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| Title        | Diversity of clustered protocadherin- $\alpha$ genes in neuronal identity and its role in short-term specific associative memory formation |
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## 論文内容の要旨

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| 氏名 (大須賀 智輝)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                   |
| 論文題名                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Diversity of clustered protocadherin- $\alpha$ genes in neuronal identity and its role in short-term specific associative memory formation<br>(クラスター型プロトカドヘリン $\alpha$ の多様性が短期記憶特異的な神経回路形成に果たす役割) |
| 論文内容の要旨                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                   |
| <p><i>Clustered protocadherins (cPcdh)</i> are a family of cell adhesion molecules that contribute to synaptic specificity and neuronal connectivity and have been implicated in cognitive function. <i>cPcdh</i> comprise 58 isoforms, classified into three subgroups: <i>cPcdh-<math>\alpha</math></i>, <i>cPcdh-<math>\beta</math></i>, and <i>cPcdh-<math>\gamma</math></i>. The expression patterns of these isoforms suggest a role in neural circuit organization, although their precise functions remain unclear. In this study, I investigated how reduced <i>cPcdh <math>\alpha</math></i> diversity affects memory function using <i>cPcdh <math>\alpha1-12</math></i> mutant mice, which express only two variable <math>\alpha</math>-isoforms. Memory function was analyzed separately for short-term and long-term memory using a modified Context Pre-exposure Facilitation Effect (CPFE) paradigm, with intervals of 2 h for short-term memory and 24 h for long-term memory. Behavioral analyses revealed that <i>cPcdh <math>\alpha1-12</math></i> mice exhibited significant impairments in short-term memory, failing to discriminate the conditioned context from a novel context at the 2 h interval, while their long-term memory at the 24 h interval remained intact. In contrast, <i>cPcdh <math>\alpha1-12</math></i> mice showed no abnormalities in spontaneous locomotion or general exploratory behavior, indicating that their impairment was specific to short-term memory rather than a general deficit in motor function or learning ability. Furthermore, Neural activity analysis during memory recall revealed significantly reduced activation in the hippocampus, amygdala, and retrosplenial cortex in <i>cPcdh <math>\alpha1-12</math></i> mice during short-term memory tasks, suggesting reduced engagement of these circuits in memory encoding. Finally, based on these findings, we examined whether similar regions were involved in short-term memory recall in wild-type mice. Analysis in wild-type mice showed that these same regions, including CA3, basolateral amygdala, and retrosplenial cortex, exhibited increased neural activity during short-term memory recall, whereas long-term memory recall did not show such activation patterns. These findings suggest that short-term and long-term memory rely on distinct neural circuits and that <i>cPcdh <math>\alpha</math></i> diversity is essential for the formation and function of circuits required for short-term memory. This study provides insights into the molecular and neural mechanisms underlying memory and highlights the importance of <i>cPcdh <math>\alpha</math></i> diversity in maintaining short-term memory processes.</p> |                                                                                                                                                                                                   |

## 論文審査の結果の要旨及び担当者

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## 論文審査の結果の要旨

クラスター型プロトカドヘリン (cPcdh) は、シナプス特異性と神経細胞の接続性に寄与し、認知機能に関与すると考えられている細胞接着分子の一群であり、神経回路の組織化に役割を果たす可能性を示唆しているが、その正確な機能は不明である。本研究では、cPcdh  $\alpha$ の多様性が低下したcPcdh  $\alpha 1-12$ 変異マウス（2つの変異型 $\alpha$ アイソフォームのみを発現する）を用いて、記憶機能への影響を解析しました。記憶機能について、短期記憶と長期記憶を別々に分析するため、改変されたContext Pre-exposure Facilitation Effect (CPFE) パラダイムを使用し、短期記憶は2時間間隔、長期記憶は24時間間隔で実施しました。行動解析の結果、cPcdh  $\alpha 1-12$ マウスは2時間間隔で条件付けられたコンテキストと新規コンテキストを区別できないなど、短期記憶に著しい障害を示しましたが、24時間間隔での長期記憶は正常に機能していました。さらに、記憶想起中の神経活動解析により、cPcdh  $\alpha 1-12$ マウスにおいて短期記憶課題中に海馬、扁桃体、および後帯状皮質における活性化が有意に低下していることが示され、これらの回路が記憶の符号化に参与する程度が低下していることが示唆されました。本研究は、cPcdh  $\alpha$ の多様性が短期記憶プロセスに関与することを明らかにしたものであり、博士の学位を授与するに値するものと認める。なお、チェックツール “iThenticate 2.0” を使用し、剽窃、引用漏れ、二重投稿等のチェックを終えていることを申し添えます。