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The demic complexity of the Mediterranean Basin, an important intersection among three continents where different people and cultures have met over time, has been widely investigated through the analysis of the prehistoric and historic events that led to the shaping of the genetic variability of the extant Mediterranean populations. However, a full understanding of the time and mode by which these numerous migrations, together with cultural exchanges, gave rise to present-day human genomes is still highly controversial and extensively discussed. The genetic continuity from Palaeolithic times, the amount of gene flow across the Mediterranean, the differential impact of the Neolithic on both shores of the Mediterranean, and the replacement and admixture of population groups in historical times are questions that are still subject to debate, despite the large amount of genetic studies performed up to the present day.

In this special issue of the Annals of Human Biology we collected both research articles and review papers to summarise current knowledge and suggest future research priorities.

The review papers outline the contribution of uniparental markers such as mitochondrial DNA (mtDNA) and the non-recombining region of the Y chromosome. In fact, mtDNA and Y-chromosomes, which in the pregenomic era have been the selected genetic markers suitable for phylogenetic and phylogeographic analyses, still provide important insights in reconstructing the genetic population history of the Mediterranean area. Regarding the analysis of mtDNA, the review by De Angelis et al. (2018) comprises the description and investigation of the variability within the Mediterranean area to clarify the genetic contributions of the various populations involved in the migration events which occurred in the area during the last 50 ky, using extinct and extant mitogenomes. The authors highlight a clear time discontinuity of female lineages suggesting a lack of Upper Palaeolithic contribution to modern Mediterranean populations, pointing to a pivotal role of the Last Glacial Maximum in the population resettlement of the Mediterranean.

The review by Larmuseau and Ottoni (2018) provides an outstanding overview of the current status of research in Y-chromosome studies. In particular, the authors stress the opportunities that Y-chromosome data currently offer for answering peculiar questions in population genetics of the Mediterranean area, notwithstanding the great importance of entire-genome and aDNA studies in the reconstruction of the genetic structure of Mediterranean populations, shaped by migratory events, common ancestry as well as past admixture episodes. To this purpose, they provide a thorough, detailed and updated description and extensive examination of new applications of Y-chromosome analysis on Mediterranean populations. These innovative utilizations encompass unfolding male-specific demographic events both in ancient times and in the more recent past, such as expansions and migrations; ancient DNA applications, such as sex identification, kinship analysis, evolution of social-cultural factors like marriage bonds, patrilocality and matriarchal/patriarchal traditions; the origin of surnames; and the investigation of the influence of patrilineal castes and clans on the genetic structure of populations among human societies. Moreover, they highlight the still relevant interest of genetic data of Y-chromosome markers in populations in forensic genetics as well as in research on male infertility and in genome-wide association studies (GWAS) between Mediterranean populations. In fact, the apparent lack of influence of human Y-chromosome variation on the physical traits or disease phenotypes studied up to now could be due to the fact that Y-chromosome data have been rather neglected in GWAS. It is worth noting that, in the conclusion of their review, the authors caution researchers involved in Y-chromosome studies, especially if combined with whole genome data, to bear in mind their strict connection with surnames and patrilineages and therefore to verify any potential correlation between genetic profiles and surnames of the donors to save and respect citizens’ privacy.

The research articles in this special issue encompass various topics concerning the analysis of the genetic pools of extant populations located along the Northern, Southern and Eastern Mediterranean coasts, North Africa, Turkey, the Arabian Peninsula and Iran as well as mainland Europe; the investigation of surname structure; the investigation of genes that affect the metabolism of many drugs; and the study of an ancient Italian population.

In four of the research articles, special attention is given to the genetic structure of Italian populations. Italy, because of its location in the middle of the Mediterranean Basin, was the site of a complex network of migrations resulting in a heterogeneous pattern of colonisation. Thus the question arises as to whether these earlier influences left their signature in the present genetic composition of the Italian populations. Serventi et al. (2018) engage in addressing this issue through the analysis of the Piceni from Novilara, a necropolis dated back to the 8th–7th century BCE, of particular interest since at present no genetic data are available on this ancient population. This study contributes to expanding the knowledge of the Italian populations of this period, for which few genetic data exist. Through the characterisation of the Piceni mtDNA variability and the comparison with other modern populations from continental Italy, Sicily and Sardinia, and published European prehistoric samples ranging from the Bronze to the Iron Age, the authors aimed to investigate likely genetic relationships between populations and to contribute to a better understanding of the European Iron Age
genetic diversity and dynamics. Their findings, even though preliminary due to the small sample size, identify a genetic continuity between the archaeological group from Novilara and the present-day local/Italian populations. This possible matrilineal genetic continuity suggests that it is very likely the migration pattern which characterised this area of Central Italy did not contribute to shaping the maternal gene pool of the inhabitants. Moreover, sex estimation and kinship assessment of two peculiar graves, each containing two individuals, was carried out by autosomal markers analysis, and no familiar relationships were detected in either case, as proposed by archaeological evidence. These results seem to suggest, at least in one case, the reuse of the same burial for unrelated or related-in law individuals, and thus contribute to a better understanding of the structure of social relations within European Iron Age populations.

In the paper by Grugni et al. (2018), the authors address the genetic history of the Italian Peninsula from a Y-chromosome perspective, by providing novel high-resolution data from informative areas of Italy and contextualising the obtained results in the framework of times and impacts of Mediterranean and European contributions. Frequency and variance distributions, and the relative age estimates of the main identified Y-chromosome lineages, R1b-M269, J2-M172, I-M170, G-M201 and E1b-M78, mark different influences from continental Europe and the Mediterranean in the Northern and Southern parts of the Peninsula, respectively. In agreement with previous studies, the dissection of Italian Y-chromosomal composition particularly confirms a North-South structuring pattern, where Southern populations show links with the Middle East and Southern Balkans, while Northern Italian groups are closer to North-Western European and Northern Balkan populations. The obtained results moreover emphasised a unique genetic structure observed in the population of Volterra, an ancient town of Etruscan origin in Tuscany, which exhibits a significant different Y-haplogroup composition compared to the rest of Italy. Overall, the study integrates the complex picture of the genetic structure of modern Italian populations, underlying the multifaceted peopling history of the Peninsula in terms of both different legacies and peculiarities of distinctive ancestral sources.

Boattini et al. (2018) in their contribution focused their interest on South Italian and Sicilian populations and investigated the possible relationships between surname distribution and all the genetic markers available in the literature, both autosomal and haploid, especially Y-chromosome lineage, since surnames are usually inherited in a patrilineal way as the non-recombining region of the Y-chromosome. The aim of the paper was to better understand and shed light on the apparent contradictory pattern of distribution of surnames and genes. In fact, previous studies highlighted that while genetic markers seem to display a homogeneous distribution pattern with no structuring signal among Sicilians, Southern Italians as well as other Southern European populations due to ancient migratory events which homogenized their genetic pools, surname analysis in Sicily and Southern Italy points to possible structuring as the result of their isolation from the other Italian regions occurred during the last centuries. Therefore, the apparent conflict between surname structure and genetic homogeneity was resolved by observing that surnames left their signature on the ancient and homogeneous genetic background of the populations reflecting their most recent genetic history. The paper aims to give a first global overview in Sicily and Southern Italy of the correlation between surnames and genetics by setting the starting point for new and very likely more informative micro-geographic surname studies designed to gain a better understanding of the problem and help develop sampling strategies for future extensive molecular surveys.

The Italian genetic structure was also investigated in the paper by Carano et al. (2018) using four clinically relevant enzymes involved in the phase I metabolism of the most common therapeutic drugs. The authors sampled only ancestrally and geographically homogeneous individuals from Northern, Central and Southern Italy and demonstrated that two (CYP2D6 and CYP2C19) of the investigated genes show a North-South pattern with statistically significant differences between the Northern Italian macro-area and particularly the Southern one. This study underlines how an accurate and geographically wide sampling strategy may be useful in pharmacogenomics studies to avoid hypothetical bias in drug trials.

In order to provide additional data to the widely used uniparental markers, two more research articles present the use of autosomal markers to unravel the population history in the Mediterranean Basin. The use of new markers provide novel insights, but also some limitations, since the data available for comparison is much scarcer than the uniparental data. Nonetheless, Santamaria et al. (2018) have addressed the genetic population structure of the Mediterranean populations through the analysis of dinucleotide STRs located on the X chromosome. Using X-chromosome markers might have some advantages since it allows the direct phasing of the data when analysing males and can address questions regarding sexual bias when comparing with autosomes or uniparental lineages. The X-chromosome analysis presented shows a clear population structure of the two shores (North and South) of the Mediterranean, suggesting a limited gene flow between both regions. In addition to the population conclusions, the manuscript also points to the relevance of the use of alternative markers to uniparental lineages.

Another interesting approach to population genetic studies of the Mediterranean populations was proposed by Messina et al. (2018). In their contribution to this special issue, the authors exploit the possibility of applying genetic data produced for forensic genetics application, i.e. the subset of Tetranucleotide Short Tandem Repeats (STRs) commonly used for individual identification, to unravel and explain key factors involved in the shaping of local populations genetic pools since they contain some degree of ancestry-related information and are therefore of great interest from a microevolutionary perspective. They also stress the importance of taking into account three factors when choosing the data for the analyses: the sample sizes, the spatial distance among samples and the genetic background. By applying spatial principal component analysis (sPCA) and
surface maps, they validate the use of such markers for unfolding the gene geography of the Mediterranean and surrounding populations, confirming the capacity of such methods to select the most informative loci/alleles to detect clinal distributions along the South East to North West axis over the area under study. Actually, the authors found a line of discontinuity along the Western boundary of Turkey and the Aegean sea, an area which played an important role as a cultural barrier, and infer that common ancestors of the populations located at the extremity of the investigated area should go back to thousands of years ago. These findings highlight that the patterns obtained for the geographically-informative subset of STRs are quite similar to some of those observed for mtDNA and non-recombining Y-chromosomes which are connected to demographic events and known human dispersal routes that occurred in the Mediterranean Basin and in general in Western Eurasia during the last 15,000-10,000 years. Therefore, it seems that it would be possible to use forensic data for the understanding of the mechanisms involved in shaping the genetic structure of human populations together with migration events that took place over several millennia in this area.

New insights into populations inhabiting the Southern Mediterranean shore are provided by two studies focused on the North African mitochondrial genetic variability. Ben halim et al. (2018) in their paper “Mitochondrial DNA structure of an isolated Tunisian Berber population and its relationship with Mediterranean populations” analyse an isolated Berber population (Douiret) from South-Eastern Tunisia, showing strong geographic and cultural isolation, and a high level of consanguinity and endogamy (98.16%). The samples were selected as representative of the eight different patrilineal lineage clans and the HVSI region was used to evaluate the mitochondrial DNA genetic structure of this population in the context of other Tunisian, North African, Eurasian and Near Eastern populations belonging to the Mediterranean region. Phylogenetic analysis reveals the predominance of Eurasian lineages (74%) with a very high frequency of the haplogroup T, and a relatively low contribution of Sub-Saharan lineages compared to the general Tunisian populations.

From a wider perspective, in their paper “The genetic landscape of Mediterranean North African populations through complete mtDNA sequences”, Font-Porterias et al. (2018) report new complete mitogenome sequences of North-African individuals that are highly homogeneous and geographically well distributed in the whole North-African region, i.e. Morocco, Algeria, Tunisia, Libya and Egypt. These sequences were analysed together with whole mitochondrial sequences from the same area reported in literature. The identified haplogroups (groups of sequences which share an identical set of mutations derived from a common ancestor) and the phylogenetic analysis performed underlie the great genetic heterogeneity of the North-African populations due to their complex demographic histories and migrations out of Africa and back which involved population movements from the Near and Middle East, South-Sahara and Western Europe. In the complex, the great majority of North-African haplotypes (70%) belong to H, HV, R0, J, T, U and W haplogroups of Eurasian origin which were very likely introduced from Western Eurasia during the Paleolithic and the Neolithic; 20% are of South-Saharan origin (L) attributed to the recent Arabic slave trade, starting in the 7th century CE and characterised by trans-Saharan migrations; and the remaining 10% are rightly assigned to U6 and M1 haplogroups, considered North-African autochthonous and present in the region since Palaeolithic times. These results confirm previous data on North-African populations. The thorough analysis carried out on the available complete mtDNA sequences led to the identification of a novel mtDNA sub-haplogroup named H1v2, which originated approximately 4000 years ago through the dispersal of the Eurasian haplogroup, and could never have been detected based on the classical sequence of the hypervariable segment I (HVS-I).

This sub-branch belongs to H1 haplogroup, the most frequent in Western Europe, which shows a clinal distribution east-westward. Its coalescence age is between 8000 and 9000 years in accordance with a dispersion from Iberia towards Africa during postglacial times. Afterwards, H1w, H1x and H1v subclades originated. The coalescence age estimation of the H1v sub-branch, comprising Berber sequences from Tunisia, Tuareg haplotypes from Libya, and the novel Mozabite mitochondrial lineage from Algeria, and possibly correlated to an ancient split of nomadic populations from North Africa, ranged from 1900 and 6100 years, in agreement with previous estimations.

In conclusion, we can state that, although the enormous impact of whole genome studies on both extinct and extant populations is evident in the reconstruction of the evolutionary history of our species, from the papers presented in this special issue it is apparent that in the post-genomic era the uniparental markers, as well as those commonly used in forensic genetics and in personal identification or surname analysis, can still be used as powerful tools for addressing special questions on the genetics of Mediterranean populations.

References


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