

**Epigenetics, Nutrition, and Disease Susceptibility Abstract**  
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Human epidemiological and animal experimental data indicate that the risk of developing adult-onset diseases, such as asthma, diabetes, obesity, and cancer, is influenced by persistent adaptations to prenatal and early postnatal exposure to environmental conditions such as nutritional privation [1]. Moreover, the link between what we are exposed to *in utero* and disease formation in adulthood appears to involve epigenetic modifications like DNA methylation at metastable epiallele and imprinted gene loci.

Genomic imprinting is an epigenetic form of gene regulation that results in monoallelic, parent-of-origin dependent gene expression [2]. Since imprinted genes are functionally haploid, only a single genetic or epigenetic event is needed to dysregulate their function. This vulnerability means that imprinted genes are prime candidates for causative roles in human diseases that have a parental inheritance bias and an environmental component in their etiology. We recently developed computer-learning algorithms that predicted the presence of imprinted genes in mice [3] and humans [4]. Not only are humans predicted to have fewer imprinted genes than mice, but there is also a mere 30% overlap between their imprinted gene repertoires. By mapping the human candidate imprinted genes onto the landscape of disease risk defined by linkage analysis, we are now poised to determine the importance of imprinting in the etiology of complex human diseases and neurological disorders.

Genes with metastable epialleles have highly variable expression because of stochastic allelic changes in the epigenome rather than mutations in the genome. The viable yellow agouti ( $A_{vy}$ ) mouse harbors a metastable *Agouti* gene because of an upstream insertion of a transposable element. We have used the  $A_{vy}$  mouse to investigate the importance of nutrition in determining the susceptibility of offspring to adult diseases [5,6]. We have shown that maternal dietary supplementation during pregnancy, with either methyl donors (i.e. folic acid, vitamin B<sub>12</sub>, choline and betaine) [5] or genistein [6], decreases adult disease incidence in the offspring by increasing DNA methylation at the  $A_{vy}$  locus. Moreover, these nutritional supplements can counteract the CpG hypomethylation caused by the endocrine disruptor, bisphenol A (BPA) [7]. (Supported by NIH grants ES13053, ES08823, ES015165 and T32-ES07031, and DOE grant DE-FG02-05ER64101)