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NATURE VERSUS NURTURE: DEATH OF A DOGMA, AND THE ROAD AHEAD

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Abstract

Interaction between the genome and the environment has been widely discussed in the literature, but has the importance ascribed to understanding these interactions been overstated? In this opinion piece, we critically discuss gene-environment interactions and attempt to answer three key questions: First, is it likely that gene-environment interactions actually exist? Second, what is the realistic value of trying to unravel these interactions, both in terms of understanding disease pathogenesis and as a means of ameliorating disease? Finally, and most importantly, do the technologies and methodologies exist to facilitate an unbiased search for gene-environment interactions? Addressing these questions highlights key areas of feasibility that must be considered in this area of research.

Introduction

Gene–environment interaction is a broad term encompassing the synergistic effect of genes and the environment on a disease or trait. In this instance, the term environment can be broadly interpreted to include lifestyle factors in addition to the more traditional physical, chemical and biological exposures that individuals are subjected to in their occupational and domestic surroundings. In many ways, the term gene-environment interaction represents a new dimension of the long-standing *nature versus nurture* debate. In part this reflects a growing realization that the notion of nature or nurture is a false dichotomy and that understanding how these two powerful forces interact is key to unraveling disease pathogenesis (Levin, 2009; Rutter, 2002; Wermter et al., 2010). In our opinion, a complete understanding of the role of environment in disease cannot be achieved in isolation, but rather must be viewed in the context of the genome and its variety.

Finding reliable environmental modifiers and risk factors for disease has long been a goal of the research community and more recently this aim has morphed to include understanding how the environment and the genome interact. This latter aim of understanding —GxE has received much lip service and funding dollars over the last decade. In this opinion piece we pose and attempt to address several critical questions around this topic. First, we ask, are such gene environment interactions likely to exist? Second, we ask is there a pressing need to search for gene environment interactions? Third, and last, we question whether such a search is feasible and if so, how it could be done and what it is likely and unlikely to yield?

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Question 1: are gene-environment interactions likely to exist?

Environmental influence in disease: guilt by plausibility

In the first section of this opinion piece we aim to address the question of whether gene-environment interactions are likely to exist. The title of this section is not meant to minimize the importance of the role environment plays in disease. Rather it is intended to highlight a problem we face in considering and discussing environment and disease, namely that there appears to be a general willingness to embrace environment factors as a cause of disease because they are attractive and easy to understand. Thus, particularly in the lay press, environmental links to disease are highly publicized and, even when only based on preliminary work with appropriate caveats from authors, reach the status of accepted facts within a short period of time. Numerous examples of this phenomenon exist, including perhaps most famously the notion that MMR vaccination causes autism, an idea based on weak data that was ultimately withdrawn from publication (Lancet, 2010). The point we are making here, is not that the concept of environment as a contributor to disease is wrong merely because it is easy to understand, but rather that because it is so plausible and accessible as a cause, the burden of proof for such factors should be set correspondingly high.

Evidence of genetic and environment influence in human life and disease

With this message of *caveat lector* in mind, it has been quite convincingly argued that nearly all human diseases and physiological traits involve genetic and environmental influences to some extent (Khoury et al., 2005; Willett, 2002). Examples abound: the average height and lifespan of a population grows in concert with a nation's economic prosperity, reflecting improved nutrition and access to healthcare (Cavelaars et al., 2000; Steckel, 2004), but there also exists a high heritability for this trait with several known genetic variants associated with height (Gudbjartsson et al., 2008; Lettre et al., 2008; Visscher et al., 2008; Weedon et al., 2008). Lifestyle choices, such as diet and exercise, influence not only an individual's risk of developing some of the commonest diseases in Western societies, such as diabetes (Williamson et al., 2004), coronary artery disease (Akesson et al., 2007) and cancer (Kolonel et al., 2004), but also modulate the expression of those phenotypes in terms of age at onset and clinical course (Hedback et al., 1993; Psaltopoulou et al., 2010). Even the *sine qua non* of environmentally-based disorders, infectious diseases, are now recognized to be significantly influenced by host-microorganism interactions with the diversity of the immune system being rooted in genetics (Burgner et al., 2006; Murphy, 1993).

Gene-environment interactions are not just relevant to disease susceptibility, but also modify expression of those phenotypes in terms of age of symptom onset and subsequent clinical course. Even in monogenic diseases, such as Huntington's disease, environmental exposures may explain why one mutation carrier develops symptoms several decades before another member of the same family carrying an identical mutation (Wexler et al., 2004). Mutations of the v*alosin-containing protein* (*VCP*) gene are a good example of the extreme clinical variability that can be observed within families. Variants within this gene are associated with an unusual clinical triad of inclusion body myopathy, Paget's disease of the bone and frontotemporal dementia (Watts et al., 2004), but with different members within the same family manifesting isolated weakness due to myopathy, or distinct phenotypes involving bone or the frontal lobes (van der Zee et al., 2009). The biological basis of this clinical heterogeneity is unknown, but environmental factors may be relevant. Thus, our current concept of purely genetic or environmental diseases needs to be rethought in terms of gene-environment interactions (Khoury et al., 2005).

Gene-environment interactions are complicated and bidirectional

Although there are many examples of environmental and genetic factors influencing the same disease or trait, it is much more difficult to describe exactly how these two forces might interact. We should only consider that a true gene-environment interaction is occurring when the two contribute to a trait in a multiplicative, rather than additive manner. This definition in itself may in the strictest sense be quite limiting, as one can certainly imagine a scenario, where particular genetic influences exert no risk (or influence) alone for disease, but rather require an environmental trigger (perhaps coupled with a precise sequential timing) before any increase in disease risk is noted.

While there is merit to the prevailing paradigm of environmental factors causing disease in genetically susceptible individuals, the interplay between genetics and the environment is likely to be multi-faceted and reciprocal. Not only do exposures to environmental agents lead to disease in those who carry specific genetic risk variants, but genetic characteristics may also influence an individual's predilection for certain behaviors that lead to the exposure in the first place. Smoking represents a case in point, where epidemiological studies showing the association between smoking and lung cancer were first published in 1950 (Doll and Hill, 1950). While the fundamental view that the number of cigarettes smoked by an individual directly correlates with their risk of lung cancer is irrefutable, it is increasingly recognized that certain individuals may be predisposed to begin smoking, or to find it particularly difficult to quit smoking (Gerra et al., 2005; Kremer et al., 2005). The neuronal substrate underlying these addiction traits is significantly driven by genetics. Neurological diseases also show evidence of genetic and environmental influences: education level and cognitively intense professions are associated with a delayed onset of Alzheimer's disease (AD) (Meijer et al., 2009; Wilson et al., 2002), and exercise may be associated with a decreased incidence of Parkinson's disease (PD) (Thacker et al., 2008). Both diseases have a substantive, and increasingly recognized, genetic component (Lambert et al., 2009; Seshadri et al., 2010; Simón-Sánchez et al., 2009; Satake et al., 2009; Hamza et al., 2010).

Thus, we come to the expected conclusion: there already exists substantive evidence implicating the environment and genetics in disease, and it is highly probably that many complex interactions exist between these two factors as the underlying causes and modifiers of disease.

Question 2: should we be looking for gene-environment interactions?

Effect of gene-environment data on healthcare

Our second question focuses on whether the research community should be expending significant resources into finding gene-environment interactions. The most obvious answer to this question rests on the value this knowledge would provide in the overall context of human disease. Many of the key advances in medicine over the last century have arisen from a better understanding of gene-environment interactions. Peyton Rous shared the 1966 Nobel Prize in Physiology or Medicine for his discovery of tumor-inducing viruses, and, more recently, Stanley Prusiner received the same prize in 1997 for his discovery of prions as infectious agents, where susceptibility to neurodegeneration after environmental exposure is strongly influenced by *PRNP* genotype (Parchi et al., 1996). Based on this, observers have argued that a better understanding of the interplay between genetics and the environment would have enormous impact on healthcare delivery by shifting emphasis away from treatment of disease towards primary disease prevention (Khoury et al., 2005). More specifically, a detailed knowledge of disease risk factors would allow the identification of susceptible individuals that could then be specifically targeted for interventions. Certainly, the ability to postpone the onset of disease, perhaps indefinitely, through targeted

intervention is particularly appealing in the context of neurological diseases where effective treatments are lacking (Corella and Ordovas, 2005).

Despite these examples, it is not clear whether a detailed knowledge about the interactions between genetics and environmental factors would directly lead to a revolution in healthcare delivery. The key variables to consider are overall cost and effectiveness of population-based disease screening and intervention, and the benefit to society based on the incidence of the disease and associated disability. One notable success in this area has been the dramatic drop in the rate of myocardial infarction over the last decade arising from routine screening for and treatment of high cholesterol levels (Yeh et al., 2010), though it is noteworthy that this improvement occurred independent of more recent advances in genetics of coronary artery disease. In contrast, MRI screening of a population looking for cerebral vascular aneurysms, for example, would not be feasible in terms of cost or scanning resources compared to the potential outcome in terms of cost per quality adjusted life years. However, identification of the genetic defects underlying this condition (Krischek and Inoue, 2006) would allow selection of at risk individuals that could then be targeted for routine screening and intervention. In that instance the cost-benefit ratio shifts in favor of instituting primary prevention strategies, especially as the cost of complete genomic sequencing continues to fall to the point that complete genome sequencing becomes a routine clinical test.

Pharmacogenomics underlying gene-environment interactions

Pharmacogenomics represents a specialized example of gene-environment interaction, especially when one considers that the same liver enzymes that metabolize pharmaceutical agents are also involved in the breakdown and excretion of chemical environmental agents (Corella and Ordovas, 2005). A full discussion of pharmacogenomics is beyond the scope of this article, but it is clear that an enhanced knowledge of the genetic factors within metabolic pathways that influence uptake, transport, binding and clearance of drugs will be directly relevant to understanding an individuals response to environmental toxins. Even in that instance, much remains to be elucidated both in terms of the importance of genetics and environmental factor metabolism before it can be applied to prevent or ameliorate disease.

Thus, in answer to our second question, we do believe there is value to understanding the role of genetics and environment in disease; such an understanding is likely to inform at the basic biological level and ultimately move us closer to etiologic based treatments and preventative therapies. However, care should be taken not to overstate the potential benefits that would be derived from such knowledge.

Question 3: How do we go about finding gene-environment interactions?

Our last question is designed to highlight the methodologies available to us to find gene-environment interactions. This is probably the most difficult question faced by the field at present, as it implies that, even if gene-environment interactions exist and even if improved understanding would have an appreciable effect on healthcare, there would still be little point in trying to unravel these interactions unless there is a reliable, high-throughput method for detecting them in the first place. Implicit in this question is the current dichotomy between our ability to identify and modify genetic and environmental factors. On one hand, it is increasingly straightforward to identify genetic factors underlying disease (Singleton et al., 2010), but these genetic factors are immutable (at least for now). On the other hand, accurate quantification of environmental exposures is laborious, but identified factors are more amenable to modification as a means to prevent or treat disease.

Collecting environmental data is complicated

Unraveling gene-environment interactions is complicated by the difficulty in accurately and rapidly collecting lifetime environmental data. The term *exposome* has been coined to encompass all of the environmental exposures of an individual (Wild, 2005). In our opinion, this term is misleading, as it implies the existence of a technology that reliably quantifies an individual's lifetime exposure. Instead, the vast majority of epidemiological studies use self-reporting questionnaires to collect the necessary environmental information, a process that relies on the patient's memory of the event in question and is subject to the vagrancies of recall bias. A number of issues further impede the accurate collection of historical environmental data. First, the timing of the exposure may be critical to the development of the disease meaning that a causative environmental exposure may have happened decades before symptom onset. For example, fetal alcohol syndrome results only during a narrow window of exposure *in utero*, and obtaining information from parents may be more appropriate in that instance. Distant exposures may also be relevant to neurological diseases: mouse experiments now suggest that head trauma, a known risk factor for later onset of PD and AD, can give rise to persistent (lifetime) changes in gene expression within the brain (Crawford et al., 2007). Second, data collection using questionnaires is resource-intensive both for the study subject and for the researcher, but briefer questionnaires run the risk of overlooking relevant data.

It is unlikely that a technology that accurately and rapidly quantifies an individual's environmental history (i.e. their exposome) will be developed in the foreseeable future. Metabolomics has been proposed as a surrogate for measuring environmental exposures (Corella and Ordovas, 2005; Ilyin et al., 2004), but this overlooks the difficulty in deconvoluting the signal to determine what arises from inherited genetic factors and what is a consequence of external environmental exposures.

Data-release of environmental data might help

One immediate way to partially overcome this bottleneck in collecting environmental data would be to place greater emphasis on making existing population-based environmental datasets standardized and publicly available. While it is correct that the principal investigators of large epidemiological studies should be allowed a period of time to analyze and publish their results, there should be a concerted effort to make environmental data publicly available along side with any corresponding genome-wide data. Such large, well-curated datasets would be invaluable to researchers around the world who wish to test specific gene-environment interaction hypotheses. The cost, resources and time necessary to complete these large-scale epidemiological studies make them essentially impossible to repeat within a reasonable timeframe. Genome-wide and clinical data is already made public in the dbGAP repository, clearly demonstrating that the bioinformatic infrastructure for sharing environmental data exists.

Collecting genomic data is tractable and can help the epidemiologists

In contrast to collecting environmental data, our technological ability to examine the genome is advancing at a phenomenal rate. As the cost of sequencing genomes continues to fall towards the $1,000 price tag (Carr, 2010), it will become feasible to identify all genetic variants and structural abnormalities in large cohorts of patients. Even today, genome-wide association studies have been highly successful in identifying risk factors for common diseases (www.genome.gov/gwastudies). Information on the underlying biology of disease obtained from genomics will play an important role in the design of future analytical epidemiological studies. Rather than pursuing the current strategy of collecting the maximum amount of information per patient, improved knowledge of biological pathways will guide epidemiologists in their selection of which environmental data to collect

(Traynor, 2009). Such targeted study design will decrease costs by decreasing sample size and by shortening completion time. It will also have the advantage of decreasing the statistical penalty accrued from the multiple testing involved in analyzing superfluous variables.

The role of epigenetics in understanding gene-environment interactions

Understanding the biological mechanisms underlying gene-environment interactions is in its infancy. While it seems fairly likely that environmental factors work by altering cellular gene expression, the exact cellular processes by which this occurs are not known. A hypothesis that is gaining ground is that environmental factors achieve their effect by altering the epigenetic profile of the cell (Bjornsson et al., 2004; Corella and Ordovas, 2005). The availability of whole genome array technology that quantifies methylation in a genome-wide manner (as well as next generation sequencing protocols for bisulfate converted DNA) makes it feasible to test this hypothesis. Genetic variation also regulates genome-wide methylation patterns (Gibbs et al., 2010), and thus may explain why certain individuals are more susceptible to certain environmental agents. Tissue to tissue variation in epigenetic patterns, as well as changes occurring as part of development or the aging process, may also be important and may explain why certain agents act in a tissue specific manner. Again, improved understanding of the effect of environmental factors on the epigenetic profile of a tissue will ultimately serve as a guide for epidemiologists in their choice of environmental agents to evaluate in their studies.

Conclusion and future possibilities

In answer to our own questions, we believe that gene-environment interactions are central to human disease, and identification of these interactions holds great promise for the treatment and primary prevention of disease in the future. That being said, our ability to routinely screen for and understand the biology of gene-environment interactions is currently limited by our inability to accurately and reliably quantify an individual's environmental and lifestyle history. For now, technological advances mean that the most logical and parsimonious approach is to concentrate on gathering genomic and epigenomic data about human disease, which may then provide clues as to which type of environmental factors should be measured in epidemiological studies. In the not too distant future, the falling cost of sequencing will make it fiscally reasonable to analyze the genomes of all neonates looking for predisposition to the whole gamut of common human diseases, similar to the current neonatal screening program. Such an endeavor would greatly facilitate our search for gene-environment interactions. Many challenges exist to the identification of gene-environment influences in disease. A primary limitation of such work will be sample size; such interactions require considerable cohorts, for discovery and replication. As a result one might suspect that reliable interactions may only be identified in common diseases, some diseases may simply be too rare to afford robust analyses. Further, we have to believe that there may be both genetic and environmental effects that are simply to small to detect. This being said, making the environmental data from existing cohort studies publicly available, especially those where have genome-wide data is also available for the subjects, will greatly facilitate hypothesis testing for specific gene-environment interactions. True, the old dogma of nature versus nurture is dead, but unfortunately it has been replaced by an even harder to solve puzzle.

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References

Akesson A, Weismayer C, Newby PK, Wolk A. Combined effect of low-risk dietary and lifestyle behaviors in primary prevention of myocardial infarction in women. Arch Intern Med. 2007; 167:2122–2127. [PubMed: 17954808]

Bertram L, Tanzi RE. The genetic epidemiology of neurodegenerative disease. J Clin Invest. 2005; 115:1449–1457. [PubMed: 15931380]

Bjornsson HT, Fallin MD, Feinberg AP. An integrated epigenetic and genetic approach to common human disease. Trends Genet. 2004; 20:350–358. [PubMed: 15262407]

Burgner D, Jamieson SE, Blackwell JM. Genetic susceptibility to infectious diseases: big is beautiful, but will bigger be even better? Lancet Infect Dis. 2006; 6:653–663. [PubMed: 17008174]

Carr, G. The Economist. London: The Economist Group; 2010. Biology 2.0.

Cavelaars AE, Kunst AE, Geurts JJ, Crialesi R, Grotvedt L, Helmert U, Lahelma E, Lundberg O, Mielck A, Rasmussen NK, et al. Persistent variations in average height between countries and between socio-economic groups: an overview of 10 European countries. Ann Hum Biol. 2000; 27:407–421. [PubMed: 10942348]

Collins FS. The case for a US prospective cohort study of genes and environment. Nature. 2004; 429:475–477. [PubMed: 15164074]

Corella D, Ordovas JM. Integration of environment and disease into ‘omics’ analysis. Curr Opin Mol Ther. 2005; 7:569–576. [PubMed: 16370380]

Crawford FC, Wood M, Ferguson S, Mathura VS, Faza B, Wilson S, Fan T, O’Steen B, Ait-Ghezala G, Hayes R, Mullan MJ. Genomic analysis of response to traumatic brain injury in a mouse model of Alzheimer’s disease (APPsw). Brain Res. 2007; 1185:45–58. [PubMed: 17961517]

Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J. 1950; 2:739–748. [PubMed: 14772469]

Gerra G, Garofano L, Zaimovic A, Moi G, Branchi B, Bussandri M, Brambilla F, Donnini C. Association of the serotonin transporter promoter polymorphism with smoking behavior among adolescents. Am J Med Genet B Neuropsychiatr Genet. 2005; 135B:73–78. [PubMed: 15806583]

Gibbs JR, van der Brug MP, Hernandez DG, Traynor BJ, Nalls MA, Lai SL, Arepalli S, Dillman A, Rafferty IP, Troncoso J, et al. Abundant quantitative trait Loci exist for DNA methylation and gene expression in human brain. PLoS Genet. 2010; 6:e1000952. [PubMed: 20485568]

Gudbjartsson DF, Walters GB, Thorleifsson G, Stefansson H, Halldorsson BV, Zusmanovich P, Sulem P, Thorlacius S, Gylfason A, Steinberg S, et al. Many sequence variants affecting diversity of adult human height. Nat Genet. 2008; 40:609–615. [PubMed: 18391951]

Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, Kay DM, Doheny KF, Paschall J, Pugh E, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson’s disease. Nat Genet. 2010; 42:781–785. [PubMed: 20711177]

Hedback B, Perk J, Wodlin P. Long-term reduction of cardiac mortality after myocardial infarction: 10-year results of a comprehensive rehabilitation programme. Eur Heart J. 1993; 14:831–835. [PubMed: 8325313]

Ilyin SE, Belkowski SM, Plata-Salaman CR. Biomarker discovery and validation: technologies and integrative approaches. Trends Biotechnol. 2004; 22:411–416. [PubMed: 15283986]

Khoury MJ, Davis R, Gwinn M, Lindegren ML, Yoon P. Do we need genomic research for the prevention of common diseases with environmental causes? Am J Epidemiol. 2005; 161:799–805. [PubMed: 15840611]

Kolonel LN, Altshuler D, Henderson BE. The multiethnic cohort study: exploring genes, lifestyle and cancer risk. Nat Rev Cancer. 2004; 4:519–527. [PubMed: 15229477]

Kremer I, Bachner-Melman R, Reshef A, Broude L, Nemanov L, Gritsenko I, Heresco-Levy U, Elizur Y, Ebstein RP. Association of the serotonin transporter gene with smoking behavior. Am J Psychiatry. 2005; 162:924–930. [PubMed: 15863794]

Krischek B, Inoue I. The genetics of intracranial aneurysms. J Hum Genet. 2006; 51:587–594. [PubMed: 16736093]

Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet. 2009; 41:1094–1099. [PubMed: 19734903]

Lancet, TEoT. Retraction—Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. The Lancet. 2010; 6736:60175–60174.

Lettre G, Jackson AU, Gieger C, Schumacher FR, Berndt SI, Sanna S, Eyheramendy S, Voight BF, Butler JL, Guiducci C, et al. Identification of ten loci associated with height highlights new biological pathways in human growth. Nat Genet. 2008; 40:584–591. [PubMed: 18391950]

Levin BE. Synergy of nature and nurture in the development of childhood obesity. Int J Obes (Lond). 2009; 33(Suppl 1):S53–56. [PubMed: 19363509]

Lindsay P, Bayley M, McDonald A, Graham ID, Warner G, Phillips S. Toward a more effective approach to stroke: Canadian Best Practice Recommendations for Stroke Care. CMAJ. 2008; 178:1418–1425. [PubMed: 18490636]

Manolio TA, Bailey-Wilson JE, Collins FS. Genes, environment and the value of prospective cohort studies. Nat Rev Genet. 2006; 7:812–820. [PubMed: 16983377]

Meijer WA, van Boxtel MP, Van Gerven PW, van Hooren SA, Jolles J. Interaction effects of education and health status on cognitive change: a 6-year follow-up of the Maastricht Aging Study. Aging Ment Health. 2009; 13:521–529. [PubMed: 19629776]

Murphy PM. Molecular mimicry and the generation of host defense protein diversity. Cell. 1993; 72:823–826. [PubMed: 8458078]

Nicoll JA, Roberts GW, Graham DI. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. Nat Med. 1995; 1:135–137. [PubMed: 7585009]

Parchi P, Castellani R, Capellari S, Ghetti B, Young K, Chen SG, Farlow M, Dickson DW, Sima AA, Trojanowski JQ, et al. Molecular basis of phenotypic variability in sporadic Creutzfeldt-Jakob disease. Ann Neurol. 1996; 39:767–778. [PubMed: 8651649]

Psaltopoulou T, Ilias I, Alevizaki M. The role of diet and lifestyle in primary, secondary, and tertiary diabetes prevention: a review of meta-analyses. Rev Diabet Stud. 2010; 7:26–35. [PubMed: 20703436]

Richardson B. Impact of aging on DNA methylation. Ageing Res Rev. 2003; 2:245–261. [PubMed: 12726774]

Rutter M. The interplay of nature, nurture, and developmental influences: the challenge ahead for mental health. Arch Gen Psychiatry. 2002; 59:996–1000. [PubMed: 12418932]

Santangelo A, Albani S, Beretta M, Cappello A, Mamazza G, Pavano S, Testai M, Tomarchio M, Zuccaro C, Maugeri D. Aging and environmental factors: An estimation of the health state of the elderly population residing in industrialized vs. rural areas. Arch Gerontol Geriatr. 2010 Epub ahead of print.

Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ito C, Kubo M, Kawaguchi T, Tsunoda T, Watanabe M, Takeda A, et al. Genome-wide association study identifies common variants at four loci as genetic risk factors for Parkinson's disease. Nat Genet. 2009; 41:1303–1307. [PubMed: 19915576]

Sebastiani P, Solovieff N, Puca A, Hartley SW, Melista E, Andersen S, Dworkis DA, Wilk JB, Myers RH, Steinberg MH, et al. Genetic Signatures of Exceptional Longevity in Humans. Science. 2010 Epub ahead of print.

Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carassquillo MM, Lambert JC, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. JAMA. 2010; 303:1832–1840. [PubMed: 20460622]

Simón-Sánchez J, Schulte C, Bras JM, Sharma M, Gibbs JR, Berg D, Paisan-Ruiz C, Lichtner P, Scholz SW, Hernandez DG, et al. Genome-wide association study reveals genetic risk underlying Parkinson's disease. Nat Genet. 2009; 41:1308–1312. [PubMed: 19915575]

Singleton AB, Hardy J, Traynor BJ, Houlden H. Towards a complete resolution of the genetic architecture of disease. Trends Genet. 2010 Epub ahead of print.

Steckel, RH. Historical perspective on the standard of living using antropometric data. In: Wolff, EN., editor. What has happened to the quality of life in the advanced industrialized nations?. Northampton, MA: Edward Elgar Publishing; 2004. p. 257-274.

Thacker EL, Chen H, Patel AV, McCullough ML, Calle EE, Thun MJ, Schwarzschild MA, Ascherio A. Recreational physical activity and risk of Parkinson's disease. Mov Disord. 2008; 23:69–74. [PubMed: 17960818]

Traynor BJ. The era of genomic epidemiology. Neuroepidemiology. 2009; 33:276–279. [PubMed: 19696518]

van der Zee J, Pirici D, Van Langenhove T, Engelborghs S, Vandenberghe R, Hoffmann M, Pusswald G, Van den Broeck M, Peeters K, Mattheijssens M, et al. Clinical heterogeneity in 3 unrelated families linked to VCP p. Arg159His Neurology. 2009; 73:626–632.

Visscher PM, Hill WG, Wray NR. Heritability in the genomics era--concepts and misconceptions. Nat Rev Genet. 2008; 9:255–266. [PubMed: 18319743]

Watts GD, Wymer J, Kovach MJ, Mehta SG, Mumm S, Darvish D, Pestronk A, Whyte MP, Kimonis VE. Inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia is caused by mutant valosin-containing protein. Nat Genet. 2004; 36:377–381. [PubMed: 15034582]

Weedon MN, Lango H, Lindgren CM, Wallace C, Evans DM, Mangino M, Freathy RM, Perry JR, Stevens S, Hall AS, et al. Genome-wide association analysis identifies 20 loci that influence adult height. Nat Genet. 2008; 40:575–583. [PubMed: 18391952]

Wermter AK, Laucht M, Schimmelmann BG, Banaschweski T, Sonuga-Barke EJ, Rietschel M, Becker K. From nature versus nurture, via nature and nurture, to gene x environment interaction in mental disorders. Eur Child Adolesc Psychiatry. 2010; 19:199–210. [PubMed: 20024596]

Wexler NS, Lorimer J, Porter J, Gomez F, Moskowitz C, Shackell E, Marder K, Penchaszadeh G, Roberts SA, Gayan J, et al. Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. Proc Natl Acad Sci U S A. 2004; 101:3498–3503. [PubMed: 14993615]

Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005; 14:1847–1850. [PubMed: 16103423]

Wildner M. Gene-environment interaction and human lifespan. Lancet. 2000; 356:2103. [PubMed: 11145526]

Willett WC. Balancing life-style and genomics research for disease prevention. Science. 2002; 296:695–698. [PubMed: 11976443]

Williamson DF, Vinicor F, Bowman BA. Primary prevention of type 2 diabetes mellitus by lifestyle intervention: implications for health policy. Ann Intern Med. 2004; 140:951–957. [PubMed: 15172920]

Wilson RS, Mendes De Leon CF, Barnes LL, Schneider JA, Bienias JL, Evans DA, Bennett DA. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA. 2002; 287:742–748. [PubMed: 11851541]

Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med. 2010; 362:2155–2165. [PubMed: 20558366]