

R&D Item

1. Comprehensive epigenome data and single-cell gene expression data for child abuse and suicidality

Progress to date

1. Outline of the project

We aim to obtain comprehensive DNA methylation data from peripheral blood samples of teenage children with histories of abuse (with or without suicidal ideation/behavior) and children in the control group, and investigate whether the epigenetic signatures we previously identified in young suicide decedents, such as “epigenetic aging, telomere shortening, and increased NK cells”, are significantly more likely to occur in (1) children with histories of abuse compared to healthy children, and (2) among children with abuse history, in the group with suicidal ideation/behavior. In addition, we aim to perform single-cell RNA sequencing on blood samples from children with histories of severe abuse and suicidality (as well as some control children), and analyze gene expressions specific in cell type and cell composition ratios at single-cell level.

R&D Item 1: Comprehensive epigenome data and single-cell gene expression data for child abuse and suicidality

Teenage cohort

Abuse history	+	+	-
Suicidality	+	-	-



Comprehensive epigenome data

- Aberrant epigenome profile of CpGs
- Abnormalities in epigenomic aging, telomeres and immune cell proportion

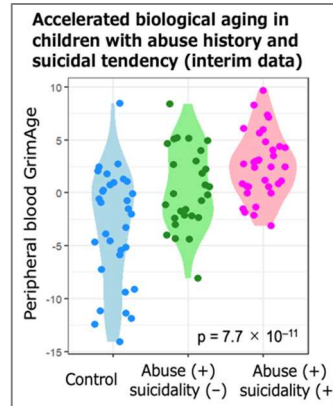


Single-cell gene expression data

- Cell type-specific gene expression
- Cellular proportion changes at single cell resolution

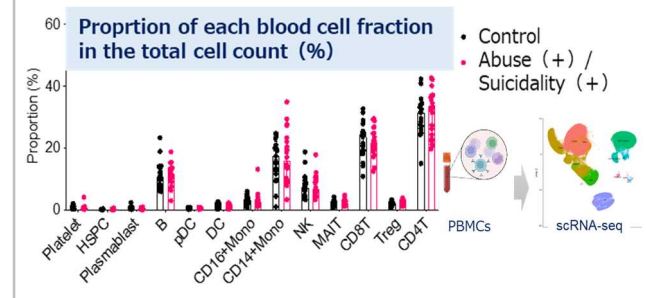
2. Outcome so far

We found that GrimAge (a measurement designed to most accurately predict healthy life expectancy among epigenetic ages) of children with histories of abuse were significantly accelerated compared to healthy controls. In particular, GrimAge was significantly accelerated in children with suicidality. We have also found that a short period of psychiatric treatment intervention can significantly reverse aberrant biological aging in the blood of depressed young patients. We believe these findings may provide positive perspective on the future of this research and development with important evidence that the aberrant biological aging that impairs the health of children with histories of abuse and suicidal tendency can be “reversible through care intervention”. As one of the results from the interim analyses, we found machine learning models using some of the information from the comprehensive DNA methylation data that can predict the risk of youth suicide with high sensitivity and specificity.



In addition, we have established a single-cell RNA sequencing experiment system using multiplexing methods to reduce costs and mitigate batch effects, and we are currently performing single-cell RNA sequencing on blood samples from individuals with a history of abuse and pronounced suicidal ideation or behavior, along with controls. Prior analyses have shown altered immune cell counts and gene expression patterns in specific blood cell types among affected individuals.

Identification of cell populations related to abuse and suicidality



3. Future plans

Through a multi-center consent and sample collection system, we will conduct epigenomic and single-cell analyses of stress cases from child abuse to suicidal tendencies in youth. The resulting database will be the largest of its kind in Asia.

Using peripheral DNA methylation data, we aim to create markers for biological aging and youth mental health (ages 10–30). We are also testing small-scale applications in collaboration with a biotech startup company.

At the same time, in collaboration with computing and emerging ethical, legal and social issues (ELSI) experts, we are developing systems for ethical biomarker use, including appropriate disclosure and infrastructure to balance benefits and risks in identifying severely stressed children.

Principal investigators (PIs)

OTSUKA Ikuo (Kobe University)

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R&D Item

2. Brain AMPA receptor data and epigenome data for abuse and suicidality

Progress to date

1. Outline of the project

By using the positron emission tomography (PET) tracer technology for alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors recognition for human living brain, which we developed for the first time worldwide (Miyazaki et al., *Nature Medicine* 2020), we aim to perform AMPA-PET imaging on young adults who have experienced abuse in childhood and analyze the densities of AMPA receptors in their brains. We compare these with AMPA-PET data from sex/age-matched healthy controls (already constructed) and identify the brain regions where AMPA receptor levels differ in relation to histories of abuse and suicidal tendency. Through these efforts, we aim to clarify the brain mechanisms underlying the emotional instability leading to suicide from the biological effects of

R&D Item 2: Brain AMPA receptor data and epigenome data for abuse and suicidality

Twenties cohort

Abuse history	+	+	-
Suicidality	+	-	-

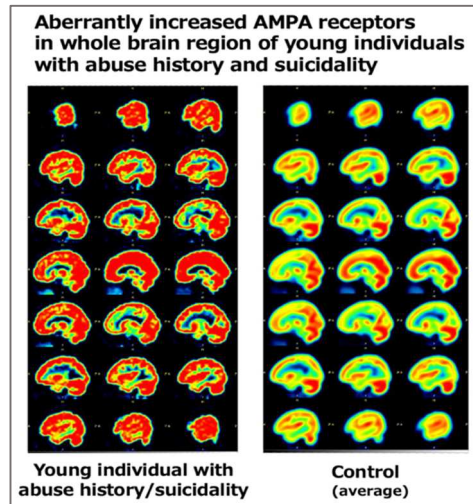
The world's first AMPA receptor recognition for human brain related to abuse and suicidality

- Amount of region-specific AMPA receptors
- Association with DNA methylation data on peripheral blood from same individuals

abuse history in childhood. We also aim to obtain comprehensive DNA methylation data for the same individuals and examine the relationship between AMPA-PET and epigenome data.

2. Outcome so far

We conducted AMPA-PET scans on three young individuals whose childhood adversity was most severe and strong suicidal tendencies. In all cases, we observed increased AMPA receptor density across the entire brain, with the most pronounced increase seen in the individual with the highest adversity score. This pattern differs from findings in other psychiatric or physical conditions and may reflect unique brain changes specific to youth with a history of abuse and suicidality.



If similar trends are observed in additional cases, it may lead to a new understanding that specific brain alterations are associated with early-life adversity and suicide risk in young people.

Early traumatic experiences may impact the biological system (HPA axis) responsible for stress responses, leading to long-term effects on brain development. Given the variability in abuse and psychological symptoms, additional data—including brain function beyond AMPA-PET, epigenomic information, and animal model results—must be collected to elucidate underlying mechanisms and identify robust biomarkers.

3. Future plans

Visualization and Classification of Brain and Mental Health

We are conducting AMPA-PET imaging in youth with a history of abuse or suicidal tendencies—an internationally rare study—to identify brain changes specific to these risks. By integrating epigenomic, EEG, and MRI data, we aim to clarify mechanisms of depression/suicide risk and contribute to the development of new treatments.

Broadening Inclusion Criteria and Strengthening Recruitment

To improve feasibility and clinical relevance, we are expanding participant criteria beyond those with recent suicide attempts, enabling more diverse data collection and practical biomarker development.

Scientific Validation and Method Optimization

The PET tracer ¹¹C-K2, developed to visualize AMPA receptor distribution, is being evaluated for accuracy and safety. To validate observed changes in individuals with adverse experiences, we are introducing rodent models of early-life stress and facilitating interdisciplinary discussions with domestic and international experts to ensure methodological robustness and applicability.

Principal investigators (PIs)

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