=0.001) genotypes. The over-presence of the C allele was also correlated with an increased risk for SZN (P=0.0001) and BC (P=0.0001). Finally, computational analysis predicted that T/C variation in this polymorphism could change the binding sites in proteins involved in splicing.

Conclusion: rs12407427 T/C as a de novo KIF26B variant might be a novel genetic biomarker for SZN and/or BC susceptibility in a sample of the Iranian population.

Keywords: KIF26B; Breast cancer; Schizophrenia; Polymorphism

Introduction

Generally, the true nature of genetic variants responsible for increasing the risk of complex diseases in humans is not well understood. These genetic variants usually contribute little to the overall genetic diversities among patients with various diseases and are moderate deleterious mutations (1). Recently, there is a shared genetic architecture between CNS-related syndromes such as schizophrenia (SZN) and cancer. Genetic variants of Kinesin Superfamily Proteins (KIFs)
are documented to play a substantial role in many types of identified disorders, including a wide range of malignancies (2). In humans, almost 45 members of KIFs superfamily proteins have been identified until now. However, the main pathways mediated by these proteins still require intense researches (3). Among the KIFs, KIF26B has evolutionarily conserved functions in modulating the development of central nervous system (CNS) besides activating anti-apoptotic pathways (4). There is a hypothesis regarding the interaction of KIF26B with the postsynaptic density protein in hippocampal neurons (5).

As a novel oncogene, KIF26B boosts VEGF signaling pathway in gastric cancer cells (6). However, the exact underlying mechanisms are still ill-defined. Genome-wide CNV analysis has been suggested KIF26B as a novel contributory candidate gene for both breast and colorectal adenomatous polyposis (7). These gene induces cell growth and also increases invasion of Breast cancer (BC) cells via activating the FGF2/ERK signaling pathway (8). A de novo KIF26B variant, p.Gly546Ser, is correlated to pontocerebellar hypoplasia (9). Accordingly, increased mRNA levels of KIF26B was found to have an impact on the enhancement of proliferation of ovarian carcinoma cells (10). KIF26B is located in1q44 with 15 exons. The reads per kilobase per million (RPKM) were 1.6 (in the placenta), 0.9 (in the thyroid), 2.9 (in the heart), and 1.85 (in the kidney) with lower values in other tissues, indicating the differential expression of this gene in various organs (11). Among KIF26B single nucleotide polymorphisms (SNPs), rs12407427 T/C (MAF=0.2408, and heterozygosity=0.33) is a novel intergenic variant of this gene which was already identified to be associated with the risk of keratoconus by conducting genome-wide association- and meta-analysis-studies (12, 13). Still, no single study has investigated the effects of rs12407427 T/C polymorphism and the risk of SZN and BC.

In this study, we aimed to determine whether there is a possible correlation between rs12407427 T/C polymorphism located within KIF26B and the susceptibility to both disorders in a sample of the Iranian population.

Materials and Methods

Subjects and DNA preparation
Following the Standards for Reporting Qualitative Research guidelines, the Ethics Committee of Zahedan University of Medical Sciences (Zahedan, Iran) approved the study's protocol. The present research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Informed consent was obtained from each subject. BC patients were selected from 159 pathologically confirmed women referring to Alzahra hospital of Isfahan, Iran from November 2015 to September 2016. These patients were recruited to perform a research project (an MSc thesis in molecular genetics, Grant number: 941819424001). One hundred and two psychologically confirmed SZN patients admitted to Baharan Hospital (Zahedan, Iran) during 2018 were also enrolled (Ethical code: IR.ZAUMS.REC.1397.323). Moreover, 155 female population-based healthy subjects (admitted to Alzahra hospital of Isfahan in the given time) and 103 randomly selected healthy individuals were considered eligible for the study as control groups. No history of psychiatric, systematic, and any other malignant disorders was found in healthy individuals. The baseline clinical and demographic characteristics of SZN and BC patients and controls are summarized in Tables 1 and 2, respectively. Using the salting-out method (14), genomic DNA was extracted from whole blood samples of healthy control and patients collected in ethylenediaminetetraacetic acid (EDTA)-contained tubes.

Available at:  http://ijph.tums.ac.ir
Table 1: Association between clinical and demographic characteristics of SZN patients and controls regarding rs12407427 T/C

| Parameter                  | Schizophrenia (n=102) (mean ± SD) | Controls (n=103) (mean ± SD) | P-value |
|----------------------------|-----------------------------------|-----------------------------|---------|
| Age (yr)                   | 35.93±10.08                       | 35.88±11.04                 | 0.62    |
| Sex (Female/Male)          | 42/60                             | 46/57                       | 0.44    |
| Isolation (Yes/No)         | 24/78                             | -                           | -       |
| Depression (Yes/No)        | 22/80                             | -                           | -       |
| Hallucination (Yes/No)     | 83/19                             | -                           | -       |

Table 2: Association between clinicopathological characteristics of BC patients and healthy individuals regarding rs12407427 T/C

| Parameters evaluated       | Breast cancer, n(%) | Controls, n (%) | P-value |
|----------------------------|---------------------|-----------------|---------|
| Age (yr)                   | 35.93±10.08         | 35.88±11.04     | 0.62    |
| <50                        | 46(29)              | 46(30)          | 0.38    |
| 50-70                      | 107(67)             | 99(64)          |         |
| >70                        | 6(4)                | 10(6)           |         |
| Number of dissected lymph nodes | 32(20)           | 127(82)         | 0.0001  |
| <10                        | 127(80)             | 28(18)          |         |
| Osseous metastases (Yes/No) | (39/120)         | (4/151)         | 0.0001  |
| Family history             | 56(35)              | 104(67)         | 0.0001  |
| None                       | 71(34)              | 35(23)          |         |
| Mother or Sister           | 24(15)              | 11(7)           |         |
| Other                      | 8(5)                | 5(3)            |         |

**Genotyping**

The sequence for the SNP was obtained from the NCBI database available at (http://www.ncbi.nlm.nih.gov). Genotyping of this variant was done using amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). One common forward primer (5’-TTTATGTGGAACGTGAGGC-3’) and two allele-specific reverse primers (reverse wild: 5’-AGAGAAGATGATGAGTCTCAAGCG-3’ and reverse mutant: 5’-AGAAGAAGATGAGTCTCAAGCA-3’) were designed using primer3 software (15). The amplicon size was 279 bp for both T and C alleles displayed in agarose gel electrophoresis (Fig.1). Using glyceraldehyde-3-phosphate dehydrogenase (GAPDH), forward 5’-AAAGAAGTGCGGTTTATGGAG-3’ and reverse 5’-TTGCTGTCTTCTCCTAGTC-3’ primers produced a 467 bp band representing the control amplicon. Each 20 µL PCR reaction was optimized to contain 10 µL of master mix (AmpliqonTaq 2x mastermix, Denmark), 2 µL of genomic DNA (~1 ng/µL), 6 µL DNase-Free Distilled Water (Parstous Biotech Co., Iran), and 1 µL of each primer (10 ng/µL). Reactions were performed in a thermal cycler as follows: 95 °C for 5 min for primary denaturation, 30 cycles at 95 °C for 35 sec, 59 °C for 45 sec, and 72 °C for 35 sec, followed by a final extension at 72 °C for 5 minutes. Using a UV transilluminator (254nm, Ultra-Lum Electronic UV Transilluminator, USA), the electrophoresed PCR products were visualized. At least 40% of the samples were re-genotyped to validate the genotyping results.
In silico analyses

In silico analyses was performed to evaluate the potential effects of rs12407427 T/C polymorphism. Splice Aid2 database was applied for predicting the possible impact of this variant on gene splicing (16). Weblogo database was used for comparing the conservation of the SNP between the different organisms (17).

Statistical analysis

Data were analyzed using SPSS version 22 (IBM Corp., Armonk, NY, USA)(18). Student’s t-test and X² test were applied for statistical analyses of the genotype/allele frequencies and variables of demographic data, while the possible correlation between polymorphism and SZN and BC were assessed by calculating the 95% CI from logistic regression analyses and odds ratio (OR) where P-values>0.05 were regarded statistically insignificant.

Results

Demographic characteristics

Among 102 patients with SZN, 41% were female, whereas 59% were male. Among 103 healthy controls for SZN, 44% were female, and 56% were male. There was no significant difference in gender and age between the SZN patients and control groups and BC patients’ age and healthy subjects (P>0.05). Comparing BC patients and healthy individuals, significant differences were found concerning the number of dissected lymph, osseous metastases, and family history (P<0.05) (Table 2).

Associations between alleles and genotypes and susceptibility to SZN and BC

The results revealed a significant association between all genotypes of rs12407427 locus and the risk of SZN in different inheritance patterns, including dominant CT+CC (OR=4.10, 95% CI, (2.50-8.17), P=0.0001), codominant CT (OR=3.21, 95% CI, (1.58-6.51), P=0.001) and CC (OR=12.38, 95% CI, (4.20-36.32), P=0.0001), and recessive CC (OR=5.43, 95% CI, (2.11-13.78), P=0.0001) genotypes (Table 3), but not in overdominant mode (P=0.36). No association was found between clinicodemographic characteristics of SZN patients with different genotypes of rs12407427 T/C (Table 4). Moreover, this genetic variant was found to be significantly correlated with BC susceptibility in models belonging to codominant CT (OR=4.00, 95% CI, (2.25-7.08), P=0.0001) and CC (OR=5.75, 95% CI, (2.69-12.30), P=0.0001), dominant CT+CC (OR=4.00, 95% CI, (2.25-7.08), P=0.0001), recessive CC (OR=2.27, 95% CI, (1.23-4.19), P=0.009) and over-dominant CT (OR=1.67, 95% CI, (1.06-2.62), P=0.026) genotypes (Table 5). Based on our findings, the presence of allele C could be a risk factor for both SZN (OR=2.31, 95% CI (2.15-3.44), P=0.0001) and BC (OR=2.04, 95% CI (1.48-2.81), P=0.0001). The data shown in Table 6 and 7, represent possible associations between clinicopathological characteristics of BC patients, healthy controls and this SNP.
Table 3: Genotypic and allelic frequencies of KIF26B polymorphism (rs12407427 T/C) in SZN patients and control subjects

| KIF26B Polymorphism | Schizophrenia, n(%) | Control, n(%) | OR (95%CI) | P-value |
|---------------------|---------------------|--------------|------------|---------|
| **Codominant**      |                     |              |            |         |
| TT                  | 14(14)              | 40(39)       | 1          |         |
| CT                  | 63(62)              | 54(52)       | 3.21(1.58-6.51) | 0.001  |
| CC                  | 25(24)              | 9(9)         | 12.38(4.20-36.32) | 0.0001 |
| **Allele**          |                     |              |            |         |
| T                   | 91(0.45)            | 134(0.65)    | 1          |         |
| C                   | 113(0.55)           | 72(0.35)     | 2.31(1.25-4.34) | 0.0001 |
| **Dominant**        |                     |              |            |         |
| TT                  | 14(14)              | 40(40)       | 1          |         |
| CT+CC               | 88(86)              | 63(63)       | 4.101(2.5058-8.174) | 0.0001 |
| **Recessive**       |                     |              |            |         |
| TT+CT               | 78(76)              | 95(93)       | 1          |         |
| CC                  | 25(24)              | 7(7)         | 5.43(2.11-13.789) | 0.0001 |
| **Over-dominant**   |                     |              |            |         |
| TT+CC               | 39(38)              | 47(46)       | 1          |         |
| CT                  | 64(62)              | 55(54)       | 1.29(0.742-2.256) | 0.364  |

Table 4: Association between KIF26B polymorphism (rs12407427 T/C) and baseline clinical characteristics of patients with SZN.

| Group/Genotype     | CC    | TT    | CT+CC | TT+CT | P-value |
|--------------------|-------|-------|-------|-------|---------|
| Patients with schizophrenia |       |       |       |       |         |
| Isolation (Yes/No) | (8/6) | (11/14)| (43/34)| (46/42)| 0.58    |
| Depression (Yes/No)| (4/10)| (4/21)| (15/62)| (15/73)| 0.24    |

Table 5: Genotypic and allelic frequencies of KIF26B polymorphism (rs12407427T/C) in BC patients and control subjects

| KIF26B Polymorphism | Breast cancer, n(%) | Control, n(%) | OR (95%CI) | P-value |
|---------------------|---------------------|--------------|------------|---------|
| **Codominant**      |                     |              |            |         |
| TT                  | 20                  | 56           | 1          |         |
| CT                  | 102                 | 81           | 3.6(2.002-6.492) | 0.0001 |
| CC                  | 37                  | 18           | 5.75(2.691-12.309) | 0.0001 |
| **Allele**          |                     |              |            |         |
| T                   | 142(0.45)           | 193(0.62)    | 1          |         |
| C                   | 176(0.55)           | 117(0.38)    | 2.04(1.48-2.81) | 0.0001 |
| **Dominant**        |                     |              |            |         |
| TT                  | 20                  | 56           | 1          |         |
| CT+CC               | 139                 | 99           | 4.001(2.257-7.088) | 0.0001 |
| **Recessive**       |                     |              |            |         |
| TT+CT               | 123                 | 136          | 1          |         |
| CC                  | 37                  | 18           | 2.273(1.230-4.199) | 0.009  |
| **Over-dominant**   |                     |              |            |         |
| TT+CC               | 56                  | 74           | 1          |         |
| CT                  | 103                 | 81           | 1.671(1.063-2.628) | 0.026  |
Table 6: Association between KIF26B polymorphism (rs12407427 T/C) and number of dissected lymph nodes and osseous metastases of breast cancer cases and controls

| Group/Genotype | Number of dissected lymph nodes (<10/>10) | Osseous metastases (Yes/No) |
|----------------|------------------------------------------|-----------------------------|
| Case CC        | (3/34)                                   | (28/9)                      |
| TT             | (18/2)                                   | (0/20)                      |
| CT+CC          | (14/126)                                 | (32/108)                    |
| TT+CT          | (29/94)                                  | (4/119)                     |
| P-value        | 0.02                                     | 0.01                        |
| Control CC     | (2/16)                                   | (3/15)                      |
| TT             | (55/1)                                   | (0/56)                      |
| CT+CC          | (72/26)                                  | (4/94)                      |
| TT+CT          | (125/11)                                 | (1/135)                     |
| P-value        | 0.0001                                   | 0.0003                      |

Table 7: Correlation between KIF26B polymorphism (rs12407427 T/C) and familial history of breast cancer patients and controls

| Groups/Genotypes | CC  | TT  | CT+CC | TT+CT |
|------------------|-----|-----|-------|-------|
| Case None        | 5   | 13  | 52    | 44    |
| Sister and mother| 17  | 5   | 54    | 66    |
| Sister or mother | 9   | 2   | 15    | 22    |
| Other            | 6   | 0   | 2     | 8     |
| P-value          | 0.00001 | 0.0001 | 0.0003 | 0.02 |
| Control None     | 6   | 42  | 97    | 61    |
| Sister and mother| 3   | 13  | 32    | 22    |
| Sister or mother | 7   | 0   | 4     | 11    |
| Other            | 2   | 1   | 3     | 4     |
| P-value          | 0.0001 | 0.0001 | 0.0001 | 0.05 |

In silico Analysis Predicted the splice sites of KIF26B polymorphism

Algorithm of the Splice Aid2 database predicted that one splice site was created by the C variant of rs12407427 polymorphism, and other binding sites in proteins were broke by the T variant (Fig.2). Analyzing the putative conservations by Weblogo database, we found that both alleles of this SNP have low genetic diversity between humans and other primates (Fig.3).

Discussion

In the current study, various inheritance models were associated with the risk of both SZN and BC as the codominant CC, CT, and the dominant CC+CT genotypes associated with the development and progression of these disorders. Furthermore, the CC genotype enhanced either SZN or BC susceptibility in the recessive model, suggesting that the C allele's presence might have a non-protective effect against them. Although CT genotype had increased the risk of BC in the over-dominant model, we did not observe the same hypothesis in patients with SZN. However, the C allele of rs12407427 polymorphism in the KIF26B gene enhanced the risk of SZN and/or BC in the Iranian population. No former studies indicated the frequency of C and T alleles of rs12407427 and the possible link between the risk of other disorders and different inheritance patterns concerning this genetic variation.

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Fig. 2: *In silico* analysis using splice Aid2 database to predict the possible effects of rs12407427 T/C polymorphism on gene splicing. It has been shown that one splice site was created by the C allele of this variant and other binding sites was broke by the T allele.

Fig. 3: Using Weblogo database to compare the conservation of rs12407427 T/C polymorphism between the different organisms. Both T and C alleles of this variant has low genetic diversity between human and other primates.

BC is accounted for almost 18% of all female tumors and has been a substantial health concern worldwide. On the other hand, SZN is a common mental disorder with wide range of psychotic symptoms, including hallucinations, delusions, depression, isolation, and disorganized behavior (19). Patients with SZN are reported to have major problems with their social activity, perception, and volition (20, 21). Despite the promising outcome of some investigations, concerning the identification of candidate genes responsible for both SZN and BC, but still, the precise etiology of these two diseases is ill defined. However, many genetic factors are proved to have pivotal roles in the progression of BC (22, 23). *KIF26B* knockdown significantly prohibited cell proliferation, colony formation, and invasion of BC cells via activating caspase3-dependent apoptosis (4). *KIF26B* promotes cell growth and migration through the FGF2/ERK signaling pathway in patients diagnosed with BC (8). Moreover, *KIF26B* has been introduced as a novel prognostic biomarker of colorectal cancer (24). *KIF26B* is usually overexpressed in patients with BC and could be considered as a potential prognostic marker (25).

Although not much is known regarding the action of *KIF26B* on microtubules, it has been mentioned to be crucial for proper axonal outgrowth and kidney development processes, as it regulates the adhesion of the embryonic kidney mesenchyme (26). To the best of our knowledge,
no investigation has already proposed the possible link between rs12407427 T/C polymorphism located in this gene and the risk of cancer and neurologic disorders. Few studies have already argued the association of rs12407427 T/C polymorphism and keratoconus susceptibility without explaining the exact underlying mechanism (12, 13). Accordingly, using cohorts from replication studies, the C allele's presence is significantly associated with the risk of keratoconus in white ethnicities (27), which was in agreement with our findings regarding this correlation with SZN and BC susceptibility. Our results are inconsistent with the reports of previously published works emphasizing the role of genetic mutations in the other KIFs and SZN development. Two of KIF2 gene polymorphisms, rs2289883 and rs464058, are located at 5q12.1 region and have been significantly correlated with SZN susceptibility (28). Dramatic associations of four KIF17 gene missense polymorphisms (rs2296225, rs13375609, rs631375, and rs522496) and the risk of SZN was also reported, while only the allelic frequency of rs2296225 locus was observed to be significantly different between these patients and controls (29).

In a study on a Chinese population, subgroup analyses showed that the G allele at rs17401966 of the KIF1B gene significantly reduced the risk for hepatocellular carcinoma (30). Moreover, no significant associations were discovered regarding rs296565, rs63668827, rs3738255, and rs3198583 polymorphisms located within the KIF21B gene and ankylosing spondylitis development in a Chinese Han population (31). Using SNP linkage panels, another KIF26B polymorphism, rs1148917, has been correlated with the risk of multiplex familial prostate cancer (32). In contrast to what we discovered, a germline mutation in KIF26B rs4498839 (located in the 1q41 region) was not linked with Barrett's esophagus and esophageal adenocarcinoma compared to the ancestry-matched population controls (33). KIF26B, a gene with evolutionarily conserved functions, plays essential roles in controlling different aspects of cell proliferation and development of the nervous system. However, the function of KIF26B is not fully understood (9). In this study, we aimed to evaluate if a novel locus located in this gene changes the risk of BC and SZN as two major disorders having possible genetic overlap. As our population differs from other ethnicities considering the genetics, lifestyle, and geographic location, similar studies with a larger sample size could provide more details on the relationship between this KIF26B variant and other malignancies and neurologic or cognitive disorders.

Conclusion

Considering all inheritance models and the frequency of associated alleles, KIF26B rs12407427 T/C gene polymorphism might be a novel genetic biomarker for the onset of SZN and BC, their progression, and development in a sample of the Iranian population. However, further studies on a larger sample size and other races are necessary to confirm our findings.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

This work was financially supported by the Cellular and Molecular Research Center of Zahedan University of Medical Sciences (Grant No. 9024).

Conflict of interest

The authors declare that they have no conflict of interest.

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