Evolution and public health
Part II - Humans' evolutionary past influences health and diseases

Neanderthal DNA in modern humans influences health and diseases

Public health integrates scientific disciplines otherwise far apart from each other. Areas of expertise are public health medicine, health policy and health economy, epidemiology and statistics, sociology, behavioral sciences, and hygiene and life sciences. A previous entry into this blog suggested taking in paleogenetic as being worthwhile to have a look at. Paleogenetic 'knocked on the door' of medicine and public health recently, identifying genomes inherited from Neanderthals as risk- and protective factors for SARS-CoV-2 infections. The specialty gained substantial public attention through the mass media in the year 2010. That year a draft of the Neanderthal genome was published, followed by reports about remarkable discoveries.

DNA from Neanderthal within modern human genomes

In 2014 two publications identified DNA from 'Neanderthal linages' within modern human genomes (1, 2). Both groups of investigators used complex statistical methods dissimilar from each other but achieving similar results. Information from whole-genome sequences for present-day individuals was derived from the 1000 Genome Project (3). Results confirmed that 1 to 3% of Europeans and East Asian humans inherited genomes from Neanderthal. The genome of modern humans includes about 20% of all Neanderthal genomes. These 20% spans 15 gigabases of 'introgressed sequences' in our genome (2). Twenty-five percent of the Neanderthal alleles are non-functional. Between 15 to 20% of alleles are promoters, enhancers, and coding regions. Especially, miRNA, regulating gene expression, seems to be important (4).

Adaptation to environments out-of-Africa to fight infections

Recent evidence gained by human sequence variation supports the hypothesis that mankind originated in Africa and, over the last 60.000 years migrated out-of-Africa, throughout the world (5). Neanderthal haplotypes helped anatomically modern humans to adapt to a non-African environment. Chances of survival were enhanced by genetic adaptation to fight infection. The different environments included a variety of threatening germs not present in Africa. The exchange of adaptive alleles helped anatomically modern humans to develop resistance predominantly against viruses (6). Genetic segments, particularly in modern Europeans, were identified with a preference for RNA viruses (7). This would explain the protective effect alleles of the Neanderthal genome have on Covid-19 (8). In general, the genes derived from the Neanderthal influence the innate immunity (9). This includes, for instance, the interferon-inducible antiviral effectors, the restriction factors IFITM 1 to 3, and the cytokines IL17A and IL 17F (10).

Pros and cons of inherited Neanderthal DNA

The cytokines mentioned are related to asthma. So, alleles derived from Neanderthal might be beneficial for health but otherwise associated with diseases. There are Neanderthal alleles with a protective effect on SARS-CoV-2 and, on the other site, aggravate Covid-19 infection (11). No advantage for 'modern humans' was the introduction of HPV16A by sexual transmission from Neanderthal. The human papillomavirus 16 is responsible for anogenital cancers (12). Additional drawbacks are related to the inherited immune response, which goes along with the disadvantage of genetic influences on inflammatory and autoimmune diseases (6, 10).

Useful for Caucasians are Neanderthal alleles related to keratin filaments and skin phenotypes (1). The alleles belong to the gene BNC2, which determines skin or hair color and causes pale instead of tanned skin (2, 13). Light skin in areas with low UV radiation, commonly in autumn and winter in the northern hemisphere, helps synthesize vitamin D.

Not related to infection and phenotypes are Neanderthal's gene variants to chronic diseases. The present-day human blood coagulation system might have been beneficial to modern prehistoric humans when life expectancy was relatively short. Nowadays, they increase the risk of blood clotting and stroke in advanced age groups (14). Interesting for public health are regions derived from the Neanderthal genome on chromosome 2 containing the gene THADA (Thyroid Adenoma Associated) (15). THADA was identified as one of twelve genes related to type 2 diabetes mellitus (T2DM) (16). The former benefit for hominins migrating from warmer zones to colder ones is obvious because THADA is involved in the organism's energy storage and heat production (17). From the data of a Hungarian databank, variants of the THADA gene show excess maternal transmission to off-springs with T2DM (18). That epigenetic mechanism is also involved was indicated by differential methylation between diabetic and non-diabetic donors.

Genomes of questionable values

Some results of paleogenetic investigations may be exciting but less critical to public health. Based on the data from the UK database, it was found that about 0.4% of unfortunate Britons are more sensitive to pain than compatriots due to Neanderthal variants in their genome (19). It is difficult for some of the findings to judge what effect these genes might have had on the Neanderthals themselves. In present-day people, some of the inherited DNA is linked to depression and addiction to tobacco and sleeping patterns and mood (13, 14). Further investigations probably will elucidate the significance of these findings for the present-day population more specifically.

Outlook

Testing vulnerability to a given health problem should not only look into age ranges and the difference between women and males. Various statistical methods are available to test for additional factors associated with a health problem. For ambitious research, advanced technologies are available now to investigate our genome as well. Several useful reference datasets are available, allowing us to embark on formerly exceptional fields of interest such as paleogenetic. An abundant scope for further exploration is open for research in Asia and the Pacific. What is known from the Neanderthal genome must not necessarily apply to the Denisovans living together with the Neanderthals and mating with them. Neanderthals made it

‘out-of-Africa’ to Eurasia, and the Denisovans going further to Micronesia and Oceana (5). Recent findings of Denisovan bones in Siberia, China, and elsewhere in the future might provide more detailed impressions of the influence of Denisovan's genome on East Asians.

Findings from various sites of Southeast Asia reveals a complex pattern of migration of prehistoric populations from north to south within continental Southeast Asia and further on to Indonesia, Papua New Guinea, and Australia (20) . A review paper published more recently mentioned that Denisovan haplotypes were found in Cambodians. The genomes are somewhat distinct from the rest of East Asia with a connection to Oceania. The ‘admixture history’ from Denisovan populations into modern humans might be more complex than from Neanderthals (21). An additional entry into this blog might follow for those interested in the topic, focusing on Asia and the Denisovans.

Literature

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