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Report of the National Heart, Lung and Blood Institute Working Group on Epigenetics and Hypertension

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Useful resources links mentioned in the text
PhysGen Knockout program ("Mechanistic Characterization of Genes for Hypertension and Renal Disease") http://rgd.mcw.edu
The Knockout Mouse Project (KOMP) http://www.nih.gov/science/models/mouse/knockout/
Link Animal Models to Human Disease http://www.lamhdi.org/
Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium http://web.chargeconsortium.com
Genotypes and Phenotypes (dbGaP) database (http://www.ncbi.nlm.nih.gov/gap)
Database of parental origin effect on mouse gene imprinting http://igc.otago.ac.nz/home.html

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Human and financial impact of essential hypertension

Hypertension, defined as a condition associated with ≥140 mm Hg systolic blood pressure or ≥90 mm Hg diastolic blood pressure, affects over one billion people worldwide[1] and in 2009 it cost the US health care system more than $73 billion[2]. Despite the availability of many anti-hypertensive therapies, individual responses vary and efficacy remains a concern. Current treatments have yielded only modest reductions in the overall disease risk even in countries where therapeutics are available and affordable. The initiating causes and the pathogenic mechanisms for disease and its comorbidities remain largely unknown, and prognostic markers for adult hypertension that could improve its diagnosis, prevention, and ultimately its management are not yet available. As a result, nearly 28% of the US population and a similar proportion of the adult Western European and Canadian populations suffer from what is known as "essential hypertension"[3], which is a primary component of several complex, multifactorial, multigenic conditions that are commonly associated with high levels of morbidity and mortality from diabetes, cardiovascular and renal disease. If the current rise in the number of hypertension cases is not abated, total annual global healthcare costs resulting from suboptimal blood pressure for those older than 30 years of age could amount to $3.6 trillion over the next 10 years[4].

Genetics, "Missing Heritability" and the Epigenetic Hypothesis

The causes of essential hypertension remain poorly understood even though the complex mechanisms for blood pressure (BP) regulation have been extensively characterized in both humans and animal models[5,6,7]. Comprehensive study of more than a dozen inbred rat strains that recapitulate many aspects of hereditary human hypertension has added substantially throughout the years to our understanding of the underlying physiological and molecular pathways, the genetic complexity of risk and treatment responses, as well as the

pathological consequences of hypertension[8]. In fact, many interventions that lead to a lowering of blood pressure were identified first with these experimental model systems[9,10]. Detailed annotations of such experimental models are currently available (PhysGen Knockout Program, http://rgd.mcw.edu). These studies in experimental models are however only the first step in the quest to clarify the genetic and phenotypic architecture of this complex human disease[11,12,13,14,15].

Hypertension is a highly heritable trait[16,17] and recent genome-wide linkage and association studies (GWAS) as well as candidate gene approaches clearly demonstrate the multigenic complexity of essential hypertension[18,19,20,21,22]. The International Consortium for Blood Pressure Genome-Wide Association Studies, which used a multistage design in 200,000 individuals of European descent, recently identified 16 novel functional genetic variants, associated with high blood pressure in human populations[20]. (These variants are commonly known as quantitative trait loci, or QTLs.) Six of these loci involve genes previously known or suspected to regulate blood pressure, with the other genetic variants pointing to novel pathways that influence blood pressure and cardiovascular disease risk.

An unexpected and disconcerting observation from these genetic studies is that the discovered genetic variants, individually and collectively, account for only a small fraction of phenotypic variation and disease risk. For example, these blood pressure QTLs together account for only a small proportion of BP variation (up to 5 mmm Hg), yet their typical effect size is sufficient to raise cardiovascular disease risk in human populations[18,19,20,21,22]. Importantly, although the CHARGE and GlobalBPgen consortia established and replicated the effects of 8 novel loci on BP, the cumulative effect of these 8 loci explained only ~1% of BP variance[18,19]. These results are especially surprising given the substantial heritability of BP, estimated between 30% and 40%[15,16]. Similar results have emerged in GWAS of other complex conditions in humans and genetic studies of other species[11,12,13,14,15]. This difference between estimated and observed variance is termed ‘missing heritability’, the search for which has now become one of the primary goals for research on hypertension and other complex conditions[11].

To explain the ‘missing heritability’ of complex traits, several hypotheses have been proposed, including over-estimates of heritability, unexplored regions of the genome, untested classes of genetic variants, the action of many rare genetic variants, and gene interactions[11,23,24]. Phenotypic variation can also be regulated independently of changes in DNA sequence, thereby escaping detection with classical genetic approaches[25,26,27,28,29,30,31]. These heritable epigenetic changes could explain some of the ‘missing heritability’ in hypertension, and some circumstantial evidence involving modification of genes that could affect important pathways in hypertension is beginning to emerge, further prompting the need for experiments specifically designed to prove a causal relationship[32].

Epigenetics

Epigenetics is defined as the transmission from one cell generation to the next (through mitosis) or from one organismal generation to the next (through meiosis) of gene expression patterns that do not rely explicitly on differences in DNA sequence[25]. The term was originally introduced to account for the maintenance of cell- and tissue-specific gene expression patterns across mitotic cell divisions throughout somatic development. Many cell functions such as tissue-specificity, germline-specificity, imprinting and X-chromosome inactivation, rely on correct epigenetic control of gene expression[30,31]. Introduction of high-throughput technologies, which now enable epigenetic features to be comprehensively and quantitatively profiled across the genome, has led to exciting evidence in animal models where epigenetic changes have been documented not only during development but also in

adult conditions such as cancer[33], cardiovascular disease[34], diabetes[35], obesity[36], and longevity[37]. Evidence for epigenetic effects in humans is more limited because of the considerable challenges in study design needed to reliably distinguish the various sources of phenotypic variation. As a result, many questions remain, such as defining the environmental and genetic factors that trigger epigenetic changes, defining the molecular mechanisms that maintain and where necessary reverse epigenetic features, assessing the relative contributions of genetic, environmental and epigenetic factors, and characterizing the impact of epigenetic changes on phenotypic variation and disease risk within and across generations.

Epigenetic changes are orchestrated by several molecular processes, including nucleic acid methylation, histone modification, nucleosome positioning, transcription control with DNA binding proteins and noncoding RNAs, and translation control with microRNAs and RNA binding proteins[26,27,28,29,30,31]. Of the many modes of epigenetic control, the best studied are histone modification and DNA methylation. Histone modification is an important mechanism that leads to changes in the nucleosome to constrain DNA wrapping around its histone core (nucleosome positioning). Chemical modification of the N-terminal tails of histone proteins forms a “histone code” that regulates gene activity. DNA methylation is another important mechanism of epigenetic control in which methylation of DNA occurs at the cytosine base of DNA, often in the context of CpG dinucleotides. In addition, other forms of chemically modified DNA have recently been reported[26]. An important but less studied mode of epigenetic control involves noncoding-RNAs (microRNAs as well as other long and short RNAs) that regulate gene expression and mRNA translation. Systematically characterizing these various kinds of epigenetic marks across the genome, during development and throughout the life of an organism, is a major challenge, as is dealing with cellular and temporal heterogeneity in these marks.

Studies in experimental animals show that epigenetic changes can arise throughout life, from early embryos to old age, as a result of developmental and physiological processes, environmental exposure, and stochastic events. The epigenome is thought to be most vulnerable to modification during embryogenesis when DNA synthesis is rapid and when both DNA methylation patterns and chromatin structure required for normal development are established. During development for example, maternal nutritional status as well as altered hormonal and stress profiles can profoundly affect epigenetic features with long-term impacts on disease risk. In addition, studies in twins at different ages show that, although identical at birth, the epigenome diverges during lifetime[38]. An understanding of the mechanisms that transmit environmental and genetic signals to the molecular machinery responsible for epigenetic changes that will undoubtedly emerge would mechanistically explain the molecular embedding of early childhood experiences (“nurture”) onto the genome (“nature”)[39].

In many organisms, some epigenetic changes are not erased during gametogenesis and can affect the phenotype and health not only of immediate offspring, but also of future generations through transgenerational effects[27,28,29,30,40,41,42,43,44,45,46,47,48]. Several studies in rodents and other species have revealed remarkable evidence for heritable epigenetic changes where the phenotypic effects of environmental exposure and genetic variants can be transmitted epigenetically across multiple generations. In some circumstances, these effects can be as strong as conventional genetic effects, endure across multiple generations, transmit through the male or the female germ-lineage, and reverse under certain conditions[44,45]. Epigenetic inheritance is usually determined by a combination of genetically-controlled susceptibility of the parental genome to various stressors and the vulnerability of the offspring’s genome to these inherited epigenetic changes. Such changes enable homeostatic adaptations of the epigenetic code in response to various environmental

and genetic stressors within a parent's lifetime to be communicated to the offspring as "preadaptations" to the particular environment in which they live and the family to which they belong[27,28,49,50,51,52].

Role of epigenetics in hypertension

Many questions emerge from these considerations: Are epigenetic marks and features a cause or consequence of hypertension? Do epigenetic changes contribute to comorbidities of hypertension such as diabetes, cardiovascular and renal disease? Are epigenetic features indicative prognostic or diagnostic biomarkers for human hypertension? Are epigenetic marks of hypertension fixed early in life rather than changing dynamically in response to various perturbations? To what extent are these epigenetic features reversible in a general or in a targeted manner? What is the molecular basis for epigenetic memory related to hypertension within and across multiple generations, how are these marks established, and how do they differ from other epigenetic features?

In parallel with studying conventional epigenetic features such as methylation profiles and histone modification, important insights could be gained from investigating the effects of environmental perturbations on mRNA, microRNA and non-coding RNA expression patterns, and their potential associations with the physiological changes during tissue and organ development as well as disease initiation and progression.

The Working Group prioritized three questions that require immediate attention:

1. ***Do epigenetic changes affect blood pressure in humans?*** A deeper understanding of epigenetic changes in response to environmental and genetic stresses is needed to generate hypothesis-driven experimental studies that can in turn establish causality as well as reveal fundamental molecular mechanisms of blood pressure regulation. For instance, studies are urgently needed to establish the chronological sequence of epigenetic and pathological changes at different life-stages (preconception, conception, development, birth, childhood, adolescence and adulthood) both during normal development and during the onset and progression of hypertension. With model organisms, experiments can be designed to rigorously characterize all life-stages, obtain diverse organs and tissues for analysis, and control age, sex, and environment factors. In parallel, human studies could examine phenotypic discordances within monozygotic (identical) twin pairs, which may provide a unique window into epigenetic control of blood pressure. Comparative genetic studies need to take advantage of the strong evolutionary conservation of DNA methylation and histone folding in species such as rats, mice, rhesus monkeys and humans[53]. Epigenetic marks that are not shared among humans and animal models could point to biological pathways and molecular mechanisms that may be highly relevant to human hypertension. Finally, advantage should be taken of the rich resources of inbred rodent models of hypertension and well-characterized consomic, congenic and recombinant inbred strains in which many allelic variants have been captured. Together these integrated studies are essential to establish basic principles of epigenetic mechanisms in health and disease as well as to meaningfully translate epigenetic research into clinical practice.
2. ***What are the relative contributions of epigenetic, genetic and environmental factors to the development of hypertension and its comorbidities?*** Assessing the relative contribution of genetic, epigenetic and environmental factors to hypertension is urgently needed. Studying large families in which hypertension segregates in members exposed to similar environments and diets would be highly informative. For instance, answers could be sought by investigating several large,

genetically and phenotypically characterized human cohorts together with family and twin studies to establish the patterns of covariation among genetic variants, epigenetic factors, and physiological phenotypes. Monozygotic (identical) and dizygotic (fraternal) twin studies allow estimation of the role of heredity on determination of many traits[54]. Perturbations that provoke disease, together with modeling of the molecular and physiological networks and pathways aimed at predicting, identifying and manipulating causality factors, will be key elements in these studies. Such approaches need to distinguish between epigenetic changes that may be simply indicative of disease, e.g., diagnostic markers, versus those playing a causal role in the development and maintenance of hypertension in response to specific environmental challenges. Parallel studies in several different environments with various perturbations will be needed in both animal models and humans to establish general versus context-dependent relationships. All these provide good opportunities to quantify the relative contributions of genetic variants and epigenetic factors to various forms of essential hypertension that can be addressed under defined environmental conditions.

3. ***Are epigenetic changes related to hypertension heritable, do they accumulate across generations, and can they be reversed?*** Recent evidence shows transgenerational inheritance of environmental and genetic influences on diverse phenotypes and disease risks. Considerable epidemiological and experimental evidence in model organisms and to a lesser extent in humans show that the consequences of environmental exposures and genetic variants can be transmitted for at least several generations after exposure. Under these conditions establishing the origins of disease resulting from the action of genetic variants in ancestral generations would be difficult to detect among affected individuals in a traditional GWAS. In addition to contributing to hypertension risk, heritable epigenetic changes may accumulate across generations and could account for the dramatic increase in hypertension, obesity and related metabolic conditions. Animal models are especially important to establish principles of study design, candidate molecular features, and relevant physiological functions to validate in humans. Genotype-phenotype associations could also be tested across generations in selected human populations.

The WG recognizes that these proposals raise considerable challenges. Epigenetic studies, especially those that involve transgenerational effects, will be complicated in humans because of issues related to study design, statistical power, environmental and genetic heterogeneity among families and populations, and the dynamic nature of epigenetic changes compared to the stability of DNA sequences. Studies with animal models face similar challenges. In addition, physiological and pharmacological research has made important contributions to treatment, and studies of both monogenic and multigenic variation have provided important insights about molecular functions and pathogenic mechanisms. But substantial problems remain for BP management. Integrating epigenetic studies with ongoing studies may lead to breakthroughs in our understanding of BP control.

Current needs, resources, and future directions of research

The NHLBI Working Group identified a remarkable number of currently existing molecular, genomic, physiological and computational tools and approaches that could meaningfully move this field forward. The WG also identified several important technology needs.

Over the past decade many genomic and proteomic databases and technologies have been developed. These databases enable systematic collection, storage, and distribution for research of tissues and cells. Appropriate databases of patient information, including their

genetics, lifestyle, clinical history, and other relevant information, have also emerged. Similar databases are related to studies of model organisms so that efficient comparative analyses are increasingly feasible. Numerous experimental models are already available and continue to be developed as information resources for many aspects of mouse genetics and biology, including the NIH-funded initiative the "Knockout Mouse Project" (KOMP) http://www.nih.gov/science/models/mouse/knockout), the Mouse Genome Database (http://www.informatics.jax.org), and the Mouse Phenome Database (www.phenome.jax.org). The Rat Genome Database (http://rgd.mcw.edu) contains all of the genomic rat model systems including inbred, consomic and knockout strains. Other resources help researchers identify appropriate model organisms, e.g. "Link Animal Models to Human Disease" (LAMHDI) (http://www.lamhdi.org), existing clinical cohorts (e.g., http://web.chargeconsortium.com) or access other information relevant for the relation between genotype and phenotype, e.g., Genotypes and Phenotypes (dbGaP) database (http://www.ncbi.nlm.nih.gov/gap). A specific catalogue enabling inquiries on the parent-of-origin effects and imprinting in mice can be found at http://igc.otago.ac.nz/home.html. Databases as well as analytical and graphical tools that specifically enable investigation of new levels of regulation and complexity associated with epigenetic studies will need continuous development and wide availability to facilitate data-mining. Computational methods to manage large genomic data sets are becoming increasingly sophisticated. Such tools can integrate information from various levels of functionality that include DNA sequence, RNA expression, protein isoforms and their post-translational modifications cell, tissue, organ and organismal phenotypes, as well as lifestyle, environmental, dietary and microbial information.

Particularly urgent research needs include development of new technologies to assess epigenetic features in single cells *in vitro* and in specific cell types *in vivo*. Surrogate markers in blood cells must also be identified as a way to interrogate cell populations that are generally inaccessible for direct analysis in humans. Finally, technologies are needed to modulate epigenetic changes with greater specificity than genome-wide targeting.

Summary

The working group concluded that epigenetics research should incorporate multispecies comparisons to benefit from evolutionary insights and perspectives. Studies will require coordination of multidisciplinary teams combining expertise in clinical and basic research, as well as in computational and modeling methods. New insights and hypotheses will be generated through genomic and epidemiological surveys, including leveraging existing clinical and epidemiological cohorts, experimental animal models and biological materials to test in new experimental and clinical studies. Study designs will need to be based on sufficient statistical power to handle the likely complexity associated with the heterogeneous causes and consequences of epigenetic changes. Phenotyping at a comparable level of rigor, accuracy, and detail as surveys of epigenetic features will be required. Multiple levels of functionality, from cells to the intact organism, should be studied, and the use of several modalities for inducing experimental hypertension in various model systems would help establish general versus context-specific principles. Finally, such endeavors will require the use and continued development of technologies that enable rigorous and quantitative measures of epigenetic and physiological changes.

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