GUEST LECTURE SERIES

January 11, 2024
5:00 p.m.
Humboldtstrasse 48, SR 44.31

Andreas Geier
Internal Medicine and Hepatology, University Hospital Würzburg, Germany

Investigating the origins of MASLD with ancient and modern human genomes

The liver is the central organ in the human body responsible for carboyhdrate and lipid metabolism and plays a key role in fat storage under conditions of overnutrition. Fat deposition is modulated by environmental factors and genetic predisposition. GWAS studies identified PNPLA3 p.I148M as a common variant that increases risk of developing non-alcoholic fatty liver. The association of this variant to harmful phenotypes including end-stage liver disease suggests a potential effect on fitness and hence a potential role of natural selection. To understand its past trajectory throughout human evolution, we turned to archaeoegenetic data spanning the last 50,000 years. Published ancient (modern humans, Neanderthal, Denisovan) and present-day genomes were used for analysis after extracting genotype calls for PNPLA3 p.I148M (rs738409). Archaic human individuals exclusively carried a fixed PNPLA3 risk allele, whereas allele frequencies in modern human populations range from very low in Africa to more than 50% in Mesoamerica. Over the last 15,000 years, distributions of ancestral and derived alleles roughly match the present day distribution, including a high frequency in the Americas even in the earliest samples from 10,000BP. Our observation might underscore the advantage of fat storage in cold climate and particularly for Neanderthal under ice age conditions. A negative genome-wide analysis without signals of natural selection during modern human history does not support the thrifty gene hypothesis in case of PNPLA3 p.I148M polymorphism where other mechanisms like gene drift may contribute to present day allele distribution.