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Has Neo-Darwinism failed clinical medicine: Does systems biology have to?

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ABSTRACT

In this essay I argue that Neo-Darwinism ultimately led to an oversimplified genotype equals phenotype view of human disease. This view has been called into question by the unexpected results of the Human Genome Project which has painted a far more complex picture of the genetic features of human disease than was anticipated. Cell centric Systems Biology is now attempting to reconcile this complexity. However, it too is limited because most common chronic diseases have systemic components not predicted by their intracellular responses alone. In this context, congestive heart failure is a classic example of this general problem and I discuss it as a systemic disease vs. one solely related to dysfunctional cardiomyocytes. I close by arguing that a physiological perspective is essential to reconcile reductionism with what is required to understand and treat disease.

1. Introduction

In this essay I want to make some observations about what I see as the application of Neo-Darwinistic evolutionary theory – whether intentional or by intellectual diffusion – to biomedical and clinical problems. The focus will be on the chronic non-communicable diseases common in the developed world and increasingly more common in the developing world as people become more sedentary and have access to "western diets" (Centers for Disease Control and Prevention, 2014; World Health Organization, 2013; Yoon et al., 2014). This is a big topic, but I think I can shed some *intentionally provocative light* on it by briefly examining five major issues.

First, evolutionary theory seeks to provide a biological explanation for the phenotypic variation seen both between species and within a given species. Does a DNA-centric view explain common disease phenotypes?

Second, a DNA-centric version of evolutionary biology has been applied to biomedical thinking and has led to the common-disease common-variant hypothesis. The Human Genome Project (HGP) has tested this hypothesis on a very large scale (Baker, 2010; Collins, 2001; Edwards et al., 2013; Shields, 2011). What are the results of this experiment so far?

Third, in clinical medicine, patients complain of physiological symptoms like shortness of breath, exercise intolerance, fever, and pain. This is consistent with the idea that many chronic diseases are complex (patho)physiological processes. What exactly are the causes, and what are some of the consequences of chronic disease (Black, 2010; Coats, 2001; Joyner, 2011)?

Fourth, effective prevention of, or therapy for, most chronic diseases is frequently at the intersection of physiology and pharmacology. If we know the omic variants, will it matter?

Fifth, will a cell-centric version of systems biology close the gaps left by a DNA-centric view of common diseases?

2. Galton & human variability

Before I examine the five issues outlined above, I want to briefly give you some background on the origins of my perspectives as physiologist-clinician. Francis Galton, a cousin of Darwin, was a Victorian polymath and a pioneer in the field of biometrics. He showed, for example, that the height of children could be predicted with real statistical accuracy based on knowledge of parental height. These observations were made in the 1880s, about 30 years prior to the appearance of the words gene, genotype, and phenotype (Forest, 1974; Galton, 1886). Based on his interest in and knowledge of what his cousin was doing, Galton also sought to develop a biological explanation for this variability.

Galton's work was extended by the statisticians Pearson and Fisher (Forest, 1974; Fisher, 1919). Around the same time, Mendel's

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work on plant breeding was rediscovered, and Johannsen first used the terms genotype, phenotype, and gene in a way that might be generally familiar to us today. The key point is that a gene in the sense used by Johannsen was seen as a de facto biological unit of inheritance that yielded a predictable phenotype (Johannsen, 1911). During that era, Morgan demonstrated that genes are located on chromosomes, and in the early 1940s the physicist Erwin Schrödinger speculated with great insight about what it is in the chromosomes that actually contains and transmits genetic information (Carlson, 2013; Schrödinger, 1948). The next big step was the DNA story culminating with Watson and Crick and, ultimately, the central dogma of molecular biology that posited information transfer from DNA to protein is a read-only biological one-way street (Crick, 1970).

When you take this intellectual history and "shake well," a DNA-based definition of a gene emerges. However the broader unit of inheritance concept of Johannsen has been retained and contributed to an oversimplified set of assumptions about DNA equaling or at least dominating phenotypic variation (Keller, 2014).

3. Does a DNA-centric view of evolution always explain human variation?

Several years ago, there was a high profile paper in *Cell* about the distribution of a variant EDAR gene in Asia (Kamberov et al., 2013). The EDAR370A variant is associated with an increased number eccrine sweat glands in the Han Chinese. The paper argues that this variant might have been selected for because it would enhance sweating, and hence thermoregulation and survival in a warm and humid environment. In a general sense, this sort of variant-to-selection chain of reasoning is common for many gene variants.

What this narrative about sweating and the potential evolutionary significance of the EDAR variant lacks is a basic understanding of the physiology of human thermoregulation. For example, it has been known since at least World War II that humans have an impressive ability to adapt to warm and humid environments, and that this adaptation can occur in a matter of days and includes a doubling of sweat rate (Robinson et al., 1943; Wyndham, 1967). Perhaps a more important point is that in a humid environment much of this extra sweat does not evaporate (Mitchell et al., 1976). Instead, it generates excess fluid loss which could potentially be maladaptive in a warm, humid environment. Consequently, the genotype-to-phenotype-to-selection assumptions in this paper can be challenged at multiple levels. I use this example to show the general need for considering omic data in a physiological context before making a case for evolutionary selection.

4. What has the HGP told us about the common-disease common-variant hypothesis?

One of the Neo-Darwinian drivers of the HGP was the idea that for conditions like diabetes, cardiovascular disease, hypertension, and some cancers, a few common gene variants would differentiate those with or at risk for the disease phenotype from those without it. Since these diseases have high statistical heritability estimates in studies on families, relatives, and populations, it was assumed that gene variant-based explanations for this apparent heritability would be found.

With this knowledge, it was further assumed that it would be possible to screen people and intervene in those deemed at higher risk in a way that would extend risk assessment tools based on family history, vital signs, clinical questions, and blood markers. Parenthetically, why variants promoting such conditions might have been selected for is a complicated issue, but one idea is that periods of scarce food selected for "thrifty genes" that allowed weight gain during times of plenty and aided survival during times of food scarcity. When such a thrifty genotype is exposed to the current low-activity, high-calorie world, these factors coupled with extended longevity make the carriers of such genes at risk for a number of chronic non-communicable diseases (McDermott, 1998). Similarly it has been argued that the salt retention critical in warm environments to maintain body fluid balance leads to hypertension in a salt-rich climate-controlled world (Young, 2007).

To test the common-disease common-variant hypothesis, a large number of genome-wide association studies have attempted to determine if variants in certain genes are more frequent in populations with or without a given disease. In general, the results have been underwhelming, showing many potential variants with small effects. More importantly, for a number of conditions of interest the distribution of risk variants is the same in patient and control groups (Paynter et al., 2010; Talmud et al., 2010). Fig. 1 shows the distribution of gene count scores from 20 differentially weighted variants previously associated with an increased risk type 2 diabetes. The cohort included ~5500 people and the gene count score distribution was similar those who did ($N = 302$) or did not develop Type 2 diabetes over a 10 year period of observation. The regression line in the figure shows the risk of developing type 2 diabetes by gene count score. The key finding is that the distribution of gene count scores was the same in those who were and were not diagnosed with diabetes over the period of the study. Additionally, traditional phenotypic based risk scores were far more predictive than gene count scores. Similar conclusions have recently been reached when more than 60 risk variants have been used in a similar analysis in a different cohort (Vassy et al., 2014).

Along similar lines, incorporating genetic information into traditional risk assessment tools does little to improve their predictive capability, and simple measures of body composition like waist-to-height ratio are likely to be far better and cheaper screening tools than omic based tests (Talmud et al., 2010; Ashwell et al., 2012). So, common diseases that have a highly heritable component based on observational studies are not explained by common gene variants. Why? Two potential answers strike me:

1) The heritability estimates from family studies and populations might be artificially high (Holmes et al., 2011). For example,

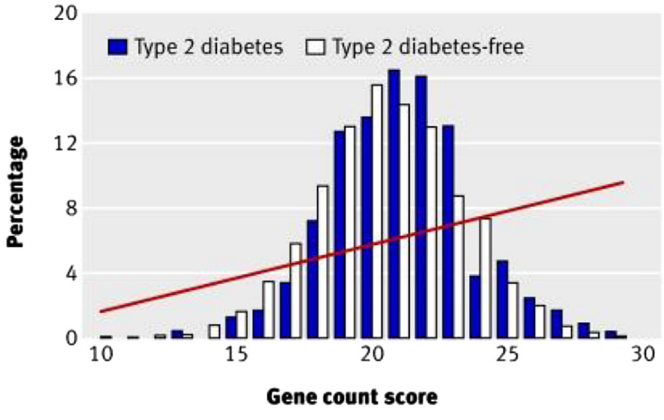

Fig. 1. Distribution of gene count scores for 20 differentially weighted alleles associated with increased risk for Type 2 diabetes in ~5500 people of which 302 developed the disease over 10 years. The distribution of the variants associated with increased risk was similar in those who did and did not develop diabetes. The red line is a regression analysis that shows the risk of developing diabetes vs. gene count score. This figure demonstrates the limited utility of gene scores in risk prediction for Type 2 diabetes and is used as a general example of the limitations of this approach for many common non-communicable diseases.
From Talmud et al. (2010).