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学　位　論　文　名	Genome-Wide DNA Methylation and Gene Expression Analyses of Monozygotic Twins Discordant for Intelligence Levels （認知能力の差が顕著な一卵性双生児の DNA メチル化解析と遺伝子発現解析）
論　文　審　査　委　員	（主査） 教　授　戸田　達史 （副査） 教　授　武田　雅俊　　教　授　竹田　潤二

論　文　内　容　の　要　旨

〔目　的(Purpose)〕

Human intelligence, as measured by intelligence quotient (IQ) tests, demonstrates one of the highest heritabilities among human quantitative traits. Nevertheless, studies to identify quantitative trait loci responsible for intelligence face challenges because of the small effect sizes of individual genes. Phenotypically discordant monozygotic (MZ) twins provide a feasible way to minimize the effects of irrelevant genetic and environmental factors.

The purpose of this study was to discover epigenetic or gene expression differences between MZ twins.

〔方法ならびに成績(Methods/Results)〕

We conducted array-based genome-wide DNA methylation and gene expression analyses using 17 pairs of healthy MZ twins discordant intelligently. *ARHGAP18*, related to Rho GTPase, was identified in pair-wise methylation status analysis and validated via direct bisulfite sequencing and quantitative RT-PCR. To perform expression profile analysis, gene set enrichment analysis (GSEA) between the groups of twins with higher IQ and their co-twins revealed up-regulated expression of several ribosome-related genes and DNA replication-related genes in the group with higher IQ. To focus more on individual pairs, we also conducted pair-wise GSEA and leading edge analysis, which indicated up-regulated expression of several ion channel-related genes in twins with lower IQ.

〔総　括(Conclusion)〕

Given that the concept of general cognitive ability has been widely accepted to depict a near-universal positive covariation among diverse measures of cognitive abilities, naming even one genetic locus that is reliably related with normal-range intelligence remains challenging. IQ is easy to quantify and compare among different individuals. Benefiting from the extraordinary similarities in genomic constitution and environmental factors, studies based on discordant monozygotic twins are capable of uncovering phenotype-associated epigenetic changes independent of underlying sequence variance.

By successfully recruiting 17 pairs of identical twins discordant for intelligence levels, we shall have a modest power in the identification of intelligence-related epigenetic differences. This is the first study that used genome-wide epigenetic and transcriptomic profiling to identify epigenetic changes related to the discordance between MZ twins with normal-range intelligence. A list of new candidate genes possibly related to cognitive abilities was generated. With further functional evaluations, these genes might provide us a key to decipher the puzzle of the mechanisms underlying the human brain.

論文審査の結果の要旨

当論文の研究目標は認知能力に関る遺伝子を同定することである。人間には認知能力のあらゆる側面において非常に大きな個人差があり、このような個人差を生じさせる因子として環境的なものだけではなく、遺伝的な要因も大いにあることが、明らかになってきた。認知機能のその遺伝学的な影響を明らかにするために、学位申請者は知能指数IQが顕著に違う一卵性双生児を用いた網羅的遺伝子発現解析やゲノムメチル化解析を行っている。

メチル化の差異程度と発現量を比較する実験手法や双生児間を互いに対照群とする解析法は、先行研究が殆どなく困難な状況に当たった。当論文には発現量を調べるアルゴリズムとメチル化差異の比較手法を確立した。

当論文は人間の認知能力に関る遺伝子の同定することに繋がる成果を挙げただけではなく、双生児サンプルを基にした正常範囲内の表現型個人差をメチル化状態と発現量を網羅的調べる研究としても初の論文になった。学位の授与に値すると考えられる。