

## Target Article

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# Epigenetic Perspectives on Development: Evolving Insights on the Origins of Variation

**ABSTRACT:** The articles in this special section of *Developmental Psychobiology* explore topics discussed at the 24th Annual Winter Conference on Current Issues in Developmental Psychobiology held in January 2009 in St. Croix. The final session of the meeting: "Epigenetics and Behavioral Development Within and Across Generations" included discussion of several emerging issues relevant to the study of individual differences, parental influences on development, and the stability versus plasticity of the underlying mechanisms involved in behavioral variation. The contributions to this special section highlight the importance of the epigenetic regulation of gene expression to the field of developmental psychobiology and the critical role of these molecular mechanisms in mediating the interplay between genes and the environment. © 2010 Wiley Periodicals, Inc. *Dev Psychobiol*

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The articles in this special section of *Developmental Psychobiology* explore topics discussed at the 24th Annual Winter Conference on Current Issues in Developmental Psychobiology held in January 2009 in St. Croix. This meeting brings together a diverse group of researchers who study the question of development from clinical, behavioral, neurobiological, cellular and molecular perspectives with a particular focus on how developmental trajectories are shaped by early life influences. During the final session of the meeting, the topic of epigenetics was discussed with highlights from numerous research groups on the role of nongenomic mechanisms in mediating individual differences in behavior and the role of epigenetics in furthering our understanding of the interplay between genes and the environment.

Though the topic of epigenetics was once confined to the field of molecular biology, in the past 5 years there have been exciting new applications of an epigenetic

perspective to the study of development and behavior with increasing appreciation of the plasticity that these mechanisms can confer. The term "epigenetic" can be used broadly to refer to variation in phenotype that is not exclusively related to genetic variation or more specifically to refer to the molecular mechanisms that regulate gene transcription without modifying gene sequence. Historically, developmental biologists and psychologists such as Conrad Waddington (1905–1975) and Gilbert Gottlieb (1929–2006), have provided strong theoretical and empirical support for the importance of gene–environment interplay in the process of development. However, identification of the factors which mediate this process has only occurred with recent advances in molecular biology. The link between genes and functional outcomes is established through the timing and degree of gene transcription. The regulation of transcription is an elegant process involving a cascade of changes to the density of chromatin and to the accessibility of DNA to transcription factors. Amongst the many epigenetic mechanisms involved in gene regulation, modifications to histone proteins and DNA methylation have been increasingly explored in the context of gene silencing versus gene expression. These modifications to the activity of genes play a critical role in

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cellular differentiation which is a clear example of how a diversity of phenotypes can be achieved from a single genotype through the epigenetic regulation of gene expression.

Evidence for the stable yet dynamic epigenetic control of transcription and cellular phenotype raises many interesting questions regarding the relationship between genotype, phenotype, and the environment. *Can these mechanisms that play so crucial a role in cellular differentiation be used to explain diversity in phenotype at the level of the organism?* For the discipline of developmental psychobiology the question might be: *Can individual differences in development, brain, and behavior be linked to these molecular mechanisms?* The answer to these questions, which has emerged from both human and animal studies, suggests that taking an epigenetic perspective, in both the broad and specific uses of the term, can advance our understanding of the origins of individual differences. Amongst the three articles included in this special issue, the common theme is that an epigenetic approach is being taken to address the topic of individual variation.

The special section begins with the article by Curley and Mashoodh who address the question: *How do mothers and fathers differentially influence their offspring's development?* One of the key concepts within Mendelian genetics is the equivalence of the parental genomes in their influence on offspring phenotype that is achieved through the law of independent assortment of genes. However, there is increasing evidence for exceptions to this law. An interesting example of this exception comes from the literature on reciprocal hybrids, where offspring are generated through cross-breeding of mothers and fathers from different species or subspecies. Comparisons of reciprocal hybrid offspring suggest that despite theoretically equivalent genomes, parental influences on development and behavior can be observed. Thus, there are “parent-of-origin” effects which illustrate the non-traditional pathways (both genetic and epigenetic) through which mothers and fathers can shape the development of their offspring. In their article, Curley and Mashoodh present a comprehensive review of the evidence for the influence of sex chromosomes and mitochondrial DNA as examples of nontraditional genetic routes through which parental influences on variation in behavior can be achieved. Their summary of the literature highlights the notion that sex chromosomes are not limited in their function to sex determination/differentiation and that despite the small complement of genes present in maternal mitochondria inherited by offspring, these genes can significantly alter development. The epigenetic mechanisms that may mediate observed parent-of-origin effects is also discussed with a focus on genomic imprinting, the gene-specific silencing of either

maternal or paternal alleles during gametogenesis, and environmentally induced epigenetic alterations in the germline that are transmitted to subsequent generations. Though these epigenetic routes of influence both rely on variations in DNA methylation, the timing and process through which this occurs differs significantly between genomic imprinting and induced germline effects. Taken together, the evidence presented of these genetic and epigenetic influences of parents leads us to speculate regarding the transmission of individual variation in phenotype across generations.

Development is a dynamic process during which interactions between and organism and its environment can have a significant impact on the brain and behavior. In the review, *Epigenetic Influence of Social Experiences Across the Lifespan*, I have explored the pervasive influence of environmental exposures, with a particular focus on quality of social interactions, occurring at various time-points, spanning the prenatal, postnatal, juvenile, and adult phases of development. Maternal stress during gestation, variations in postnatal mother–infant interactions, the social context of juvenile development, and adult social stress can exert long-term effects such that the influence of these experiences can be observed in adulthood. Evidence for the role of epigenetic mechanisms in mediating the persistent effects of the environment has emerged from animal models and suggests that changes to DNA methylation and histone modifications may play a critical role in maintaining environmentally induced individual differences in phenotype. Importantly, this plasticity extends beyond the early phases of development. This literature highlights an issue of significant clinical relevance: the biological substrates through which intervention at later periods of the lifespan can be achieved. Similar to the article by Curley and Mashoodh, this review provides evidence for the trans-generational impact of social experiences, suggesting that environmental insults or interventions may have consequences beyond the life history of the individual leading to the inheritance of risk or resilience.

Though molecular approaches to the understanding of disease risk have traditionally taken a genetic perspective, there is increasing evidence that individual differences in clinical outcomes may be linked to epigenetic variation. In the final article in the special issue, Bredy et al. review the emerging literature on the association between epigenetic modifications and psychiatric illness, with a particular focus on schizophrenia, drug addiction, depression, and anxiety disorders. This review highlights important methodological considerations in the study of epigenetics as well as speculation on the efficacy of pharmacological targeting of the epigenome as a possible treatment of psychopathology. In considering the origins of individual differences in psychiatric illness in humans,

cognition is particularly relevant, with aberrant learning and memory processes often being critical to the persistence of symptomatology. Bredy et al. demonstrate the effectiveness of manipulating the epigenome as a strategy for enhancing the acquisition and extinction of learned behaviors, with implications for the development of therapeutic strategies. These studies provide an interesting link to theoretical work by Griffith and Mahler (1969) who suggested that mechanisms such as DNA methylation may be a route through which long-term memories are stored. Recent advances to the study of epigenetics, learning, and memory suggest that despite the prevailing dogma that postmitotic cells do not undergo changes in DNA methylation, dynamic epigenetic changes are possible in the adult brain, thus creating limitless potential for re-programming of pathological cognitive processes.

These articles provide a diverse and evolving perspective on the role of epigenetics in shaping development and in mediating the relationship between genotype and phenotype. The advances in molecular biology that have

made this revolution possible will continue to inform and refine our understanding of the role of epigenetics in mediating individual differences in brain and behavior. In the meanwhile, speculation on the role of these mechanisms in mediating the inheritance of acquired traits suggested by Lamarck and the implications of epigenetics for evolution has led to a revival of ideas once thought heretical to the biological sciences. Though this field is in its infancy, the study of epigenetics as an interface between an organism and its environment has great promise for generating novel approaches to research and clinical intervention with implications for our theoretical perspectives on the origins of variation in traits between and within individuals.

## REFERENCE

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