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学位(専攻分野)	博士(医学)
学 位 記 番 号	総研大甲第 2092 号
学位授与の日付	平成 31年 3 月22日
学位授与の要件	生命科学研究科 生理科学専攻 学位規則第6条第1項該当
学 位 論 文 題 目	Transcriptomic immaturity inducible by neural hyperexcitation is shared by multiple neuropsychiatric disorders
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博士論文の要旨

氏　　名　村野　友幸

論文題目　Transcriptomic immaturity inducible by neural hyperexcitation is shared by multiple neuropsychiatric disorders

Neuropsychiatric disorders　such as schizophrenia, bipolar disorder, major depressive disorder, and autism spectrum disorder—are common, with over a third of the population in most countries being diagnosed with at least one such disorder at some point in their life. Almost all neuropsychiatric disorders are currently classified mainly on the basis of clinical signs and symptoms. However, there is evidence that patients with different clinical diagnoses share similar biological features, such as genetic mutations, molecular expression, and brain activity. Recently, psychiatry has undergone a tectonic shift to incorporate the concepts of modern biology. There have been recent attempts to reclassify psychiatric disorders according to biological domains (e.g., genes, neural circuits, behavior), such as through the Research Domain Criteria initiative. Therefore, identifying appropriate biomarkers that can be used for transdiagnostic assessment of neuropsychiatric disorders is essential for improving the classification of these diseases and understanding their biological basis. Recent studies suggest that the neural hyperexcitation may induce pseudoimmaturity of the brain in adulthood. Additionally, some studies suggest that hyperexcitation of neurons may underlie abnormalities related to certain types of neuropsychiatric disorders. Considering these findings, I hypothesized that the immature-like gene expression patterns induced by neural hyperexcitation may overlap with the abnormal gene expression patterns in the brains of patients with neuropsychiatric disorders and the related animal models. If this

is the case, I hypothesized that this overlap can be used to perform transdiagnostic characterization of neuropsychiatric disorders. I characterized different disease conditions by mapping changes in the expression patterns of maturation-related genes whose expression was altered by experimental neural hyperexcitation in published studies.

I performed a meta-analysis of datasets comparing the changes in gene expression of the neural tissues from patients and corresponding animal models. The 99 gene expression datasets used in this study were obtained from publicly available databases. The similarities between any two datasets were evaluated by overlap p-values using the Running Fisher test**,** which is a rank-based nonparametric statistical method. In this study, I demonstrated that neural hyperexcitation induces changes in the pattern of gene expression in the DG that are significantly similar to the patterns in the immature hippocampus of typically developing human fetuses. From the pool of genes, I identified two groups of genes, which I named hyperexcitation-induced maturity-related genes (hiM genes) and hyperexcitation-induced immaturity-related genes (hiI genes). I investigated whether and to what extent the expression changes in maturation-related genes induced by hyperexcitation overlap with gene expression patterns in various neuropsychiatric disorders.I found that the expression changes in maturation-related genes are shared by multiple neuropsychiatric disorders, such as schizophrenia, Alzheimer disorders, and amyotrophic lateral sclerosis.

Many of the datasets from patients with schizophrenia and from the postmortem brains of patients with Alzheimer’s disease exhibited hiM- dominant pattern changes. The hiM genes include genes encoding a GABA receptor, voltage-dependent calcium channel, glutamate receptor, and voltage-dependent sodium channel. These genes have been implicated in the pathological changes in the brains of patients with schizophrenia and Alzheimer’s disease. Thus, many of the synaptic genes that changed in the brains of patients with schizophrenia or Alzheimer’s disease could be genes whose expression

increases during maturation and decreases with neural hyperexcitation. Most of the datasets from patients with amyotrophic lateral sclerosis and Alzheimer's disease exhibited hiI- dominant patterns. The hiI genes include genes that are known to be important in chromosomal modification and DNA repair, and abnormal functioning of these systems has been observed in patients with amyotrophic lateral sclerosis and Alzheimer's disease. Thus, some of the genes that are considered to be important in the development of these disorders are immaturity-related genes, whose expression decreases during maturation and can be increased by neural hyperexcitation. As for the datasets from patients with Parkinson disease, Bipolar disorder, Huntington disease, and Major depressive disorder, most of them did not show significant overlap with either hiM or hiI genes, suggesting that there might not be major pathological changes in transcriptomic pseudoimmaturity inducible by neural hyperexcitation in the datasets of these four diseases. Thus, I was able to characterize the gene expression patterns in disease datasets of each disease category using the hiI- and hiM-indexes.

In conclusion, the biological domain of pseudoimmaturity inducible by neural hyperexcitation is a common endophenotype among several neuropsychiatric disorders. Future studies are needed to find translational indices that correspond to these features and can be applicable to human patients for better diagnosis of these neuropsychiatric disorders. My findings here may promote the development of biomarkers, leading to a better diagnosis of neuropsychiatric disorders.

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(様式8・別紙)

Results of the doctoral thesis screening

博士論文審査結果

Name in Full
氏　名　村野　友幸

Title
論文題目　Transcriptomic immaturity inducible by neural hyperexcitation is shared by multiple neuropsychiatric disorders

精神神経疾患の生物学的指標に基づいた診断・治療・研究を可能にするためには、患者集団に共通して存在する中間表現型を同定することが不可欠であり、これは現在の精神医学研究における最も重要な課題の一つである。本論文は、様々な精神神経疾患において脳の未成熟様の遺伝子発現パターンや神経細胞の過剰興奮が見られるという先行研究に基づき、神経の過剰興奮によって引き起こされる未成熟様の遺伝子発現パターンが、様々な精神神経疾患の中間表現型となりうることを証明した興味深い研究である。

出願者はまず、マウス海馬歯状回における発達過程およびけいれん誘発における変化に伴う網羅的遺伝子発現解析データをそれぞれ取得し、これらを用いたメタ解析を行った。その結果、発達変化とけいれん誘発に伴う遺伝子発現変化の間にはトランスクリプトームレベルで強い負の相関があることを明らかにした。この結果はすなわち、神経の過剰興奮が成体の海馬歯状回において遺伝子発現パターンの未成熟化様の変化を引き起すことを示唆している。さらに、詳細な解析を行い、このような未成熟化様の遺伝子発現変化には時間変化と空間局在のパターンが異なる二つの遺伝子群の寄与が含まれていることを同定した。さらに出願者は、精神神経疾患患者の死後脳や患者 iPS 細胞由来の神経組織のデータベースから網羅的に取得した遺伝子発現データを対象に、未成熟様の遺伝子発現パターンが存在するか検証した。その結果、統合失調症、ALS、アルツハイマー病といった複数の疾患の患者由来の遺伝子発現データにおいて、共通して未成熟様の遺伝子発現パターンが見られることがわかった。また、同様の解析を ALS とアルツハイマー病のモデルマウスに対しても適用したところ、そのいずれにおいてもヒト患者データと同様の未成熟様の遺伝子発現パターンが見られることを明らかにした。

本研究成果は神経の過剰興奮が網羅的発現解析のレベルで未成熟様の遺伝子発現パターンを誘導することを明らかにしたものであるとともに、そのような未成熟様の遺伝子発現パターンが複数の精神神経疾患において疾患横断的に存在していることを明らかにした画期的な知見であり、博士学位にふさわしい成果と評価できる。