DEFINING EPIGENETIC MECHANISMS INVOLVED IN GENERATING THE *CURLY TAIL* PHENOTYPE

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Numerous studies have been performed that address the relationship between environmental factors and phenotypic variation, resulting from epigenetic or heritable modifications in gene expression caused by changes other than an alteration in DNA sequence. Nonetheless, epigenetic mechanisms responsible for phenotypic variation remain poorly understood.

Studies of inositol-phosphate biosynthesis in the developing brain of normal (CBA) and *curly tail* mutants suggest that abnormal levels of inositol may be involved in generating the phenotypic variance and susceptibility to a neural tube disorder, spina bifida, observed in *curly tail* mice. Mutants with the curly tail (CT) phenotype exhibit spina bifida coupled with high levels of brain inositol and are unable to regulate the constitutive expression of *myo*- Inositol 1-Phosphate Synthase (MIP), the only enzyme known to synthesize inositol. In contrast, littermates with a straight tail (ST) appear normal and are able to down regulate inositol production in the adult brain. It is hypothesized that epigenetic mechanisms regulate inositol biosynthesis in the *curly tail* brain.

An analysis of MIP promoters was used to question the involvement of one epigenetic mechanism, DNA methylation. DNA was isolated from the brain of juvenile and adult CBA, ST and CT mice, treated with bisulfite, amplified with primers targeting an enriched CpG island in the promoter, cloned and sequenced to compare DNA methylation patterns.

Results of these experiments suggest that aberrant DNA methylation occurs in the adult CT MIP promoter. This finding implicates a role for DNA methylation in the constitutive production of inositol-phosphate in the CT mutant.