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Review

Genetics of complex diseases: An evolutionary perspective

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ABSTRACT

The advent of the human genome project and the subsequent technological advances in genomic research have provided an unprecedented opportunity, not only to dissect the genetic basis of complex diseases, but has also provided researchers with the means to study the impact of evolution on the genomic architecture of the human genome. In this context, evolution can be defined as a gradual change of genetic information across generations, resulting in an adaptation to the current environmental conditions. From an evolutionary perspective, disease associated mutations should be removed from the population over time. However, recent advances in genomics have shown that various diseases causing mutations have been fixed within the population or are the result of recent adaptations to an ever changing environment. In this review, we provide an overview of the different layers of evolutionary changes affecting the manifestation of disease variants within and between populations. We highlight the impact of evolutionary dynamics as a driving force in the spread of complex diseases and summarize social and cultural effects that may contribute to the different prevalence of common and rare diseases among populations worldwide.

KEYWORDS: complex disease, recent positive selection, adaptation, genomic architecture, epigenetics, evolutionary medicine

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INTRODUCTION - FROM EVOLUTIONARY THEORY TO APPLICATION

Before the invention of antibiotics and improvements in hygiene, infectious diseases were the primary cause of death. Since antibiotics became broadly available in the middle of the 20th century, there has been a shift towards diseases that affect the human population long after the reproductive stage [1, 2, 3]. In contrast to infectious diseases, most complex diseases do not directly affect the fitness of an individual because the onset of the disease is late in life and thus does not directly influence reproductive success. While the evolutionary dynamics of infectious diseases and host parasite interactions have been extensively studied, less is known about the evolution of complex diseases. Both, complex diseases and infectious diseases, are strongly linked to the immune system. On one hand, this may promote chronic inflammation, on the other hand, it provides an effective system to reduce the load of pathogens in the organism. Thus, the evolution of an effective immune response may have led to a higher prevalence of autoimmune diseases and chronic inflammation in the absence of pathogens in a new environment as implied by the hygiene hypothesis [4]. Consequently, in order to understand the evolution of complex diseases, the immune system as well as environmental conditions and changes in lifestyle need to be understood. Figure 1 highlights the different functional layers, which may contribute to the individual disease prevalence as a result of distinct environmental conditions.

Studying the environmental factors that lead to disease progression and onset is a challenging

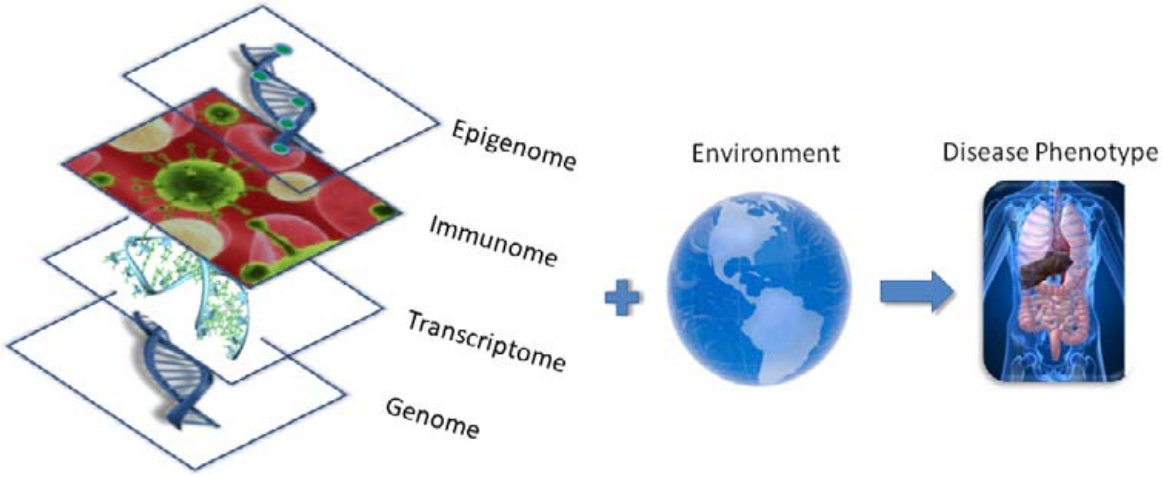

Figure 1. Different layers of functional-environment interactions have an impact on complex disease phenotypes. There are different layers that are associated with functional changes, which can jointly affect the phenotype and in turn the individual prevalence for complex diseases. Changes on the genetic level may lead to a disruption of the transcriptional and translational machinery or to misfolded proteins. Alternative splicing events or RNA editing can disrupt expression levels of disease associated transcripts. On the cellular level, differences in the individual immune response to external stimuli may or may not cause an overreaction of the immune system resulting in chronic inflammation. Finally, epigenetic changes due to lifestyle preferences or developmental constraints can interfere with the expression of genes or silence important transcription factors. However, with natural selection acting directly on the phenotype functional implications can have distinct consequences for the individual disease prevalence.

task, especially in light of an ever changing environment and differences in lifestyle preferences between the western world and developing countries. For this reason, the focus on studying the evolution of complex diseases has been rather on the genotype effect on the phenotype than on environmental factors. However, these genetic studies revealed a number of loci that have been under selection and are associated with complex disease phenotypes, such as Crohn's disease, diabetes or coronary artery disease. Even more interesting is the distribution of genotypes across the world that may or may not have an impact on disease prevalence in the distinct populations.

In this review article we will round up the recent advances on the genomic and non-genomic aspects of common complex disease and the link to evolutionary changes. We will provide insights into how evolutionary studies can reveal important candidate loci for diseases in the human genome and, further, how epigenetic research may contribute to a better understanding of the evolutionary origin of common complex diseases.

Genetic studies

The advent of the genomic era has provided novel insights into the genetic architecture of common complex and infectious diseases. With the widely available sequencing and genotyping technologies, millions of genetic markers across the whole human genome can be tested for an association with a disease phenotype. Since 2006, a growing number of genome wide association studies (GWAS) for common complex diseases has revealed new candidate loci and genomic regions that play an important role in disease progression and are linked to the immune system.

However, the link from disease-associated genetic variation to recent adaptation to an ever changing environment has been difficult to establish. Several statistical methods have been developed, based on haplotype divergences and differences in

allele frequencies across populations, to identify genetic variants that have risen in frequency over time as a direct result of selection pressure. Most of these methods, such as the integrated haplotype score developed by Voight *et al.*, are outlier statistics that aim to find regions across the genome which have most likely been under recent natural selection [5].

This method revealed several new loci that have likely played a role in recent evolutionary change and which are associated with complex disease phenotypes. The most prominent example is located on chromosome 2, where genetic variants in the lactase gene, which plays a role in milk digestion, have been the consequence of change in dietary habits, and resulted in lactose intolerance in different populations. Furthermore, a gene cluster on chromosome 12 exhibiting associations with numerous disease phenotypes has been associated with signs of recent positive selection in the European population [6]. An overview of disease loci that have been both associated with complex disease and recent adaptation for the three HapMap populations (Europeans, Asians and Africans (Yoruba)) is provided in Table 1. Notably, there is a high proportion of disease loci under recent positive selection that have been both associated with chronic inflammation and the regulation of immune function, including Crohn's disease, Type 1 diabetes or Rheumatoid arthritis [7]. This highlights the importance of understanding the link between the evolution of the immune system and the origin of complex disease phenotypes. Deleterious variants within immune genes may have hitchhiked along beneficial variants as a result of selective sweeps. The distribution of deleterious alleles is higher in hitchhiking regions and genetic hitchhiking has had an effect of the distribution of deleterious variants. This implies that beneficial and disease causing variation may be interdependent. There is evidence that this effect has led to a clustering of disease variants in genomic regions harboring multiple immune genes [8, 9].

Epistatic interactions are likely to play an important, but so far, underscored role in complex diseases because they are difficult to assess. Regulatory and coding variants often modify the functional impact of each other. Notably, regulatory variants associated with quantitative traits (eQTLs) showed an enrichment of epistatic effects compared to eQTLs, which have not been associated with common complex diseases. This suggests that some of the associations observed in GWAS might arise from interactions between regulatory and rare coding variants [10].

More importantly, little is known about the standing genetic variation between adjacent populations. The vast majority of GWAS on complex disease phenotypes were so far performed in populations of European ancestry. GWAS on

Table 1. Evidence of selective sweeps and genetic hitchhiking for loci associated with complex diseases.

Chromosome	Genes	Disease Phenotype	Population	Reference
1p32	PCSK9	Cholesterol levels, Coronary heart disease	AFR	Ding and Kullo 2008 [29]
2p13	NAT8	Metabolic Traits	CEU	Nicholson *et al.* 2011 [30]
2q21	LCT	Lactose intolerance	CEU	Nielsen *et al.* 2005 [31]
3p21	GPX1	Crohn's Disease	ASN	Foster *et al.* 2006 [32]
5q31	OCTN1	Crohn's Disease	CEU	Huff *et al.* 2011 [14]
10q24	PYROXD2	Metabolic Traits	CEU	Nicholson *et al.* 2011 [30]
12q24	ATXN2, PTPN11, SH2B3	Blood Parameters, Coronary heart disease, Celiac disease, Type 1 diabetes	CEU	Soranzo *et al.* 2009 [6]
16q21	NOD2	Crohn's Disease	CEU	Nakagome *et al.* 2012 [33]
20q11	GDF5	Height, Osteoarthritis	ASN	Wu *et al.* 2012 [15]
22q13	MYH9	Kidney Disease	AFR	Oleksyk *et al.* 2010 [34]

other, larger and probably more diverse, human populations are trailing behind and just start to appear in the literature. However, very recent insights from whole-genome sequencing approaches in populations in Africa revealed a higher genetic variation between populations than expected, with significant impact on genetic association studies and the effects of rare vs. common variants on common complex diseases.

The role of recent positive selection in complex diseases

Several disease genes have been found to be targeted by recent positive selection as a result of changing environmental conditions and cultural influences. These differences in selection pressures may have led not only to different disease prevalence patterns but also to a divergent haplotype frequency in different populations. Eichler *et al.* for example showed that a haplotype, which is associated with neurological disorders, resents from an ancient haplotype, which is common only in western Africa [11]. These mechanisms contribute to the genomic architecture and to population specific allele frequencies, thus explaining why some populations exhibit a higher disease prevalence than others [12].

A recent study highlighted the importance of variants under positive selection for complex disease phenotypes [13]. Deleterious variants can increase in frequency when a selective sweep runs through the population due to a beneficial effect of an advantageous mutation eliminating haplotype diversity. In an extreme scenario, only one haplotype could be present in a population on which deleterious variants have hitchhiked along the beneficial variants. This effect is called genetic hitchhiking and has played an important role in the fixation of detrimental variants within populations. One example for such a genetic hitchhiking effect can be found on chromosome 5, where the *IBD5* (inflammatory bowel disease 5) locus contains a haplotype of about 250kb, which is associated with an increased risk of Crohn's disease in the European population. Recently, Huff *et al.* showed that the frequency of deleterious variants, forming the IBD5 risk haplotype, increased by hitchhiking due to recent positive selection acting on alleles in linkage disequilibrium [14]. For the Asian population, regulatory variants for the *GDF5* gene that have been associated with height and osteoarthritis on chromosome 20 are also under recent positive selection. Interestingly, there appears to be a link between decreased body size and osteoarthritis in Asians. This link could indicate disease pleiotropy, meaning that the variants under selection are beneficial in one scenario but deleterious in another [15]. This idea is in line with recent findings in African populations, where a locus that confers susceptibility to malaria disease is also associated with decrease in height in pygmies [16, 17].

Altogether, every population has a unique environmental history and encountered different pathogens and diets by undergoing the process of sociocultural selection. All these factors left traces in human genomes and contributed to population-specific haplotypes and allele frequencies. Therefore, some populations are more likely to be susceptible to a disease than others, which is crucial under socioeconomic aspects, particular disease prevention and the development of therapeutic strategies.

Ancient origin of disease genes

As proven by several studies [18, 19], different evolutionary events have driven the formation of genome architecture and led to a clustering of disease genes in the human genome. Figure 2 provides an overview of the different evolutionary dynamics that appear to play an important role in the divergence of disease phenotypes. In general, functionally related genes tend to cluster along the chromosomes and share similar expression patterns. However, little is known regarding the mechanisms affecting gene architecture or the preservation of gene clusters, thus recombination continually breaks down linkage between them. Domazet-Loso & Tautz showed that disease genes are evolutionary conserved and can be traced back to the early emergence of life [18]. The vast majority are yet present in eukaryotic ancestors whereas other genes originated during the early formation of multicellularity. If disease genes are conserved, one might question how these genes with a negative fitness effect are maintained

across lineages within eukaryotic genomes and which evolutionary dynamics put them in place.

Interestingly, regions displaying a high orthologous gene density show an enrichment of deleterious variants associated with common complex diseases. These gene clusters show lineage specific concerted rearrangements over time, which finally led to the preservation of linked gene clusters in mammals. In Figure 3, the relationship between disease associated orthologs in human and mouse are displayed as an example. Furthermore, Makino and McLysaght highlighted that genes with immune related functions and associated with autoimmune disorders also tend to cluster over evolutionary time [19]. Besides genomic rearrangements, gene duplications are a key factor in driving evolutionary innovation and producing new genetic variation across lineages. The question on how duplicated genes are maintained in the genome remains controversial. However, gene duplications produce paralogous genes exhibiting similar biological functions or code for similar proteins and have a striking dosage effect. A couple of them diverge after diverse mutations and acquire new functions or lose functionality and become pseudogenes. Dickerson and Robertson revealed that the majority of disease genes (80%) have been duplicated in their evolutionary history [20]. Specifically, many duplicated and evolutionary old disease genes came to origin with the advent of vertebrate species and are associated with whole-genome duplications. Examples of disease-related dosage effects are manifold and often associated with complex neurological disorders such as Parkinson's disease or Alzheimer's disease [21]. Besides whole genome duplications and the functional divergence of duplicated genes, other factors played an important role in shaping structural genomic diversity as well. Approximately 42% of the human genome originated by retrotransposition events and, therefore, can be one of the driving forces of evolution. However, the influence of jumping genes affecting adaptive evolution is currently under study as well as their impact on disease development.

Hence, deciphering the complex organization of human and mammalian genomes might provide new insights into the dynamics acting on the preservation of beneficial allele combinations during evolution as well as on the development of disease variants. Since then, distinct studies addressed the exertion of selective pressure on gene formation and the link to disease susceptibility [13]. These studies might give novel insights into the evolutionary origin and epidemiology of disease variants as well as in the adaptation of the human immune system. Although the role of recent evolutionary events for complex diseases is partially understood, the question remains which other evolutionary dynamics may have contributed to the emergence of complex diseases.

Impact of epigenetic alterations on disease susceptibility

With the emergence of new technologies enabling the detection of epigenetic marks, current research highlights the interplay between epigenetic modifications, such as DNA-methylation, diverse histone modifications, nucleosome positioning and the posttranscriptional regulation by noncoding RNA (ncRNA, inlcuding miRNA and siRNA among others), and the underlying genetic architecture [22]. Epigenetic mechanisms may contribute another layer of information to the complex genomic architecture of common diseases and may have a stronger influence on disease susceptibility than expected in previous years. Particularly, epigenetic marks play a key role in cell and tissue specific activation or repression of gene transcription and, thus have a major impact on the complex gene regulatory network structure in organisms. For instance, DNA-methylation is involved in a variety of gene regulatory processes, including transcription regulation in embryonic development, genomic imprinting and X-chromosome inactivation [23].

In general, epigenetics can be defined as the stable alteration in gene expression without changes in DNA sequence, however undergoing epigenetic modifications which may directly be affected by environmental exposures, e.g. nutrition, drugs and toxins. Therefore, epigenetic alterations of DNA contribute to the diversity of phenotypes in populations and may explain why some individuals are affected by a disease while others are not. For instance, monozygotic twins share

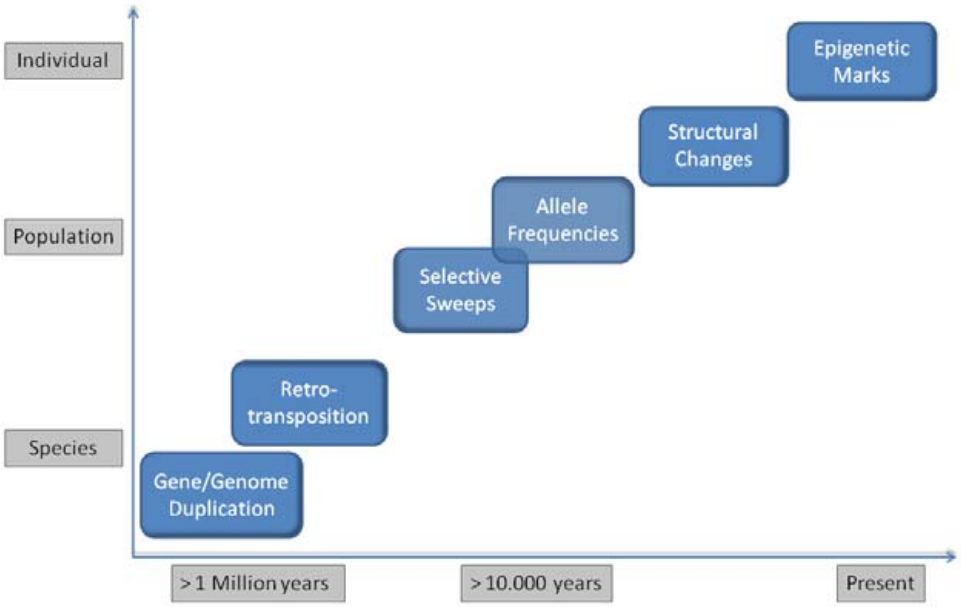

Figure 2

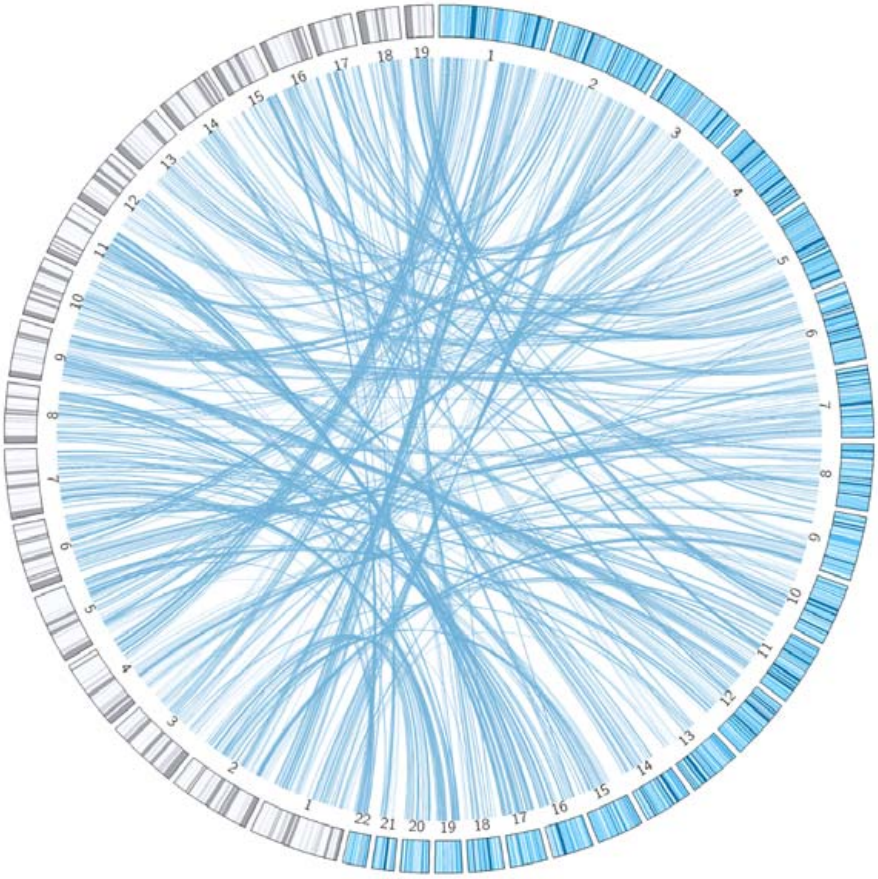

Figure 3

similar DNA sequences but may or may not share distinct disease phenotypes. Thus, epigenetics may potentially contribute to evolutionary biology when taking into account that epigenomic regulation may lead to phenotype plasticity and individual specific variation between and among populations [24]. Due to epigenetic modifications one genotype can result in different phenotypes in response to divergent environmental conditions, which in turn could contribute to an improved individual fitness. Therefore epigenetics provide a direct link between genes and environmental influences. However, the extent by which epigenetic marks may contribute to adaptive evolution is still poorly understood. Since epigenetic alterations have little heritable potential it remains enigmatic whether and how epigenetic alterations may contribute to evolution and adaptation [25].

DNA methylation is widely spread in a plenty of organisms i.e. prokaryotes, fungi, plants and animals, whereas other organisms completely lack or exhibit very little DNA methylation, e.g. yeast [26]. Moreover, the functional role of DNA methylation may differ between lineages. Since DNA methylation is conserved in multiple lineages, a crucial role for several regulatory mechanisms and an organism's complexity is supposed for this epigenetic mark. Accordingly, epigenomic DNA methylation may be an important molecular mechanism which drives divergence of gene expression during speciation. However, the differences in methylation patterns between and within species remain unclear. Future studies on comparative epigenomics could shed light on the evolutionary significance of epigenetic mechanisms and alterations between species. For instance, methylome and gene expression analyses in human and chimpanzee brains revealed major differences in the degree of methylation in brain tissues between both species [27]. This study uncovered crucial differences in methylation patterns of gene promoters, with patterns of hypermethylation in chimpanzee and hypomethylation in human brain tissue. Interestingly, these genes may be associated with common diseases, comprising diverse neurological and psychiatric disorders affecting human populations. These findings lead to the assumption that DNA methylation may not only contribute to species divergence due to gene expression regulation, it also may concurrently contribute to the evolution of disease susceptibility. Therefore, unraveling epigenetic changes and variation in populations could enhance the understanding of evolutionary forces driving the divergence of species as well as the evolution of diseases affecting modern humans today.

OUTLOOK

Evolution as one of biology's most important principles has been neglected in the medical field for a long time until the advent of the genomic age. With the broad availability of sequence information, we can now extend our perspectives on the origin and evolution of complex traits that are associated with diseases. Within this review

Legend to Figure 2. Timescale of evolutionary events which contribute to disease phenotype divergence. The graph displays the different evolutionary dynamics shaping genomic diversity in an individual over time. Ancient events, such as gene or whole genome duplications, led to an expansion of gene and transcription factor families in early vertebrates. Neo and sub-functionalization resulted in gain or loss of function of genes that contribute to disease. On the population level, changes in allele frequencies occurred due to natural selection favoring distinct beneficial allele combinations. More recently, within the last 100.000 years selective sweeps and the effect of genetic hitchhiking led to a fixation of disease alleles in different populations. The combination of these different evolutionary mechanisms shaped the genome of modern humans. While evolution is an ongoing process, even present lifestyle changes can affect the individual human genome on the level of histone modifications or methylation.

Legend to Figure 3. Human-Mouse Disease Orthologs. Gene annotation for 2230 orthologous human mouse gene pairs was retrieved from the ENSEMBL [35, 36] database for OMIM [37] disease loci. The circular graph represents chromosomal locations for genes that are linked to disease in the human genome for all autosomal chromosomes (highlighted in blue).

article, several layers of genetic and epigenetic mechanisms have been discussed, which likely played a crucial role in recent evolutionary change and the adaptation of human populations to different environments. Diseases, which are often viewed as a defect in the perfect machinery of the human organism, may be a byproduct of natural selection favoring a distinct genotype under specific environmental conditions. As Randolph Nesse pointed out: “there is neither a master plan behind the human genome nor is there “the” human genome” [28]. The emerging field of evolutionary medicine will likely help characterize the individual contribution of genetic variance to disease prevalence as well as the role of environmental effects on our genomic architecture in an ever changing environment. In the years to come, evolutionary medicine will likely provide important insights into the complex interplay between genetic makeup and its complex environment and hopefully towards a more guided health care practice. It will also give rise to new ideas and questions on how diseases can emerge within a population and how we can adapt to new lifestyle conditions, such as diet or climate change.

REFERENCES

1. Fleming, A. 2001, Bulletin of the World Health Organization, 79(8), 780-90.
2. Sykes, R. 2001, Bulletin of the World Health Organization, 79(8), 778-9.
3. Otten, H. 1986, The Journal of Antimicrobial Chemotherapy, 17(6), 689-96.
4. Strachan, D. P. 1989, BMJ (Clinical research ed.), 299(6710), 1259-60.
5. Voight, B. F., Kudaravalli S., Wen, X. and Pritchard, J. K. 2006, PLoS Biology, 4(3), e72.
6. Soranzo, N., Spector, T. D., Mangino, M., Kühnel, B., Rendon, A., Teumer, A., Willenborg, C., Wright, B., Chen, L., Li, M., Salo, P., Voight, B. F., Burns, P., Laskowski, R. A., Xue, Y., Menzel, S., Altshuler, D., Bradley, J. R., Bumpstead, S., Burnett, M. S., Devaney, J., Döring, A., Elosua, R., Epstein, S. E., Erber, W., Falchi, M., Garner, S. F., Ghori, M. J., Goodall, A. H., Gwilliam, R., Hakonarson, H. H., Hall, A. S., Hammond, N., Hengstenberg, C., Illig, T., König, I. R., Knouff, C. W., McPherson, R., Melander, O., Mooser, V., Nauck, M., Nieminen, M. S., O'Donnell, C. J., Peltonen, L., Potter, S. C., Prokisch, H., Rader, D. J., Rice, C. M., Roberts, R., Salomaa, V., Sambrook, J., Schreiber, S., Schunkert, H., Schwartz, S. M., Serbanovic-Canic, J., Sinisalo, J., Siscovick, D. S., Stark, K., Surakka, I., Stephens, J., Thompson, J. R., Völker, U., Völzke, H., Watkins, N. A., Wells, G. A., Wichmann, H. E., Van Heel, D. A., Tyler-Smith, C., Thein, S. L., Kathiresan, S., Perola, M., Reilly, M. P., Stewart, A. F., Erdmann, J., Samani, N. J., Meisinger, C., Greinacher, A., Deloukas, P., Ouwehand, W. H. and Gieger, C. 2009, Nature Genetics, 41(11), 1182-1190.
7. Corona, E., Dudley, J. T. and Butte, A. J. 2010, PloS One, 5(8), e12236.
8. Cotsapas, C., Voight, B. F., Rossin, E., Lage, K., Neale, B. M., Wallace, C., Abecasis, G. R., Barrett, J. C., Behrens, T., Cho, J., De Jager, P. L., Elder, J. T., Graham, R. R., Gregersen, P., Klareskog, L., Siminovitch, K. A., van Heel, D. A., Wijmenga, C., Worthington, J., Todd, J. A., Hafler, D. A., Rich, S. S. and Daly, M. J.; FOCiS Network of Consortia. 2011, PLoS Genetics, 7(8), e1002254.
9. Traherne, J. A. 2008, International Journal of Immunogenetics, 35(3), 179-92.
10. Lappalainen, T., Montgomery, S. B., Nica, A. C. and Dermitzakis, E. T. 2011, American Journal of Human Genetics, 89(3), 459-63.
11. Steinberg, K. M., Antonacci, F., Sudmant, P. H., Kidd, J. M., Campbell, C. D., Vives, L., Malig, M., Scheinfeldt, L., Beggs, W., Ibrahim, M., Lema, G., Nyambo, T. B., Omar, S. A., Bodom J. M., Froment, A., Donnelly, M. P., Kidd, K. K., Tishkoff, S. A. and Eichler, E. E. 2012, Nature Genetics, 44(8), 872-880.
12. Feldman, M. W. and Laland, K. N. 1996, Trends in Ecology & Evolution, 11(11), 453-457.
13. Chun, S. and Fay, J. C. 2011, PLoS Genetics, 7(8), e1002240.
14. Huff, C. D., Witherspoon, D. J., Zhang, Y., Gatenbee, C., Denson, L. A., Kugathasan, S., Hakonarson, H., Whiting, A., Davis, C. T., Wu, W., Xing, J., Watkins, W. S., Bamshad, M. J.,

Bradfield, J. P., Bulayeva, K., Simonson, T. S., Jorde, L. B. and Guthery, S. L. 2011, Molecular Biology and Evolution, 29(1), 101-11.
15. Wu, D.-D., Li, G. M., Jin, W., Li, Y. and Zhang, Y. P. 2012, PloS One, 7(8), e42553.
16. Lachance, J., Vernot, B., Elbers, C. C., Ferwerda, B., Froment, A., Bodo, J.-M., Lema, G., Fu, W., Nyambo, T. B., Rebbeck, T. R., Zhang, K., Akey, J. M. and Tishkoff, S. A. 2012, Cell, 150(3), 457-469.
17. Timmann, C., Thye, T., Vens, M., Evans, J., May, J., Ehmen, C., Sievertsen, J., Muntau, B., Ruge, G., Loag, W., Ansong, D., Antwi, S., Asafo-Adjei, E., Nguah, S. B., Kwakye, K. O., Akoto, A. O., Sylverken, J., Brendel, M., Schuldt, K., Loley, C., Franke, A., Meyer, C. G., Agbenyega, T., Ziegler, A. and Horstmann, R. D. 2012, Nature, 489(7416), 443-6.
18. Domazet-Loso, T. and Tautz, D. 2008, Molecular Biology and Evolution, 25(12), 2699-2707.
19. Makino, T. and McLysaght, A. 2008, Molecular Biology and Evolution, 25(9), 1855-1862.
20. Dickerson, J. E. and Robertson, D. L. 2012, Molecular Biology and Evolution, 29(1), 61-9.
21. Wolfe, N. D., Dunavan, C. P. and Diamond, J. 2007, Nature, 447(7142), 279-83.
22. Zhou, V. W., Goren, A. and Bernstein, B. E. 2011, Nature Reviews Genetics, 12(1), 7-18.
23. Robertson, K. D. 2005, Nature Reviews Genetics, 6(8), 597-610.
24. Johnson, L. J. and Tricker, P. J. 2010, Heredity, 105(1), 113-21.
25. Hirt, R. P. and Horner, D. S. 2004, Organelles, Genomes and Eukaryote Phylogeny: An Evolutionary Synthesis in the Age of Genomics, CRC Press, pp. 353-370.
26. Feng, S., Cokus, S. J., Zhang, X., Chen, P.-J.,Bostick, M., Goll, M. G., Hetzel, J., Jain, J., Strauss, S. H., Halpern, M. E., Ukomadu, C., Sadler, K. C., Pradhan, S., Pellegrini, M., Jacobsen, S. E. 2010, Proceedings of the National Academy of Sciences of the United States of America, 107(19), 8689-94.
27. Zeng, J., Konopka, J., Hunt, B. G., Preuss, T. M., Geschwind, D. and Yi, S. V. 2012, The American Journal of Human Genetics, 91(3), 455-465.
28. Nesse, R. M. 2001, The Western Journal of Medicine, 174(5), 358-60.
29. Ding, K. and Kullo, I. J. 2008, Pharmacogenetics and Genomics, 18(3), 169-179.
30. Nicholson, G., Rantalainen, M., Li, J. V., Maher, A. D., Malmodin, D., Ahmadi, K. R., Faber, J. H., Barrett, A., Min, J. L., Rayner, N. W., Toft, H., Krestyaninova, M., Viksna, J., Neogi, S. G., Dumas, M. E., Sarkans, U.; MolPAGE Consortium, Donnelly, P., Illig, T., Adamski, J., Suhre, K., Allen, M., Zondervan, K. T., Spector, T. D., Nicholson, J. K., Lindon, J. C., Baunsgaard, D., Holmes, E., McCarthy, M. I. and Holmes, C. C. 2011, PLoS Genetics, 7(9), e1002270.
31. Nielsen, R., Williamson, S., Kim, Y., Hubisz, M. J., Clark, A. G. and Bustamante, C. 2005, Genome Research, 15(11), 1566-1575.
32. Foster, C. B., Aswath, K., Chanock, S. J., McKay, H. F. and Peters, U. 2006, BMC Genetics, 7, 56.
33. Nakagome, S., Mano, S., Kozlowski, L., Bujnicki, J. M., Shibata, H., Fukumaki, Y., Kidd, J. R., Kidd, K. K., Kawamura, S. and Oota, H. 2012, Molecular Biology and Evolution, 29(6), 1569-85.
34. Oleksyk, T. K., Nelson, G. W., An, P., Kopp, J. B. and Winkler, C. A. 2010, PloS One, 5(7), e11474.
35. Hubbard, T., Barker, D., Birney, E., Cameron, G., Chen, Y., Clark, L., Cox, T., Cuff, J., Curwen, V., Down, T., Durbin, R., Eyras, E., Gilbert, J., Hammond, M., Huminiecki, L., Kasprzyk, A., Lehvaslaiho, H., Lijnzaad, P., Melsopp, C., Mongin, E., Pettett, R., Pocock, M., Potter, S., Rust, A., Schmidt, E., Searle, S., Slater, G., Smith, J., Spooner, W., Stabenau, A., Stalker, J., Stupka, E., Ureta-Vidal, A., Vastrik, I., Clamp, M. 2012, Nucleic Acids Research, 30(1), 38-41.
36. Vilella, A. J., Severin, J., Ureta-Vidal, A., Heng, L., Durbin, R. and Birney, E. 2009, Genome Research, 19(2), 327-335.
37. McKusick, V. A. 1998, Johns Hopkins University Press, (12th edition).