

“Recurrent debates on the causal role of genes”–

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Abstracts

Garland E. Allen, Washington University, St. Louis: "Mechanistic Materialism and the Classical Gene: Scientific and Social Consequences"

ABSTRACT: Much has been written in the past twenty years about the evolving use of and meaning attached to the term "gene". During the first half of the twentieth century the "classical gene" came to dominate our understanding and conceptualization of the very process of heredity itself. Genes were portrayed as atomistic units, even when interacting in epistatic relationships, and more frequently the phrase "the gene for . . ." appeared when describing the inheritance of a given phenotypic trait. The fertilized egg was a mosaic of genes and the adult organism a mosaic of traits. While most practicing geneticists knew the picture was more complex, the representation of genes as independent units persisted partly because it fit so well the reigning philosophy of mechanistic materialism in the sciences in general and biology in particular in the first half of the twentieth century. It provided a highly quantitative way to understand hereditary transmission between generations and evolution in populations, even as it excluded embryonic development from its concerns. It also fit well with a variety of social and political trends such as the professionalization of biology (which through genetics could be fashioned in the mould of physics and chemistry), the industrialization of agriculture (where genetic strains could be modified), and with eugenics (where undesirable traits could be eliminated from the population by controlled breeding). This talk will discuss the nature of mechanistic materialism and trace through its effects of the conceptualization of the gene that in many quarters persisted well into the end of the twentieth century.

Rivka Carmi, Ben-Gurion University of the Negev: “Lessons on Genes (and Genies) Learned from the Negev Bedouins”

ABSTRACT: The Negev Bedouin community is a tribal, traditional society in transition from a semi nomadic life style to a sedentary, urban one for the past 4 decades. Consanguinity is deeply rooted in the Bedouin culture and consequently rare recessive diseases are highly prevalent. For almost 3 decades I studied genetic disorders in the Bedouin community. Before the Human Genome Project era, those studies involved mainly observations and clinical delineation of known and unknown syndromes. After HUGO the research was set at a systemic identification of recessive new genes/mutations in known genes for various genetic diseases in that community, first by linkage analysis and later by applying new genomic technologies to identify gene mutations. This research has resulted in the findings of numerous new genes and mutations in known genes and also, new insights and hypothesis related to genes functions and roles in bringing about certain phenotypes.

In parallel to bench work, we were involved in challenging community based projects to promote accessibility to genetic testing, both prenatal and carrier detection, in a highly traditional society. Those programs were aimed at various audiences within the community, using different methodologies dependent on the specific target population.

Those projects were followed by a socio-anthropological research that provided deep insights into approaches and attitudes towards genetic knowledge and usage of genetic diagnosis among community members, based on cultural believes and perceptions.

This talk will discuss insights gained on both the biological and the sociological aspects of the genetic research in the Negev Bedouin community.

Eric Davidson, California Institute of Technology: “Causality of Gene Regulation in Animal Biology”

In terms of process and mechanism there are three great conceptual domains within which the biology of any given animal can be understood: where the animal and its functional capabilities came from, in terms of development during its life cycle; where the animal came from in terms of its evolutionary antecedents; and how the animal works during its post- developmental life, that is, how it executes its reversible physiological responses to the environment it lives in, aside from the innumerable organ specific functions with which it was endowed in the later stages of its development. All three, development, evolution, and physiological response are causally all the output of genomic sequence. All three depend directly on regulatory deployment of continuous gene expression, and underlying all three classes of process are genomically encoded networks of regulatory gene interactions.

I shall discuss mainly development and evolution here, but begin with two examples of gene regulatory networks (GRNs) that control reversible physiological processes. One of these controls responses of certain innate immune cells to pathological challenge; the other healing of integumentary wounds.

Development is directly a process in which spatial regulatory states are formulated which determine gene expression at every time and at every place in the organism. This fundamental function is organized by species specific, genomically encoded GRNs, which consist of regulatory genes that make the spatial regulatory states, and their interactions. As I shall show by example, we now can prove that, if complete, GRNs per se can suffice to explain the developmental process of embryogenesis, both directly and indirectly.

Evolution of the animal body plan means evolution of the GRNs controlling animal development, since change in developmental GRNs is what causes change in the body plan. Thus evolution can be regarded as the deep time derivative of encoded GRN structure. Since the dawn of the Cambrian, animal lineages have

undergone large evolutionary changes and we can now begin to understand how this happened by considering the process through the lens of GRN structure.

It is necessary to think carefully to distinguish what is directly controlled by the regulatory genome from what is downstream apparatus or is not genetically specified. We must carefully note what is biochemical machinery deployed in response to genomic regulatory events; recognize those typically late developmental events which are left to stochastic processes; and be aware of those features of the organism in which the hardwired template with which it is developmentally endowed is modified for a given organism by the events of its life. From the point of view of the basic processes of animal biology, however, the essential control functions are genomically encoded; these are the functions which determine which way the process will go, and qualitatively how it will come out.

Ute Deichmann, Ben-Gurion University of the Negev: “The Concept of the Causal Role of Chromosomes and Genes in Heredity and Development and its Opponents from Darwin to Lysenko”

ABSTRACT: In 1865 Mendel laid down the basis of modern genetics by empirically relating discrete and blending phenomena of heredity to the combination of elements in the cell in a statistically predictable way. Three years later, 1868, Darwin proposed his speculative theory of Pangenesis, a comprehensive theory of heredity and development. Pangenesis, by attributing a causal role for heredity and development to the environment, was a materialistic theory for so-called Lamarckian inheritance.

Despite its fruitfulness for future genetic research, the notions of independent genes and randomness appeared unappealing and insufficient to many for explaining complex biological phenomena, such as development. I show that philosophical outlooks played a significant role in scientists’ rejection of genes as causal factors. Among them were widespread "Lamarckian" and holistic predilections as well as vitalistic assumptions of the existence of a pre-established

design and non-material guiding principle. Apart from very few scientists, prominent among them Boveri and Wilson, mechanistic biologists, too, refrained from dealing with the role of genes in development or relativized it. A long conceptual gap between genetics and developmental biology ensued.

The strongest attack on the causal role of genes was launched by agronomist and politician Lysenko in Stalinist Russia. Brushing aside "Mendelist-Morganist" methods and the notion of randomness therein, he put forward a holistic concept of heredity, which incorporated development and heritable responses to environmental conditions, in fact, not altogether dissimilar to Darwin's Pangenesis, though of course some sixty years later. As is well known, Lysenko's pre- and antiscientific views became the official genetic doctrine in the Soviet Union for decades.

This paper will review the fertility of approaches based on the causal role of genes, and competing approaches, in early research on heredity and development and analyze the motivations behind them. I argue that the recognition of genetic causality was a prerequisite for fruitful experimental research related to heredity and development. Significantly, this role was not called into question by the recent systems approaches based on embryological gene regulatory networks founded by Davidson in the late 20th century. "Epigenetic" changes, too, were recently shown to be dependent on the genomic sequence, i.e. they are controlled by sequence specific DNA recognition events and transcriptional networks.

Raphael Falk, The Hebrew University of Jerusalem: *"The Rise and Fall of the Gene"*

Gary Felsenfeld, National Institute of Health, Maryland : *"The Evolution of Epigenetics"*

ABSTRACT: The term 'epigenetics' was first used to denote the series of events that govern the transformation of the fertilized egg into the adult organism. It was

clear that during development individual tissues and cells acquired distinct phenotypes, but it was a mystery as to how the initial genetic information contained in a single cell could be used to determine the architecture of a complex organism. Studies in *Drosophila* in the 1930s by H. J. Muller showed that rearrangements that moved a chromosomal segment to a different position could result in changed phenotypes. But perhaps most important was the demonstration in 1970 by Gurdon that the DNA in somatic cell nuclei could be used to reprogram an enucleated oocyte and lead to development of a complete organism. Since differentiation did not involve loss of DNA sequences, it must reflect targeted activation and repression of cell type specific genes. The term epigenetics thus began to refer to these mechanisms, and particularly to the ways in which modifications of DNA such as methylation, or interactions of DNA with protein complexes, could create an 'inheritable' state that could survive cell division. This change in point of view has resulted in considerable confusion and disagreement about what definition of epigenetics would be most useful. It has also tended to obscure the chain of events that initiates gene activation or repression. However recent results from Yamanaka and others have provided detailed information about the mechanisms that govern the transformation from a single pluripotent stem cell to a complete organism, perhaps returning us to the original definition, but this time with a detailed understanding of the associated biochemical events.

While reviewing this history, I will discuss various regulatory mechanisms that can contribute to maintaining cell type specific gene expression once it is established, particularly histone modifications, DNA methylation and their effects on chromatin structure. It is now becoming clear that large scale architecture within the nucleus may also be important in transmitting epigenetic information. The more we know about how things work, the less important a definition becomes.

Snait Gissis, Cohn Institute, Tel Aviv University: "Biological Conceptualization of 'Jewish Difference' - 1945-2012. The work of Israeli population-geneticists"

ABSTRACT: The ways boundaries are delineated to create and maintain dichotomous individual and collective identities apart, such as ‘Jew’ and ‘non Jew’, are intertwined with the work of culture and its practices, and, since the establishment of the state of Israel, of state policies and practices. To understand the endeavor of the three generations of Israeli population geneticists, who have worked on the genetics of Jews and in order to conceptualize the mutual constituting and entanglement between science, culture and state, I have surveyed and analysed all the relevant genetics papers by Israelis from 1946 until 2012 appearing in major research publications (both in Hebrew and in English, local and international). The scientific work has been deeply affected by the changing tools and technologies during the period, and in particular, by the advances in *genomics*. I have come to see the investigations by these population geneticists, and their transformations while maintaining biological boundaries, as part of the work of culture and state.

Myles Jackson, New York University, New York City: “The CCR5-Delta32 Allele: Reintroducing Race at the Level of DNA”

ABSTRACT: The *CCR5* gene has been used to reintroduce race at the level of the DNA. Interestingly, the U.S. federal government has paved the way for the gene to enter into the treacherous world of race and ethnicity. The gene and its various alleles have become the center of a heated debate about whether or not one can speak of race at the molecular level. How do biomedical researchers and geneticists deal with human diversity and the corresponding politics thereof? Such genetic diversity and how it was defined and characterized are precisely what fuels pharmacogenomics, as scientists claim that single nucleotide polymorphisms (SNPs) found throughout the genome may explain our specific responses to medications. Billions of dollars are in play: we truly are in the age of biocapitalism

Bertrand Jordan, CoReBio PACA, Marseille: *“Genes and Non-Mendelian Diseases: Dealing with Complexity”*

ABSTRACT: The first two decades of the new medical genetics (post-recombinant DNA) were marked by resounding successes, such as the isolation of the genes responsible (when defective) for muscular dystrophy, cystic fibrosis, Huntington’s chorea, to name just a few of the more than 1,000 Mendelian genetic conditions whose cause is now known - even though therapy has not progressed very significantly. In contrast, the search for genes involved in common diseases such as diabetes, hypertension, schizophrenia or autism failed miserably in the 1990s, with inconsistent and conflicting results – nevertheless the strong genetic component of these disorders (that also involve environmental factors) has been proved beyond doubt.

In the last 5 or 6 years, thanks to huge progress in technology and analytical methods, it has become possible to identify genes influencing the risk of complex diseases reliably, using the so-called GWAS (Genome-Wide Association Study) approach. The recent development of new generation sequencing promises to accelerate this progress. Yet many problems remain, such as the vexing question of the “missing heritability”, or the difficulty of translating these (now reliable) scientific results into genetic tests with real clinical validity and utility.

I will present these issues using the case of autism (1), one of the disorders for which a strong genetic component has been demonstrated but where the search for causative genes remains difficult and where attempts at developing valid genetic tests have largely failed.

1 Bertrand Jordan. «Autisme, le gène introuvable» (Autism, the elusive gene), Ed du Seuil, Paris 2012.

Sophie Kohler, Ben-Gurion University of the Negev: *“Genes as an Historical Archive”*

ABSTRACT: Over the last years several population geneticists have made Jewish tradition and history an object of research. They have, for example, tried to shed light on the degree of the relatedness of Jewish communities to each other and to other population groups. I would like to discuss from the point of view of an historian of Jewish history whether their findings contribute to our understanding of Jewish history and if so, in how far. I would also like to point out the limitations of genetics as a tool for historians.

Michel Morange, École Normale Supérieure, Paris: “Genome as a Multi-Purpose Structure”

ABSTRACT: After the genetic code had been deciphered, it was widely accepted among molecular biologists that the genome was an internal image – blueprint – of the organism, faithfully transmitted through descent and permitting the reconstruction of organisms at each generation. Nucleic acids were the bearers of information, whereas proteins were in charge of cellular functions.

Already in the 1960s some observations opposed this vision, and the clear-cut separation between information and function. Ribosomal and transfer RNAs had functions essential in protein synthesis, and regulatory sequences in the genome stood at an intermediate position between information and function. The major regulatory role of micro RNAs, the complexity of the regulatory sequences demonstrated by the ENCODE (Encyclopedia of DNA Elements) post-genomic programme, and the importance of epigenetic modifications have more recently contributed to erase the distinction between information and function, the genome and the other components of the cells.

One way to reconcile these recent observations with the obvious importance of genes demonstrated in other communications is to consider that the genome plays different roles that have been progressively associated with it in the early steps of life. To encode the structure of proteins, to regulate the expression of genes by the action of transcription factors or by chromatin modification, and to control the

level and translatability of RNAs through the action of micro RNAs are different functional roles that have been gathered on the same material structure, the genome, through a historical process that remains totally unknown. To consider the genome as an ensemble of progressively associated and interlinked functional DNA elements explains why answering the question «What is a gene?» remains so difficult.

Nils Roll-Hansen, University of Oslo: “Whatever Happened to Wilhelm Johannsen’s Genotype?”

ABSTRACT: Apparently there is a revolution going on in fundamental theories of biology. New concepts and ideas are radically changing our understanding of heredity and development, of the evolution of species and the development of the individual, the relationship between phylogeny and ontogeny - as they used to be called. The gene is dissolving into the biochemical machinery of the cell, and the genotype is being displaced by the genome. Is the biological discipline of genetics simply collapsing into biochemistry?

In this situation it may be helpful to have a look at the origins of genetics about a century ago. Developments in cytology, plant and animal breeding and evolutionary studies during the final decades of the 19th century had prepared the ground for this new fundamental subdiscipline of biology. It was appropriately born in the year 1900 with the so-called rediscovery of Mendel’s laws, and baptised as “genetics” a few years later by William Bateson. By 1915 T.H. Morgan and his collaborators had published a paradigm for the new discipline, *The Mechanism of Mendelian heredity*. The intervening period saw intense discussion to clarify the theoretical basis.

The ability to clearly distinguish hereditary from non-hereditary variations - theoretically as well as experimentally - was essential to the new discipline. The terms “genotype” and “phenotype” were introduced in 1909 by the Danish plant physiologist Wilhelm Johannsen, and his bean selection experiment (first

published in 1903) became a classic demonstration of genotype stability and how to distinguish genotype from phenotype. Johannsen also coined the term “gene” for the hereditary factors that had been demonstrated so impressively by Mendelian hybridization experiments.

Johannsen, however, was deeply critical of the version of the chromosome theory that continued to dominate genetic thinking - the popular as well as the scientific - through the 20th century. According to Johannsen the fundamental biological entity was the genotype, not the gene. He insisted on a holistic interpretation of the genotype, characterized his own view as “physiological” in contrast to the widespread “morphological” view of heredity, and drew historical lines back to Antiquity. Aristotle represented the physiological view and Hippocrates the morphological. According to Johannsen the segregating genes were only identifiable as changing elements of a genotype that reacted as a whole to impulses from the environment. The “most comprehensive and most decisive part of the genotype does not seem to be able to segregate into units,” he explained. Johannsen saw Weismann as his arch-opponent, but he found similar tendencies, e.g., in de Vries and Bateson. They were not able to quite let go of the idea that phenotypic characters are transmitted from one generation to the next. A spirited explanation and defence of his genotype as fundamentally different from any morphological interpretation is found in Johannsen’s brief 1923 paper, “Some remarks about units in heredity” (*Hereditas* 4: 133-141). Here he also admitted that even he had struggled to grasp a clear concept of genotype: “... originally I was somewhat possessed with the antiquated morphological spirit in GALTON’S, WEISMANN’S and MENDEL’S viewpoints.”

At a time when the genotype is being identified with DNA structures and the gene is dissolving, it may be useful to take a closer look at the ideas and arguments of the individual scientist who introduced the genotype- phenotype distinction. For instance, one might ask: Is there not a logically troublesome consequence of current descriptions of genotype and phenotype in biochemical terms? The

genotype appears to be simply a part of the phenotype. The phenotype has swallowed the genotype. Is one result that the difference between heritable and non-heritable variations - which is essential to our understanding of the evolution of species - is slipping?

Ellen Rothenberg, California Institute of Technology: “Remembrance of Things Past, and Constructive Forgetting: Transcription Factor-Directed Remodeling of Epigenetic Marks in Development”

ABSTRACT: In any given cell type of a complex organism, a sequence-specific transcription factor may not have equal access to all its potential binding sites across the genome. As a result, the same transcription factor can be used to help control the expression of different target genes in one cell type as it does in another. A number of mechanisms contribute to the selective access to some sites as opposed to others in a given cell type. One mechanism is the effect of local modifications to chromatin structure or DNA methylation which impede transcription factor binding, modifications which by default may be passed along through cell division. These “epigenetic mechanisms” have become popular to consider as if they represented a source of information for development and physiology separate from the information in the genome itself. However, this is a mistaken view, based on “snapshot” assessments of cells which do not take into account their histories of development and prior transcription factor activity. In fact, longitudinal tracking of epigenetic marks and transcription factor binding through a major developmental transition such as T-lymphocyte lineage commitment shows that epigenetic marks are emplaced and removed at specific sites across the genome as a result of dynamic changes in transcription factor expression and binding. Silencing marks do not mandate permanent silence and are not the mechanism through which active genes are turned off. Instead, they are emplaced during development to create a steep, nonlinear dependence of future target gene activation rates on transcription factor levels in the cell’s descendants.

Stage-to-stage tracking of RNA expression vs. epigenetic marking across the genome clearly reveals the magnitude and ordering of these effects. Crucial to an understanding of what is happening is the fact that most transcriptional regulation in complex organisms depends on concurrent binding of several, different transcription factors within close proximity. Not all transcription factors are equally blocked by “silencing” marks, and those that disregard silencing marks can act as pioneers for recruitment of others. Gene loci then become activated as combinatorial action of transcription factors recruit enzymes that remove repressive marks, and the default propagation of these marks sets a new “normal” state of access for the future. Thus, epigenetic marks reflect the regulatory state history of the ancestors of a given cell, and like human history, they can cast a shadow but also be rewritten in the future.

Stephen Small, New York University, New York City: *"How Gene Regulation Mechanisms Establish Body Plans in Developing Embryos"*

ABSTRACT: Temporal and spatial patterns of gene expression foreshadow the formation and positioning of specific structures along the major body axes of developing embryos. We study the network of genetic interactions that controls body plan formation, using the fruit fly as a model system. These studies have led to the discovery of gene regulatory processes that seem to function throughout the animal kingdom.

Diethard Tautz, Max Planck Institute for Evolutionary Biology, Plön: *"De novo Evolution of Genes"*

ABSTRACT: Discussions about the evolution of new genes started soon after the first (protein) sequences of genes became available. Already in 1970 Ohno developed major ideas on gene duplication models in a ground-breaking monograph. This was followed in 1977 by Francois Jacob's famous paper on "tinkering" where he considered specifically the question of whether new genes

could emerge *de novo* out of non-coding DNA. He concluded with the often cited statement: "... creation of entirely new nucleotide sequences could not be of any importance in the production of new information." This has influenced the research agenda for a long time, and it turned in fact out to be very fruitful and to deliver abundant evidence for the model of gene emergence through duplication. On the other hand, this early conceptualization has also limited the experimental breadth and thinking towards focusing attention on conservation, rather than divergence of proteins. In another seminal paper, Cyrus Chothia concluded in 1992 that there might be not more than 1,000 basic folds that make up all known proteins. It was therefore a bit surprising that the very first systematic genome project, the sequencing of the yeast chromosome III in 1996 turned out to harbor a significant set of open reading frames that did not seem to be related to any previously known gene family. These were therefore termed "orphans". However, it was initially thought that this fraction of genes that could not be associated with any other gene would gradually disappear once more and more genomes were sequenced. But this was an expectation that was clearly not fulfilled. Every new genome turned out a similar high fraction of orphan genes, implying that the list of known orphans is currently expanding exponentially, while the list of known protein families comes indeed to saturation. Contrary to Jacob's expectation, it is now becoming clear that genes can indeed frequently arise *de novo* out of the genomic background and thus form new orphan genes. In my talk I will address the history of this conceptual shift, as well as the implications for our understanding of the generation of evolutionary novelties.