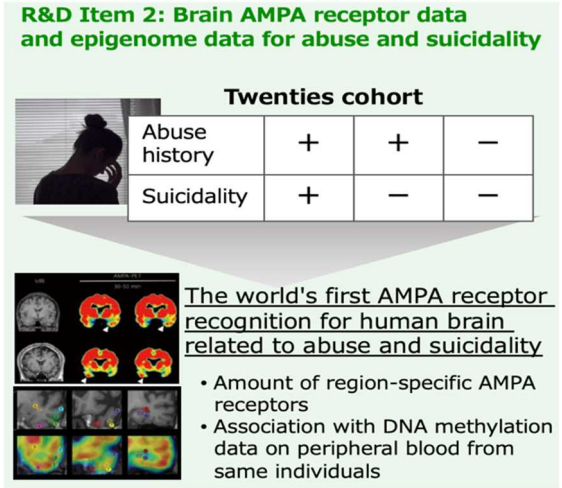
R&D item

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

Progress to date

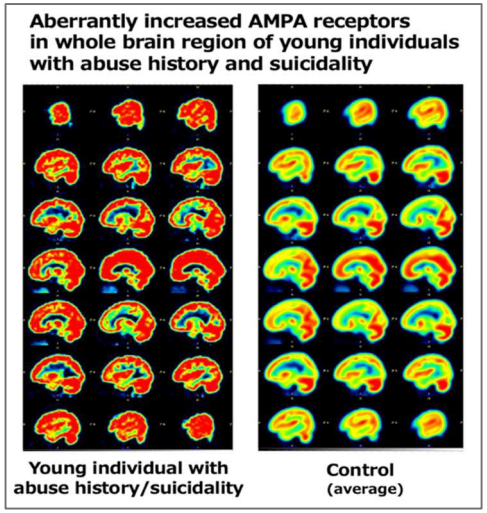
1. Outline of the project

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 that can lead to suicide from the biological effects of 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 have started to obtain AMPA-PET data and comprehensive DNA methylation data from the individuals after completing the ethical approval procedures. As the result of the interim analyses, we found that the densities of AMPA receptors are significantly increased throughout the whole brain in all three cases with histories of severe abuse and current suicidal tendency, compared to the healthy controls. Particularly, the increases in AMPA receptor densities were most prominent in the case individual with the highest score for adverse experience. The findings here were completely different AMPA receptor changes from those we have ever seen in patients with other psychiatric and physical diseases in our AMPA-PET research. If similar changes are observed in other future cases of abuse history and suicidal tendency, we believe that we acquire new findings that the increase in AMPA receptors throughout the brain have relation with biological basis of the abuse and suicidal tendency of young people, independent of the effects of other psychiatric diseases and problems.



3. Future plans

Even worldwide, this is the first study focusing the histories of abuse and suicidal tendency using AMPT-PET imaging, which may discover central nervous system changes specific to young people with the histories of abuse and suicidal tendency the first in the world. We keep to promote recruitment (the below) and aim to accumulate more data (e.g. conducting multi-center research). We also perform correlation analysis with the epigenome data in the peripheral blood samples obtained from the same time and investigate the utility of the epigenome data as a peripheral biomarker of changes in brain AMPA receptors.

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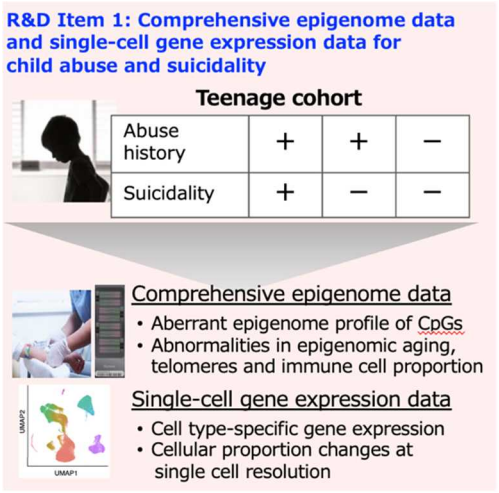
R&D item

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

Progress to date

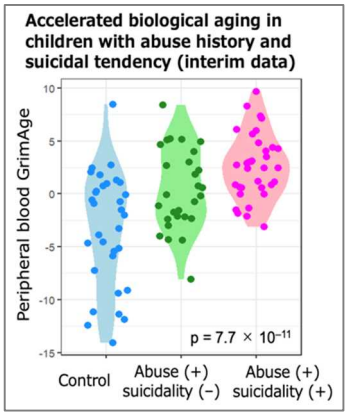
1. Outline of the project

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.

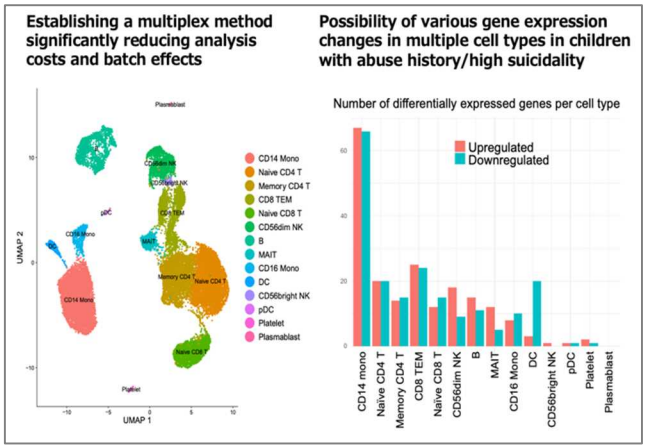


2. Outcome so far

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 of blood samples from children with histories of abuse and severe suicidal ideation/behavior (as well as control groups). As the result of interim analyses, we have found there may be changes in the number of immune system cells and the gene expression of multiple blood cell types in children with abuse history and severe suicidal tendency.



3. Future plans

We plan to collect samples on a scale that exceeds our initial expectations. In addition, based on the results so far, we have started to develop “biological aging indicators” and “markers to accurately reflect mental health conditions” that are specific to young people, using comprehensive DNA methylation data from peripheral samples. At the same time, we are working closely with experts in the field of emerging ethical, legal and social issues (ELSI) to precisely identify and discuss the benefits and risks of biomarkers to detect children exposed to severe stress.

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