News Release

Title

iPS cells reveal the molecular pathology in brains of patients with 22q11.2 deletion.

Key Points

- Patients with 22q11.2 deletion syndrome (22q11.2DS) have the extremely high-risk for the onset of various neuropsychiatric disorders. However, the cellular and molecular mechanisms underlying 22q11.2DS-related brain pathology remains unknown, largely due to no way to directly investigate brain of living patients at a molecular or cellular level.
- Using iPS cells, midbrain dopaminergic neurons derived from healthy controls and 22q11.2DS patients were examined.
- Dysfunction of PRKR-Like Endoplasmic Reticulum Kinase (PERK) caused various vulnerabilities in 22q11.2DS patient-derived midbrain dopaminergic neurons.
- These findings suggest that PERK is one of the key factors for understanding the 22q11.2DS-related pathology in midbrain dopaminergic neurons and may act as a candidate target for the development of therapeutic and preventive strategies for diseases encountered in the future.

Summary

Dr. Yuko Arioka, Prof. Norio Ozaki (Department of Psychiatry, Nagoya University Graduate School of Medicine) and their co-workers revealed “PRKR-Like Endoplasmic Reticulum Kinase (PERK)-dependent vulnerabilities in midbrain dopaminergic neurons” as one of the molecular pathologies in brains of 22q11.2 deletion syndrome (22q11.2DS).

Patients with 22q11.2DS develop various neuropsychiatric disorders such as intellectual disability, autism spectrum disorders, attention-deficit hyperactivity disorder, schizophrenia, and early-onset Parkinson’s disease, dependently on their life-stage. However, the cellular and molecular mechanisms underlying 22q11.2DS-related brain pathology remains unknown, largely due to no way to directly investigate brain of living patients.

Many of previous studies that address the 22q11.2DS-related brain pathophysiology focus on only psychiatric disorders. To consider both of psychiatric disorders and Parkinson’s disease, this team targeted midbrain dopaminergic neurons. The researchers generated iPSCs derived from healthy controls and 22q11.2DS patients, differentiated them into midbrain dopaminergic neurons, and then examined their differences between healthy controls and 22q11.2DS patients. Based on proteomic results, the researchers identified PERK as one of key factors that contributes to the 22q11.2DS-related brain pathology.

Patients with 22q11.2DS suffer from the onset risk for neuropsychiatric disorders over their lifetime. Patients and their families hope the way to stop/prevent the onset of neuropsychiatric disorders. This study will contribute to not only understand 22q11.2DS-related brain pathology but also realize the wishes of patients and their families.

Research Background

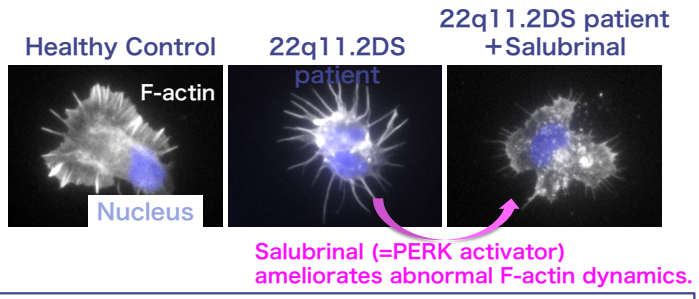
22q11.2DS causes severe disfunction in multi-organ including central nervous system, cardiovascular system, immune system, and endocrine system. As a result, patients with 22q11.2DS life-stage dependently develop various neuropsychiatric disorders such as intellectual disability, autism spectrum disorders, attention-deficit hyperactivity disorder, schizophrenia, and early-onset Parkinson's disease, with multiple organ disorders. However, the cellular and molecular mechanisms underlying 22q11.2DS-related brain pathophysiology remains unknown, largely due to no way to directly investigate brain of living patients at a molecular or cellular level. Despite of these high possibilities to develop neuropsychiatric disorders, patients with 22q11.2DS have no means of preventing future occurrences or stopping the progression of the diseases.

Research Results

Many of previous studies that address the 22q11.2DS-related brain pathophysiology focus on only psychiatric disorders; therefore, they mainly examined the cortex and hippocampus, both of which are considered to be involved in psychiatric disorders. To consider both of psychiatric disorders and Parkinson's disease, this team targeted midbrain dopaminergic neurons. The researchers generated iPSCs derived from healthy controls and 22q11.2DS patients, differentiated them into midbrain dopaminergic neurons, and then examined their differences between healthy controls and 22q11.2DS patients.

Semi-quantitative proteomic analysis identified 'protein processing in the endoplasmic reticulum (ER)' as the most altered pathway in 22q11.2 DS patients. 'Protein processing in ER' is responsible for ER stress response and protein quality control. Thus, the researchers further examined the cellular & molecular system involved in this pathway. They found that 22q11.2DS patient-derived cells had the severe dysfunction of PERK proteins with low expression and hypoactivity. In agreement with this, 22q11.2DS patient-derived cells showed the low tolerance to ER stress. Moreover, they showed the abnormal F-actin dynamics, the loss of ER-mitochondria contact, defect in protein synthesis. Some of these phenotypes were dependent on PERK dysfunction and could be ameliorated by activating PERK (Figure1).

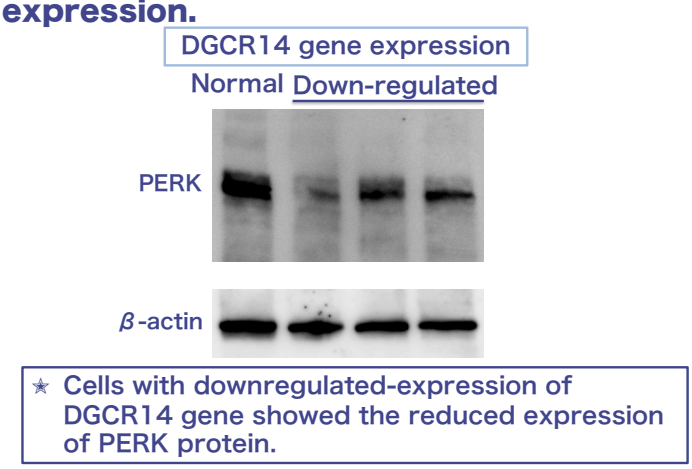
Figure1.
Activation of PERK ameliorates abnormal F-actin dynamics in patient-derived cells.



★ Patient-derived cells showed the defective structure of F-actin (white-marked in above images).
★ PERK activation ameliorated this phenotype.

Lastly, the researchers addressed the reason why PERK expression is reduced in 22q11.2DS patients, and found that DGCR14, one of genes located in 22q11.2 deletion was associated with reduction in PERK expression (Figure2).

Figure2.
DGCR14 gene is associated with PERK expression.

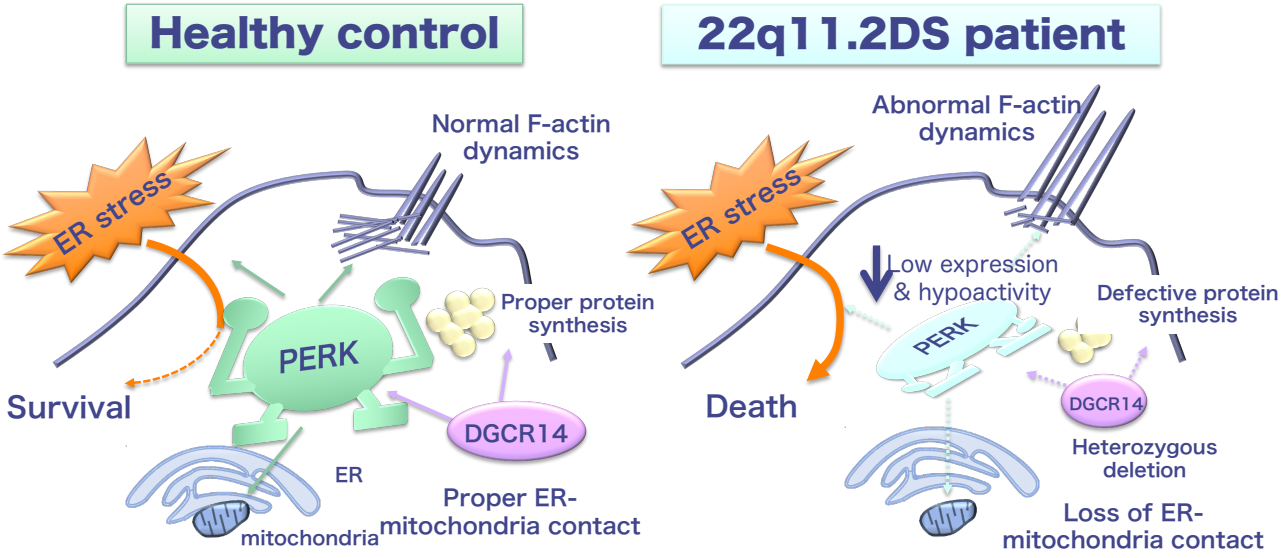


★ Cells with downregulated-expression of DGCR14 gene showed the reduced expression of PERK protein.

Research Summary and Future Perspective

This study showed that " PRKR-Like Endoplasmic Reticulum Kinase (PERK)-dependent vulnerabilities in midbrain dopaminergic neurons" as one of the molecular brain pathophysiologies in 22q11.2 deletion syndrome (22q11.2DS) (Figure3). Patients with 22q11.2DS suffer from the onset risk for neuropsychiatric disorders over their lifetime. Patients and their families hope the way to stop/prevent the onset of neuropsychiatric disorders. This study will contribute to not only understand 22q11.2DS-related brain pathophysiology but also realize the wishes of patients and their families.

Figure3
PERK-dependent vulnerability in patient-derived cells.



Publication

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Chromosome 22q11.2 deletion causes PERK-dependent vulnerability in dopaminergic neurons.

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