Evolution and public health
PART 1: Paleogenetic – a new scientific discipline being of interest for public health might not be as absurd as it seems

Paleogenetic merged genetics with paleontology and disclosed that our evolutionary past is more complex than previously thought. DNA of archaic hominins in our genome influences present day population's health and disease. An example is genetic elements inherited from the Neanderthal modifying the outcome of Covid-19 infections.

Risks factors for catching SARS-CoV-2 are discussed in almost all available communication media. But, certain causes, claimed to be important, seem to be far-fetched. Two authors from the Max-Planck Institute for Evolutionary Anthropology, Leipzig, Germany, published two papers implying that 'major genetic risk factor for severe COVID-19 is inherited from Neanderthal's (1) and that another genomic region received from this extinct hominins protect against Covid-19 (2).

Epidemiology and statistics are well-established methodological approaches for the assessment of risk factors. How come that scientists from a field called 'paleogenetics', never heard of before, invade a domain of public health?

What is paleogenetic?

In paleogenetic, two words are merged: Paleontology and genetics. Genetics is familiar for those interested in and working in the academic sector of public health. Genetic factors are known to increase the risk of diseases, such as diabetes mellitus. Also, epigenetic is of interest to public health. Through epigenetic mechanisms, such as DNA methylation, 'environmental factors' determine how our genes work in health and disease (3). For example, a pregnant woman suffering from undernutrition might have a child acquiring chronic diseases in their adulthood.

Paleontology studies ancient life. The essential tool applied is sequencing the genome. Genome sequencing significantly improved research in science and medicine. The newest genome sequencing techniques brought genetics and paleontology together in the new scientific discipline 'paleogenetics'. Paleogenetics studies the genome derived from artifacts of ancient material such as bones from archaic hominins. The results of very complex investigations opened a fascinating look at our evolutionary history.

Meet Mrs. Neanderthal

From high school days, one might vaguely remember the Neanderthal. Some bones were found, more than 150 years ago, at a place called Neanderthal in western Germany. Paleoanthropologists claim that they originated from the forefathers of modern humans. In Eurasia, they were around back as 400.000 years and vanished 30.000 years ago (4, 5). The

Neanderthal, so to say, walked out of its museums, such as in Germany and Croatia, close to the sites where their traces were found and made it into the public media in 2010.

In fact, not 'he' but three Neanderthal females emerged. An international group of scientists published a paper entitled 'A draft sequence of the Neanderthal genome' in the Science magazine (6). To the educated layman, the main findings of this key paper and its background were explained by Ann Gibbons, a contributing correspondent for Science. She might have triggered the enthusiasm about the notion that modern humans and Neanderthals mated. They might have had sex together some 50.000 years ago. As a result of this sexual interaction, Europeans and Asians today have 1% to 4% of Neanderthal DNA in their genes (7). After the publication and in the following years, 'romantic' pictures, like the one of this link, stimulated the viewers, and even science fiction dreamed of cloning the Neanderthal.

Sequencing the genome of Neanderthal

The very complex and carefully thought-out investigation sequenced the DNA from bones found at the Vindija Cave in Croatia and compared parts of the genome with those derived from Neanderthal bones found in Spain, Germany, and Russia. Primitive ancestral genetic variants were verified from chimpanzees. With the Neanderthal genome, the complete genome of five living humans, namely from an indigenous tribe, the San, from South Africa, Yoruba from West Africa, one individual from Papua New Guinean, and one Han Chinese, and one French European were studied. Comparing the Neanderthal genome with the apes and present-day man was necessary to ensure that the genome on hand stems from the Neanderthal.

It was found that Europeans and Asians, but fewer Africans, are related to the Neanderthals. Interbreeding might have happened with ancestors of Europeans and Asians but not with Africans. The gene variants of the Neanderthals persisted throughout the following generations in modern humans, who spread the Neanderthal's DNA further on.

Denisovans appear and join the Neanderthals

From 2010 onwards, the science of paleogenetic rapidly proceeded. A highlight surfaced with sequencing the total genome of a mitochondrial DNA from a fragment of a juvenile female finger bone. The fragment belonged to a formerly unknown hominin from southern Siberia, now named Denisovan (8). Neanderthals and Denisovans have a common ancestor in Africa. While the Neanderthals seem to have migrated into Eurasia, the genetic material of the Denisovans is found to 4 to 6% in present day Melanesians (9).

Sort of sensation for science was a publication in 2018 about the genome of a daughter from a Neanderthal mother and a Denisovan father (10). Denisovans also mixed with modern humans. Gene variants from Denisovans related to immunity and diet were extracted from present-day Indonesia and Papua New Guinea individuals. In Australia, patients were found to have a gene (TNFAIP3) linked to autoimmune disease. Among the anthropologists, the probability is discussed that ancestors of Denisovans and Neanderthals 'interbred' with a still unknown and extinct 'super archaic member' of the human family about 700.000 years ago, possibly H. erectus (11, 12).

The tree of evolution

It is obvious now that human evolutionary history is much more complex than formerly thought. This includes the 'way out of Africa' by ancient hominins and the various migration routes back and forth from Africa and throughout the world. There is evidence not only for the interbreeding of archaic hominins with anatomically modern humans but also a genetic mixture between the various branches of the tree of evolution (13).

The evolution tree is the phylogenetic tree from molecular data visualizing the interconnection and the unimaginable time spans along the hominin timeline. With the help of advanced statistics, specific software was developed to help scientists create phylogenetic trees (14). With 'Ensemble 2020', one of the newer releases of software spans the phylogenetic across a wide range of species (15).

The problem evolutionary genomics face is linked to dating when different hominins split from each other or admixture. As some sort of clock, mutation rates across the human genome could be used. Yet, the use of mutation rates is still controversially discussed. Mutation rates are rather low in humans, such as one point mutation per 100 megabases (MB) or about 60 MB genome-wide per generation (16).

Hominis split from chimpanzee and the ultimate origin LUCA

Somehow the human linage separated from the chimpanzee 'only' 9.3 to 6.5 million years ago. For humans, it still seems to make sense to discuss phylogenetic uncertainties (17). For bacteria, in comparison, the vertical and horizontal (or lateral) phylogenies are much more uncertain (18, 19). When looking at life on earth, the most universal common ancestor, called LUCA, is supposed to be a microbe 4 billion years ago. So, every living organism on earth, including us, goes back to LUCA.

Technical challenges for paleogenetics

Establishing the phylogenetic tree is not the only difficulty paleogenetic faces. The remains of Neanderthals and Denisovans are of very low quality. The material is contaminated with bacterial DNA and modern humans DNA while handling the specimens. To distinguish between Neanderthal and modern human mtDNA (mitochondrial DNA) PCR amplification was not suitable since the genome between Neandertals and modern humans don't differ much, even our linage separated 500.000 years ago. Very ingenious statistics and computer techniques had to be used to identify the base pairs of Neanderthal finally. The one who manages to enable this was Richard Green, the first author of the publication listed under (6). He was able to provide the 'qualitative and algorithmic horsepower' to interpret the Neanderthal data. (Elizabeth Pennisi in (7)).

Besides all these difficulties, paleogenetic made its inroad into science and the archaeological community and split the archeologist into two groups 'half thinking ancient DNA can solve everything and for another half ancient DNA is the devil's work' (20, 21). In comparison to

humanities versus science, medicine and public health might have less difficulties in inaugurating results of paleogenetics related to an immediate problem when it comes to SARS-CoV-2.

SARS-CoV-2 - ACE2, blood group 0, and paleogenetic

That certain genes increase the risk to acquire Covid-19 was assumed even at the beginning of the pandemic. ACE2, the enzyme enabling the virus to enter the cell, was linked to diabetes mellitus (22). A protective influence was seen within the ABO blood group system, in that group 0, compared to the other groups, had a protective effect on the course of infection (23). That also locations in our genome, inherited from Neanderthal, influence the course of infection of Covid-19 came as a surprise.

The paleogenetic investigation data for risk assessment used the COVID-19 Host Genetic Initiative (24). From this database 3.199 hospitalized COVID-19 patients were taken as well as 897.488 population controls. Patients and controls were derived from Belgium, Brazil, Finland, Italy, UK, Germany, and Norway. Data from the UK Biobank were also chosen (25, 26). The risky gene cluster was detected on chromosome 3 on rs35044562. The summary effect was assessed with an odds ratio of 1.60 (CI 1.42 – 1.79) (1).

The allele of interest is absent in Africa but assumed to be derived from the Neanderthals on other continents. According to the 1000 genome project the frequency differs around the world. Thirty percent of the population in South Asia are carriers, about 8% Europeans and 4% admixed Americans. The highest carrier frequency was found with 63% in the population of Bangladesh. For instance, Bangladeshi living in the UK have a two times higher risk of dying from the virus compared to the general population (hazard OR 2.0 (95% CI 1.7 – 2.4)) (1). The gene, however, is missing in East Asia.

The protective part of the genome is situated on chromosome 12, and the protective haplotype was identified as ‘rs10735079’. The haplotype lowered the relative risk to require intensive care when infected with Covid-19 by 22% (OR 0.78 (95% CI 0.71 – 0.85) (2).

Outlook

The indication that archaic DNA in our genome might endanger or protect us from Covid-19 isn’t the only point of interest for medicine and public health. Interbreeding between anatomically modern humans and archaic hominins, and the need for genetic adaptation to different local environments on the way out of Africa, left traces within our genome, which affects our responsiveness to the challenges of the environment we are living in. The following entry to this blog will report various additional discoveries from paleogenetic being of relevance for health sciences.

Literature

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