A missense mutation in the ITGA8 gene, a cell adhesion molecule gene, is associated with schizophrenia in Japanese female patients

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学位論文の内容要旨

A missense mutation in the ITGA8 gene, a cell adhesion molecule gene, is associated with schizophrenia in Japanese female patients

細胞接着分子遺伝子である ITGA8 遺伝子のミスセンス変異と統合失調症の日本人女性患者との相関研究

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Introductions

The etiology of schizophrenia is still unclear, therefore reliable treatments have yet to be established. Changes in groups of molecule as well as genetic vulnerabilities in schizophrenia have been reported to be distributed across molecules and genes that shared a common biological function or pathway, such as cell adhesion molecules (CAMs). CAMs have been implicated in the pathophysiology of schizophrenia. They play important roles in the maintenance and modulation of synapse formation and plasticity, axonal/dendritic growth, and neurotransmission, which are thought to be impaired in schizophrenia. The CAMs pathway reported in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Figure 1) has been reported to be associated with schizophrenia and bipolar disorders susceptibility in genome-wide association study (GWAS) populations. Therefore we studied whether amino acid changes in CAMs are associated with schizophrenia and conducted a genetic association study.

Materials and methods

We selected 15 missense single nucleotide polymorphisms (SNPs) in the CAMs genes of the CNS reported in the KEGG and examined their association with schizophrenia in 278 patients and 284 control subjects (first batch). We genotyped the positive SNPs in 567 patients and 710 control subjects (second batch) and in 635 patients and 639 control subjects (replication samples).

Results

We found significant association of rs2298033 in the ITGA8 gene with schizophrenia. Gender based analysis revealed the same results for rs2298033 in ITGA8 and rs282808 in NFASC genes but only in female. We then genotyped the two SNPs in a larger sample and found the significance remained only for the ITGA8 gene. We replicated the results in an independent replication sample, but failed to find the significance. However, the combined analysis of the two group samples showed a more significant result for the rs22298033 of the ITGA8 gene.

Discussion

ITGA8 gene encodes integrin α8 subunit. Integrins have been implicated in synaptic and behavioral plasticity, long term potentiation (LTP), and placement of cortical neurons, suggesting that they might play some role in the pathogenesis of psychiatric disorders. Amino acid change in the integrins structure can strongly affect their binding affinity and capacity. The rs2298033 (Ser577Phe) of the ITGA8 gene is a non conservative amino acid change that has been reported to be intolerant and deleterious. Our results showed that this amino acid change might have protective effect against schizophrenia, particularly in female. Although there is no direct evidence of gender specific effect of CAMs in neurodevelopment, it has been reported that short-term changes in female sex hormone levels could modulate expression of soluble CAMs.

We cannot fully rule out the possibility of a type 1 error due to our relatively small sample size and lack of power to detect minimal differences in our samples. We did not check SNPs in the promoter region which might as well functional. It is very unlikely that amino acids changes in the ITGA8 gene alone will suffice as predisposing factors towards schizophrenia. Predisposition to schizophrenia is thought to be caused by multiple mutations

in genes in neural development pathways. Nevertheless, our results showed that CAMs might play significant roles in the pathophysiology of schizophrenia, particularly in female Japanese patients.

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はじめに

統合失調症の病因は依然として解明されていない。統合失調症における分子群の変化および遺伝子的脆弱性が、細胞接着分子（CAM）等の共通の生物学的な機能や経路を持つ分子や遺伝子に関係していることがこれまで報告されてきた。CAMはシナプスの形成や可塑性、軸索/樹枝状の成長および神経伝達の維持や調節にあたって重大な役割を果たしている。統合失調症の病態生理学にも関与し、統合失調症が発症するとその働きが損なわれてしまうと考えられている。Kyoto Encyclopedia of Genes and Genomes（KEGG）のデータベース（図1）にて報告されているCAMの経路は、ゲノムワイド関連研究（GWAS）の対象母集団における統合失調症および双極性障害に対する感受性との関連が発表されている。そこで、我々はCAM遺伝子におけるアミノ酸の変化が統合失調症と関連するかどうかを研究し、相関研究を行った。

対象と方法

我々は、KEGGにて報告されているCNS（コアグラーゼ陰性ブドウ球菌）のCAM遺伝子における、15のアミノ酸置換を伴うSNPを選び出し、278人の統合失調症患者および284人の健常対照者との相関を調べた。その後、サンプル数を増やし567人の統合失調症患者および710人の健常対照者で調べた。更に635人の統合失調症患者および639人の健常対照者の独立したサンプルにおいても遺伝子型解析を行った。

結果

我々は、ITGA8遺伝子のSNP（rs2298033）で有意な関連性を発見した。性別による解析からも、ITGA8におけるrs2298033、ならびにNFASC遺伝子におけるSNP（rs282808）で有意な関連性が得られたものの、このことは女性に限定されていた。そこで、より大きなサンプルで2つのSNPの遺伝子型解析を実施したところ、ITGA8遺伝子にのみ有意性が保持されていた。我々は、独立したサンプルにてこの結果を再現してみたが、その有意性を特定することはできなかった。しかしながら、2つのサンプル集団の解析を行ったところ、ITGA8遺伝子のrs22298033に関してより有意な結果を得ることができた。

考察

ITGA8（インテグリン）遺伝子はインテグリンαサブユニットをコードする。インテグリンは、シナプスと行動の可塑性、長期増強（LTP）および皮質ニューロンの配置に関与し、精神疾患の発病機序に何らかの役割を果たしているのではないかと考えられてきた。インテグリン構造におけるアミノ酸の変化はその結合の親和性と能力に大きな影響を及ぼしうる。ITGA8遺伝子のrs2298033（Ser577Phe）は、忍容性がなく、有害であると報告されてきたアミノ酸変化である。よって、研究結果から、アミノ酸の変化は特に女性において統合失調症から保護する効果を発揮するのではないかと考えられる。神経発達におけるCAMの性別特有の効果に関する直接的な証拠はないものの、女性の性ホルモンのレベルの短期的な変化は、可溶性CAMの発現を調整しうることがこれまで報告されてきた。

我々は、比較的小さいサンプルサイズ、ならびにサンプルにおける最小限の差異

を検出するだけの力量が不足していることを理由として、type 1 error の可能性を完全に排除することはできない。また、機能性ともいうべき、プロモーター領域のSNP を確認しなかった。しかし、ITGA8 遺伝子単独のアミノ酸変化が、統合失調症を発症する素因と考えるのに十分である可能性は極めて高い。統合失調症になりやすい素因は、神経発達経路の遺伝子の多くの突然変異に起因すると考えられる。今回、我々の研究結果から、CAM が統合失調症の日本人女性患者の病態生理に有意な役割を果たしているのではないかということが判明した。

神戸大学大学院医学系研究科（博士課程）

論文審査の結果の要旨			
受付番号	甲 第２３６７号	氏　名	Irwan Supriyanto
論文題目 Title of Dissertation	A missense mutation in the ITGA8 gene, a cell adhesion molecule gene, is associated with schizophrenia in Japanese female patients 細胞接着分子遺伝子であるITGA8遺伝子のミスセンス変異と統合失調症の日本人女性患者との相関研究		
審査委員 Examiner	主　査 Chief Examiner 西尾久英 副　査 Vice-examiner 上野易弘 副　査 Vice-examiner 寺島俊雄		

（要旨は１，０００字～２，０００字程度）

The etiology of schizophrenia is still unclear, therefore reliable treatments have yet to be established. Cell adhesion molecules (CAMs) have been implicated in the pathophysiology of schizophrenia. CAMs play important roles in the maintenance and modulation of synapse formation and plasticity, axonal/dendritic growth, and neurotransmission, which are thought to be impaired in schizophrenia. The CAMs pathway reported in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database has been reported to be associated with schizophrenia and bipolar disorders susceptibility in genome-wide association study (GWAS) populations. Irwan Supriyanto et al. studied whether amino acid changes in CAMs are associated with schizophrenia and conducted a genetic association study.

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It is very unlikely that amino acids changes in the ITGA8 gene alone will suffice as predisposing factors towards schizophrenia. Predisposition to schizophrenia is thought to be caused by multiple mutations in genes in neural development pathways. Nevertheless, their results showed that CAMs might play significant roles in the pathophysiology of schizophrenia, particularly in female Japanese patients.

The candidate, Irwan Supriyanto, having completed studies on schizophrenia, with a specialty in molecular genetics, and having advanced the field of knowledge in the genetic epidemiology area of schizophrenia-related SNPs, is hereby recognized as having qualified for the degree of Ph.D. (Medicine).