DNA methylation changes in cord blood of pregnant woman in the area of high $PM_{2.5}$ concentration in Myanmar

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Introduction

Particulate matter (PM) pollution has been shown to impose a number of health related deleterious effects including cardiovascular, respiratory, neurological systems and birth related outcomes. It has been reported that $PM_{2.5}$ exert deleterious effects not only on human exposed to $PM_{2.5}$ directly but also on children prenatally exposed to $PM_{2.5}$.

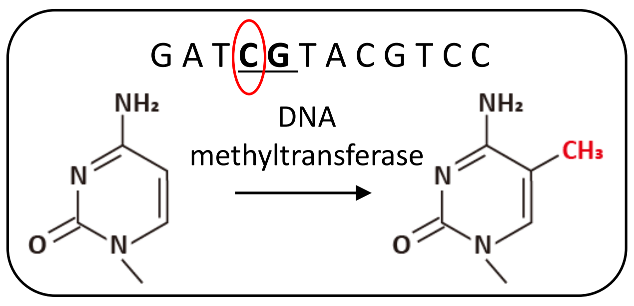
For example, autism spectrum disorder (ASD) is one of the developmental disorders with increasing reported prevalence worldwide. Although genetics plays a strong role in ASD, recent studies suggest that environmental exposures, particularly in utero or during early life, also affect ASD risk. It has been reported that higher maternal exposure to $PM_{2.5}$ during pregnancy, particularly the third trimester, was associated with greater odds of a child having ASD.

It is important to develop biomarkers for early detection of future diseases caused by exposure factors. We are searching for biomarkers by focusing on DNA methylation changes. To use DNA methylation change as a marker for early detection, it is important to clarify DNA methylation sites that changes with exposure factors. Oxytocin receptor (OXTR) is one of the genes involved in developmental disorders including autism spectrum disorder. Although it has been reported that the association between DNA methylation changes and autism spectrum disorder, the association between $PM_{2.5}$ exposure and DNA methylation changes of OXTR gene has not been investigated.

DNA methylation marker

DNA methylation is one of the most broadly studied and well-characterized epigenetic modifications regulating gene expression that do not involve changes to the underlying DNA sequence.

Features of DNA methylation
1) sensitive to environmental changes
2) more frequent than mutation
3) specific to inducing factors and tissues
4) accumulate and impact on future health condition
5) DNA is easy to handle as a sample



If there exist DNA methylation changes that are specific to exposure and disease, they should be useful markers for early detection of exposure and disease.

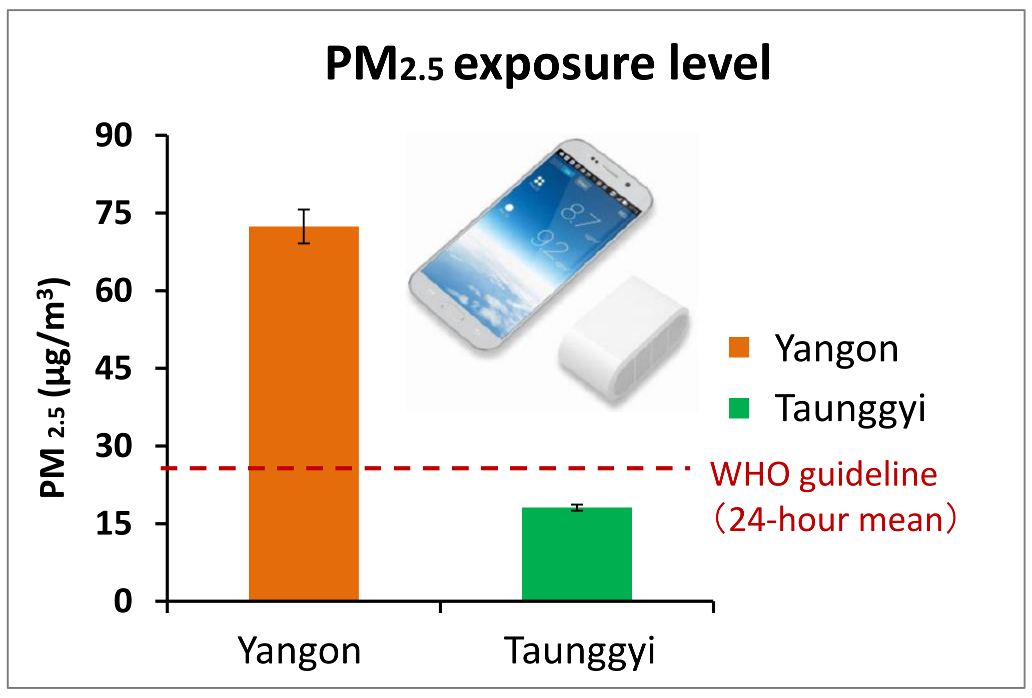
The aim of this study

In this study, we investigated the association between DNA methylation changes of cord blood genomic DNA and $PM_{2.5}$ concentration to develop DNA methylation makers detecting future health effects by $PM_{2.5}$ exposure.

Materials and Methods

This study was approved by Research Ethics Committee, University of Medicine 1, Yangon (114/UM1, REC.2017) and by Medical Ethics Committee, National Institute for Environmental Studies (2018-004). $PM_{2.5}$ concentration was measured using Pocket $PM_{2.5}$ Sensor (Yaguchi Electric Co., Ltd., Miyagi, Japan) in Yangon, a city with high $PM_{2.5}$ levels and Taunggyi, a city with low $PM_{2.5}$ levels. DNA methylation levels at 493 bp and 503 bp downstream from transcription start site of OXTR gene were measured using Pyrosequencer. Furthermore, to detect the other differentially methylated cytosines on a genome-wide scale, we performed reduced representation bisulfite sequencing (RRBS) using next-generation sequencer.

Results-1 $PM_{2.5}$ exposure measurement



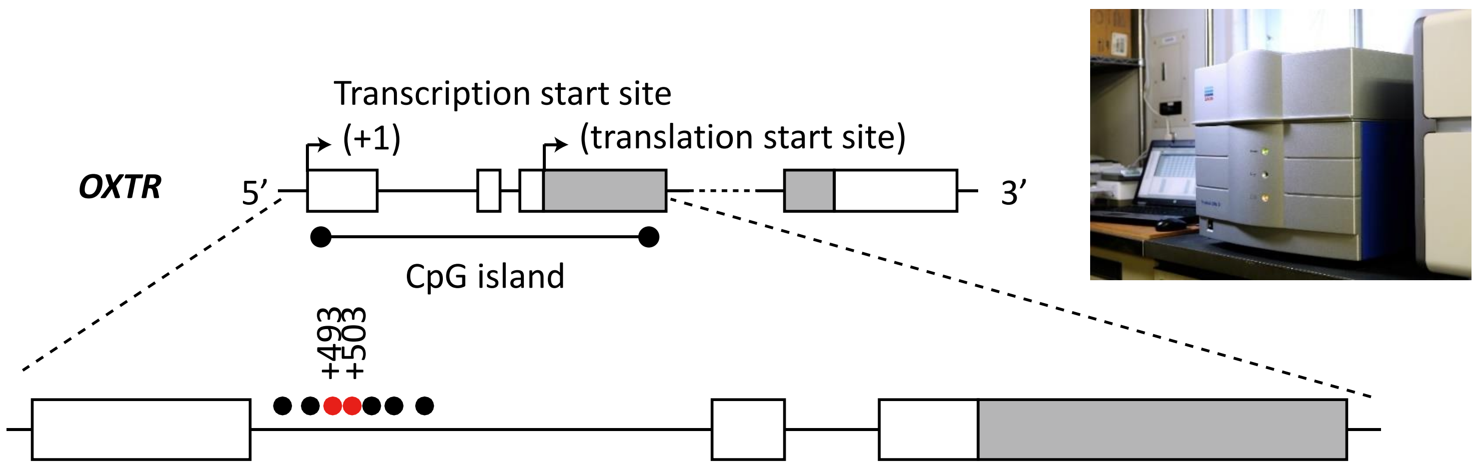
We found $PM_{2.5}$ concentrations of Yangon (72.4±3.3 μg/m³) were significantly higher than Taunggyi (18.1±0.6 μg/m³).

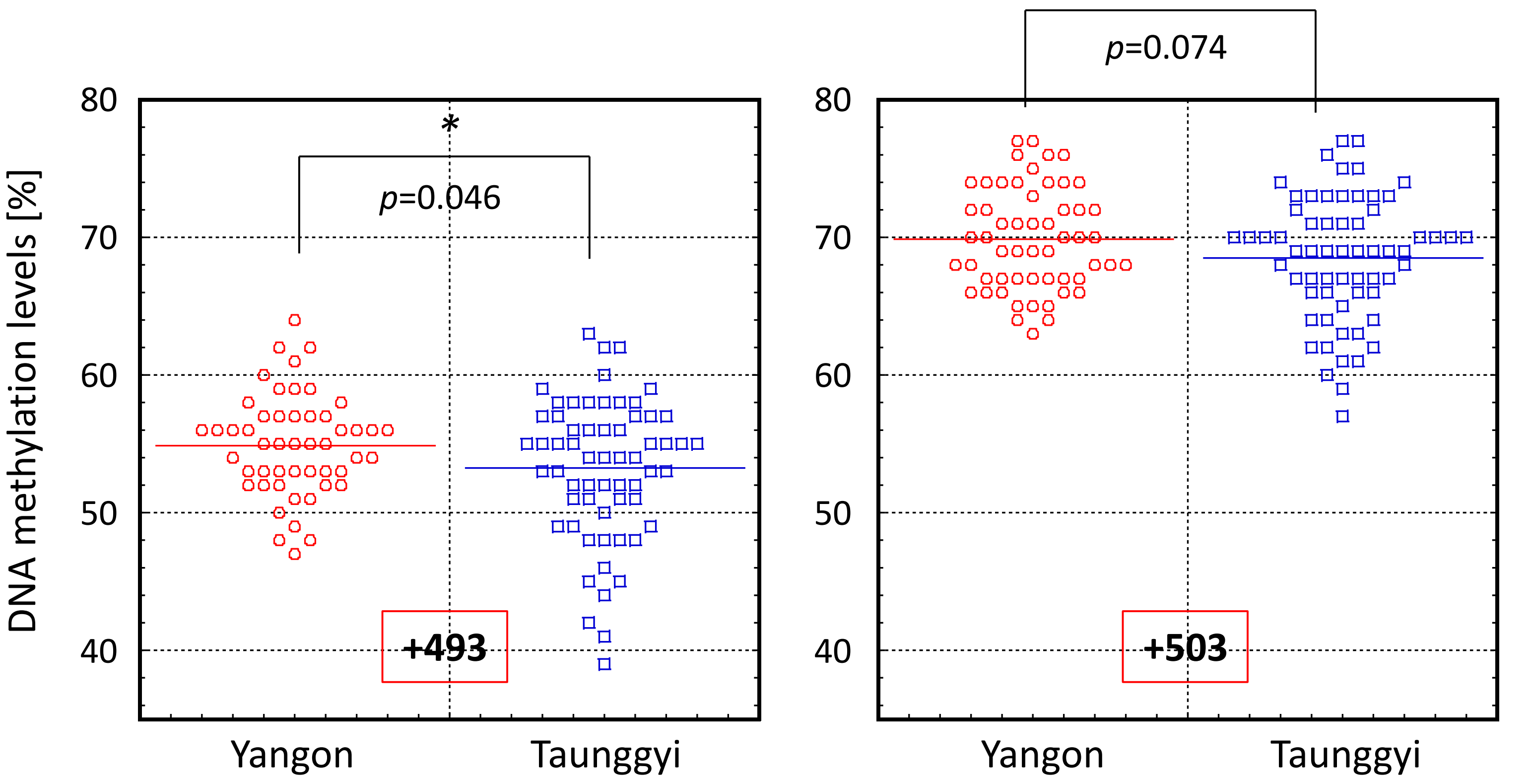
Results-2 Birth Outcomes

	Yangon (n=55)	Taunggyi (n=58)	p-value
Maternal Age	26.7 (19 -42)	26.7 (18 -47)	NS
Offspring (Female %)	53%	46%	NS
Birth Weight (Kg) (Female/Male)	3.06±0.06 2.9±0.05, 3.2±0.1	3.06±0.04 3.1±0.06, 3.1±0.07	NS
MBD (week) (Female/Male)	38.8±0.3 39.2±0.2, 38.2±0.5	39.3±0.3 39.4±0.3, 39.1±0.3	NS

There was no significant difference between Yangon and Taunggyi.

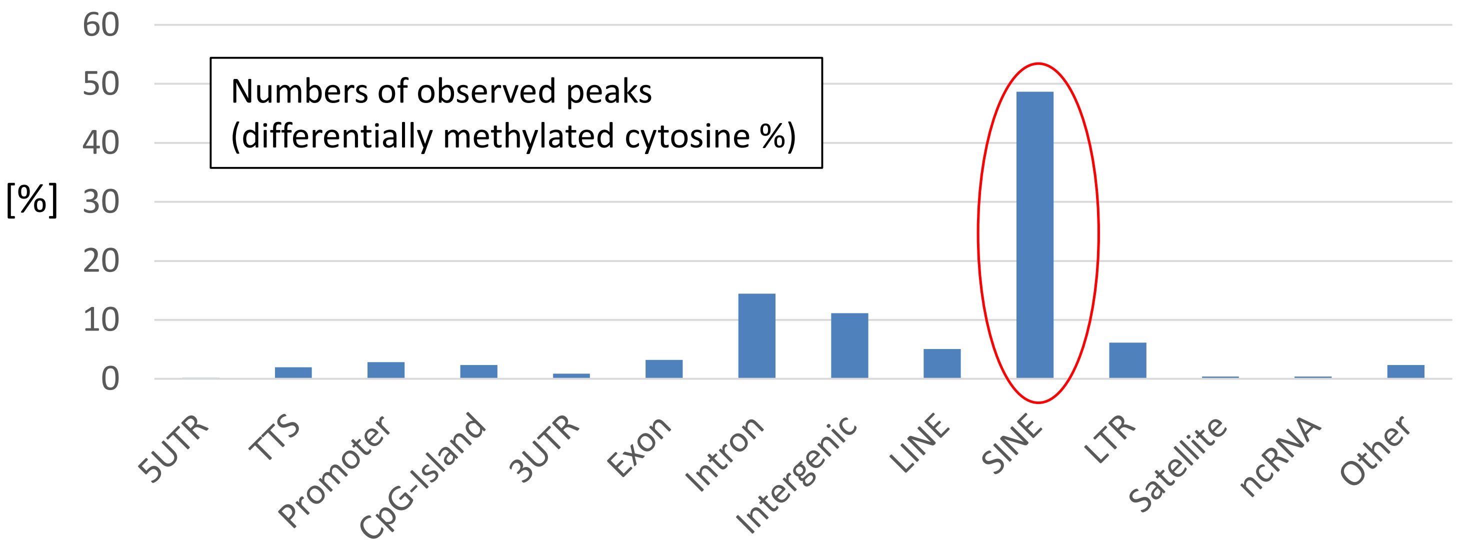
Results-3 DNA methylation changes of OXTR gene

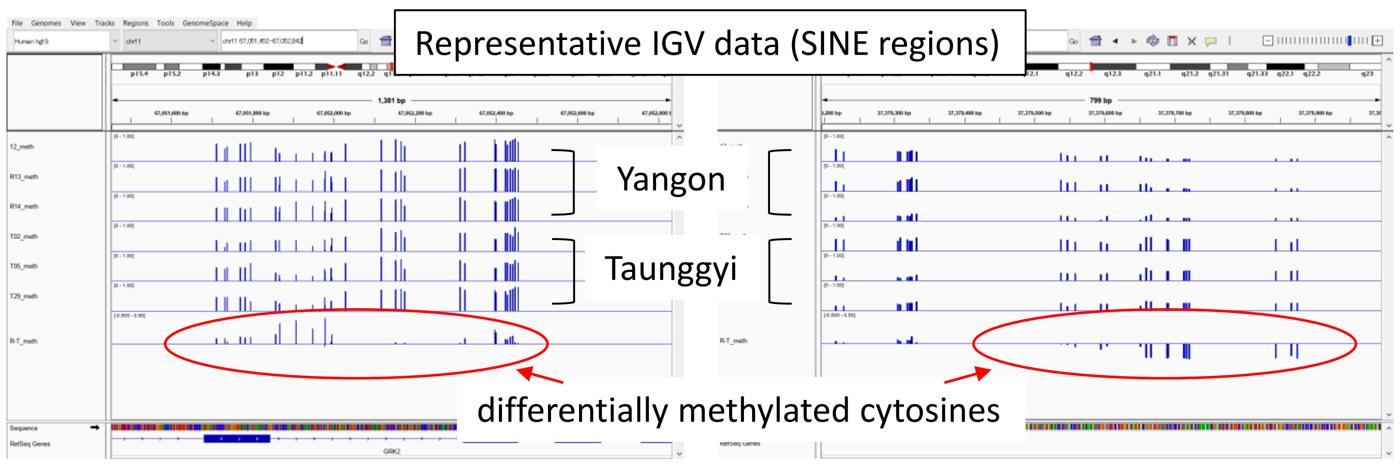




Pyrosequencing analysis revealed that DNA methylation levels at 493 bp and 503 bp downstream of OXTR were increased in Yangon compared to Taunggyi.

Results-4 Genome wide analysis of DNA methylation changes





Genome wide DNA methylation analysis revealed that DNA methylations of SINE retrotransposon regions were mainly changed in cord blood DNA of pregnant woman in the area of high $PM_{2.5}$ concentration in Myanmar.

Conclusions

1. $PM_{2.5}$ concentrations of Yangon were significantly higher than Taunggyi and about 3 times higher than the guideline value.
2. The DNA methylation changes of OXTR and SINE regions in cord blood genomic DNA can be the useful markers for developmental disorders caused by $PM_{2.5}$ exposure and for $PM_{2.5}$ exposure assessment, respectively.
3. Further studies will be needed to clarify the association between $PM_{2.5}$ exposure during pregnancy and risk of developmental disorder in children.

Maternal Exposure to $PM_{2.5}$ during Pregnancy

DNA methylation changes in cord blood genomic DNA

developmental disorders in children

No conflict of interest