Rise and fall of deleterious variants: the origins of modern genetic diseases

Essor et déclin des variants délétères : quelles origines pour les maladies génétiques modernes ?

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Rise and fall of deleterious variants: the origins of modern genetic diseases

Essor et déclin des variants délétères: quelles origines pour les maladies génétiques modernes?

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For two decades, sequencing genomes has significantly helped to identify genetic causes of diseases observed in modern humans, leading to the emergence of genetic medicine. This raises questions about the presence of deleterious variants, and consequently diseases, in ancient humans too, as well as when and where these variants first appeared during human evolution. As the Neolithic transition brought a major change in diet and lifestyle in Western Eurasia, we examined the health status of pre-Neolithic hunter-gatherers and early Neolithic farmers, as well as their contribution to the present-day burden of deleterious alleles. We analyzed 24 high-coverage (>10X) ancient genomes of individuals from Upper Paleolithic to Neolithic times and 65 genomes of modern humans from Europe and South-West Asia. We find that some variants associated with diseases in modern humans (from the public collection of disease-variant associations DisGeNET) were already present during Neolithic times and even during the Mesolithic and Paleolithic. Contrary to the hypothesis of a mutation load building up over time, we find that disease variants were more frequently homozygous in the ancient genomes than in modern ones, with hunter-gatherers showing higher recessive mutation load than farmers. Moreover, we found evidence of past derived alleles at sites under strong evolutionary constraint (i.e. with large GERP score) that have been eliminated since the Paleolithic or Neolithic times in Western Eurasia. This result can be explained by past episodes of negative selection. Finally, we tried to assess the disease profile of ancient individuals from their genomes, thus complementing paleopathological reports for diseases leaving no trace on skeletal remains. In conclusion, this study of relatively high-coverage whole ancient genomes allowed us to assess the presence in past populations of...
mutations that contribute to modern-day diseases and to bring insights on the health status of ancient individuals.

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