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Integrating genomics into evolutionary medicine

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The application of the principles of evolutionary biology into medicine was suggested long ago and is already providing insight into the ultimate causes of disease. However, a full systematic integration of medical genomics and evolutionary medicine is still missing. Here, we briefly review some cases where the combination of the two fields has proven profitable and highlight two of the main issues hindering the development of evolutionary genomic medicine as a mature field, namely the dissociation between fitness and health and the still considerable difficulties in predicting phenotypes from genotypes. We use publicly available data to illustrate both problems and conclude that new approaches are needed for evolutionary genomic medicine to overcome these obstacles.

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Introduction. Two views of medicine

The field of evolutionary medicine, also called Darwinian medicine, was established in the seminal papers by Paul Ewald (1980) [1] and by George C. Williams and Randolph Nesse (1991) [2••], who first advocated the idea that natural selection and, in a wider sense, evolutionary biology, could help understanding the origins and causes of disease in our species. However, the links between evolutionary and medical thought are older than that. For example, evolutionary principles had been unwittingly applied by slave traders, who would lick the skin of African slaves to ascertain their chances of surviving the lengthy and arduous journey to the New World. Individuals tasting less salty were less prone to experience dehydration and thus more likely to survive the trip [3]. In perhaps one of the first uses of evolutionary thought, Muller, in 1948, attempted to explain *why* an ailment existed rather than focusing on *how* it appears and *how* to alleviate it — suggesting that fevers could be an adaptation in response to bacterial toxins. This idea was proven correct almost 40 years later [4,5] and, since then, Darwinian medicine has been providing insight into the evolutionary causes of complex diseases, such as cancer [6] and processes like ageing [7,8••].

In contrast, the field of medical genomics focuses on immediate questions about *how* diseases appear and how they advance within an organism [9,10]. Over the last 50 years, genotype-phenotype studies aimed to identify genetic variants responsible for disease susceptibility and elucidate their molecular mechanisms. As early as the mid-1960s, an HLA haplotype had been associated to Hodgkin's disease [11,12], and by the early 1970s, several other HLA loci were linked to autoimmune conditions, like type 1 diabetes [13]. Thanks to these and other studies, some of the molecular mechanisms behind many diseases were unraveled prior to the genomics era. Two notable cases are the mutations associated with Huntington's disease and cystic fibrosis. The first caused by the expansion of the simple repeat "CAG" in the *HTT* (huntingtin) gene [14] and the second due to the deletion of a phenylalanine in the *CFTR* gene [15]. Progress in this area accelerated once the human genome was completed in 2001 [16], and continues to advance as high-throughput-omics technologies become more accessible [17]. Many of these advances are already resulting in new diagnostic and therapeutic tools that are improving human health world-wide [18].

Unfortunately, these two views of medicine have not yet fully converged. The potential benefits of an evolutionary approach are not widely recognized within medical genomics, and much less within clinical practices. Although many efforts are currently under way to raise awareness about evolutionary thought [19,20], most medical schools still lack an evolutionary biology course [21••]. This state of affairs is somewhat surprising, as a combined formulation of the two views of medicine presented above would result in a much deeper understanding of disease. This combined field could be called *evolutionary genomic medicine* or EGM, even if other names emphasizing the genomic, rather than the medical, aspect have been proposed [22]. EGM studies disease at different levels:

from its ultimate evolutionary origin to its immediate molecular mechanisms. EGM research is gathering momentum and should eventually become a burgeoning area. This type of research has already proved constructive but two main blockers hinder its full-fledged application. We review them below.

Evolutionary genomic medicine: successes thus far and challenges ahead

Examples of case studies for EGM are piling up. Perhaps the better known instances of a successful application of this perspective are the text-book example of sickle-cell anemia [23,24] and the identification of several mutations associated to lactase persistence [25], whose celebrated explanation is the co-evolution of dairy farming cultures and lactose tolerance in adults [26,27]. The consequences of the artificial selection imposed by slave licking have also been understood thanks to EGM. Since genetic variants favoring salt and liquid retention were positively selected before and during the ocean trip, current African Americans have increased odds of developing hypertension [3]. Another example is the impact that the Black Death possibly had on gene frequency variation in Europeans. It has been hypothesized that this epidemic shaped variation at the CCR5 locus that now provides resistance to other infectious diseases, such as AIDS [28].

In spite of these cases illustrating the value of EGM, evolutionary approaches are far from being commonplace. The slow advance of EGM has many causes [21••], but we believe that two of them are particularly challenging since they highlight two glaring gaps in our knowledge: the twin dissociations between health and fitness and between genotypes and phenotypes.

Dissociation between fitness and health

Natural selection favors reproduction over health. So, in taking an evolutionary standpoint it is crucial to enquire about the reproductive consequences of any ''disease'' or ''condition'' since, in the end, what we call a ''disease'' may have no consequences in terms of natural selection or evolution [29]. It has been postulated that certain diseases may be the result of adaptations to ancient environments that would have lost their advantage today [30]. For example, the thrifty genotype hypothesis [31•] follows this line of reasoning by posing that alleles conferring risk for certain ''affluence diseases'', such as type 2 diabetes, are common today because they were advantageous in the past. During situations when food resources were scarce those individuals with a more efficient or *thrifty* metabolism would be more likely to survive and pass on their now disadvantageous alleles [32]. Recently, a consortium of type 2 diabetes provided functional evidence for the idea that the Hispanic Mexican population presents higher frequency for risk alleles of type 2 diabetes as an adaptation to a harsher past environment [33]. Already in his 1962 paper, Neel had foreseen this result ''*[...] diabetes mellitus as an untoward aspect of a thriftiness genotype, which is less of an asset now than in the feast-or-famine of hunting and gathering cultures*'' [31•].

Not all diseases have the same relation to fitness. Rather than past adaptations rendered useless in modern times, some conditions are more likely to represent complex trade-offs arising from adaptive pressures toward different directions. Consider, for instance, elevated testosterone levels. They are known to be beneficial in increasing reproductive success, but it has recently been suggested that they may decrease resistance to infections, since the immune system reallocates to perform further tasks in situations where testosterone and stress hormones are released [34,35].

Given these uncertainties, one of the major challenges of EGM is coming up with an adequate proxy of fitness that adequately reflects the reproductive impact of a disease. The difficulty of this endeavor can be grasped by considering current estimates of the burden of disease in terms of a standardized measure: Disability-Adjusted Life Years, or DALYs [36]. The number of lost DALYs is a unit used by the Institute for Health Metrics and Evaluation [37], to measure how many life years are lost due to sickness, living with a disability or premature death. Some conditions score very low in the DALY scale. For instance, no deaths and nearly no DALYs are lost due to psoriasis, an autoimmune disease with around 2–3% prevalence in populations of European ancestry. Interestingly, the prevalence of psoriasis in Africans is about half of that proportion [38], which may be suggestive of an adaptation to different out-of-Africa conditions. Other diseases, such as child cancers or prenatal disorders, are far more burdensome.

DALYs lost due to six conditions in five world superregions are presented in Figure 1. There are remarkable differences in lost DALYs even between bordering regions within the same continent, such as between Western & Central Europe in DALYs lost to coronary artery disease or between Western & Eastern Africa in DALYs lost to rheumatoid arthritis. These striking variations in the present impact of disease are good indicators of the difficulties of inferring the past fitness impact of disease. Consider, for example, the late Pleistocene, when living circumstances were radically different from now. Even if we can be sure that infection was a basic component of health in these times [39], the field still needs much effort on quantifying the prevalence of many other conditions, including fatal diseases such as childhood cancers.

Difficulties are increased in the likely scenario that most genetic variants causing complex disease are shared across human populations [40], and that, therefore, most of the differences in DALYs are due to environmental and lifestyle causes. In short; disease must be sought in