From the Alps to the Mediterranean and beyond: genetics, environment, culture and the "impossible beauty" of Italy

Paolo Anagnostou[†1,2], Francesco Montinaro[3,4], Marco Sazzini[5,6], Fabio Di Vincenzo[7,8] & Giovanni Destro Bisol[1,2]

1) *Department of Environmental Biology, Sapienza University of Rome, Piazzale Aldo Moro 5, Rome, Italy*
   e-mail: giovanni.destrobisol@uniroma1.it

2) *Istituto Italiano di Antropologia, Piazzale Aldo Moro 5, Rome, Italy*

3) *Department of Biosciences, Biotechnologies and Environment, University of Bari "Aldo Moro", via Edoardo Orabona, Bari, 70124*

4) *Institute of Genomics, University of Tartu, Riia 23b, Tartu, 51010, Estonia*

5) *Laboratory of Molecular Anthropology & Centre for Genome Biology, Department of Biological, Geological and Environmental Sciences (BiGeA), University of Bologna, Bologna, Italy*

6) *Interdepartmental Centre Alma Mater Research Institute on Global Challenges and Climate Change, University of Bologna, Italy*

7) *University of Florence, Museum of Natural History, via Giorgio La Pira 4, Firenze, Italy*

8) *Istituto Italiano di Paleontologia Umana, Piazza Ruggero Bonghi, 2, 03012 Anagni, Italy*

Summary - *Since prehistoric times, Italy has represented a bridge between peoples, genes and cultures. Its peculiar geographical position explains why: it is located in the center of the Mediterranean Sea, flanked by the Balkans and the Hellenic Peninsula to the east, Iberia to the west and surrounded by North Africa to the south and central Europe to the north. This makes Italy of extraordinary interest for the study of some different aspects of human diversity. Here we overview current knowledge regarding the relationships between the structure of the genetic variation of Italian populations and the geographical, ecological and cultural factors that have characterized their evolutionary history. Human presence in Italian territory is deeply rooted in the past. Lithic artifacts produced by the genus* Homo *and remains of* Homo sapiens *are among the earliest to have been found on the continent, as shown by the lithic industry of Pirro Nord (between 1.3 and 1.6 Mya) and the dental remains of the "Grotta del Cavallo" (between 45 and 43 Kya). Genetic and genomic studies relating to existing and extinct human groups have shed light on the migrations from Europe, Africa and Asia that created the ancient layers of the genetic structure of today's Italian populations, especially before the Iron Age. The important role of isolation (genetic and cultural) in shaping genetic structure is clearly visible in the patterns of intra- and inter-population diversity observed among Italian ethno-linguistic minorities that settled on the peninsula and on the major islands until the 19th century. Finally, selective pressures have likely driven the distribution of originally adaptive variants and haplotypes that now confer protection or susceptibility to major diseases such as diabetes and cardiovascular disease (in northern Italy) and tuberculosis and leprosy (in the south). What emerges is a picture where the combined effects of migration, isolation and natural selection generated by the interplay of geography, environment and culture have shaped a complex pattern of human diversity that is unique in Europe and which goes hand in hand with today's rich animal and plant biodiversity. In a nutshell, scientific evidence and cultural heritage paint Italy as a place with extremely diverse environments where distant peoples have met since the deep past, bringing and sharing genes and ideas.*

Keywords - *Genomic history, Ethno-linguistic minorities, Isolation, Migration, Natural selection.*

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† *Our beloved friend Paolo Anagnostou passed away on October 26*[th]*. His quiet, sweet, diamantine memory will remain with us forever.*

Take me at least out of this terrible Italy,
where everything mocks and reproaches
and torments and eludes me!
Take me out of this land
*of impossible beauty*
(Henry James, "Roderick Hudson", 1875)

A bridge between peoples, genes and cultures

Looking at a map, it becomes immediately clear why the territory we now call Italy, since prehistoric times, has represented a bridge between peoples, genes and cultures. It lies in the centre of the Mediterranean Sea with a latitudinal extension of 1,300 km, flanked by the Balkans and Hellenic peninsula to the east, and Iberia to the west. North Africa and central Europe are found respectively to the south and north, while Sicily and Sardinia, its two major islands and the largest in the Mediterranean, overlook the Maghreb and Western Europe. Although the extension of the emerged lands is substantially reduced compared to that hypothesized for the Last Glacial Maximum (LGM, between 25 and 19.5 Kya) (Becker et al. 2015; see Figure 1), even today Italy appears to us as a wide and long strip of land with two large rafts; ideally it can be seen as an ancient vestige of a suspension bridge between central Europe and north Africa and the eastern and western coasts of the old continent.

There is a deep history of human presence in present-day Italian territory (see the section "Early human peopling"). The first occupation by the genus *Homo* is testified by the lithic industry of Pirro Nord (between 1.3 and 1.6 Mya), while the dental remains of the "Grotta del Cavallo" (between 45 and 43 Kya) are among the most ancient testimonies of *Homo sapiens* in Europe. Before the recent mass migrations that started in the mid-1970s, the last important migratory flow came from Albania in the last decades of the eighteenth century. Between these two extremes, Italy was inhabited by at least two other *Homo* species (*H. heidelbergensis* and *H. neanderthalensis*). In the last 45 Kya, there has been a complex stratification of migratory waves and arrivals from the Mediterranean, Middle East, continental Europe and North Africa. Even ancient peoples from the Pontic-Caspian steppe and Iranian Neolithic farmers seem to have left their signature on populations that have settled along the Italian peninsula, Sicily and Sardinia. While DNA is a very powerful tool for shedding light on the events leading to ancient peopling (as discussed in the section "Digging into the past through DNA"), present linguistic diversity mirrors some relatively recent migratory events (section "Languages and genes"), adding another important layer to the reconstruction of cultural and biological changes experienced by Italians' ancestors.

Its peculiar geographic placement is not the only feature which makes the Italian peninsula an area of extraordinary interest for the study of human diversity. The considerable latitudinal extension, one of the largest in Europe, is combined with a very irregular territory and highly diversified topography and geology, where the plains cover a fifth of the total area and the remainder is divided almost equally between mountains (above 700 and up to 4,800 meters above sea level) and hills. Consequently, Italy is characterized by a remarkable climatic diversity, ranging from hot semi-arid (in Apulia, Sicily and Sardinia) to ice-cap climates (at the highest points in the Alps). Given the interconnections between nature and culture (Berkes and Folke 2002; Maffi & Woodley 2007), this peculiar scenario creates the conditions for further human diversity. From a cultural point of view, climate, landscape and the natural environment may have a profound impact on aspects such as values, norms, livelihoods, knowledge and languages (Milton 1998; Posey 1999; Berkes 2008). Furthermore, the heterogeneity of environmental features has created the conditions for the establishment of diets and the spread of pathogens which, in turn, have triggered processes of natural selection in the northern and central-southern parts, providing another source of genetic diversity within and among populations (see the sections "Environment, genes and diseases" below).
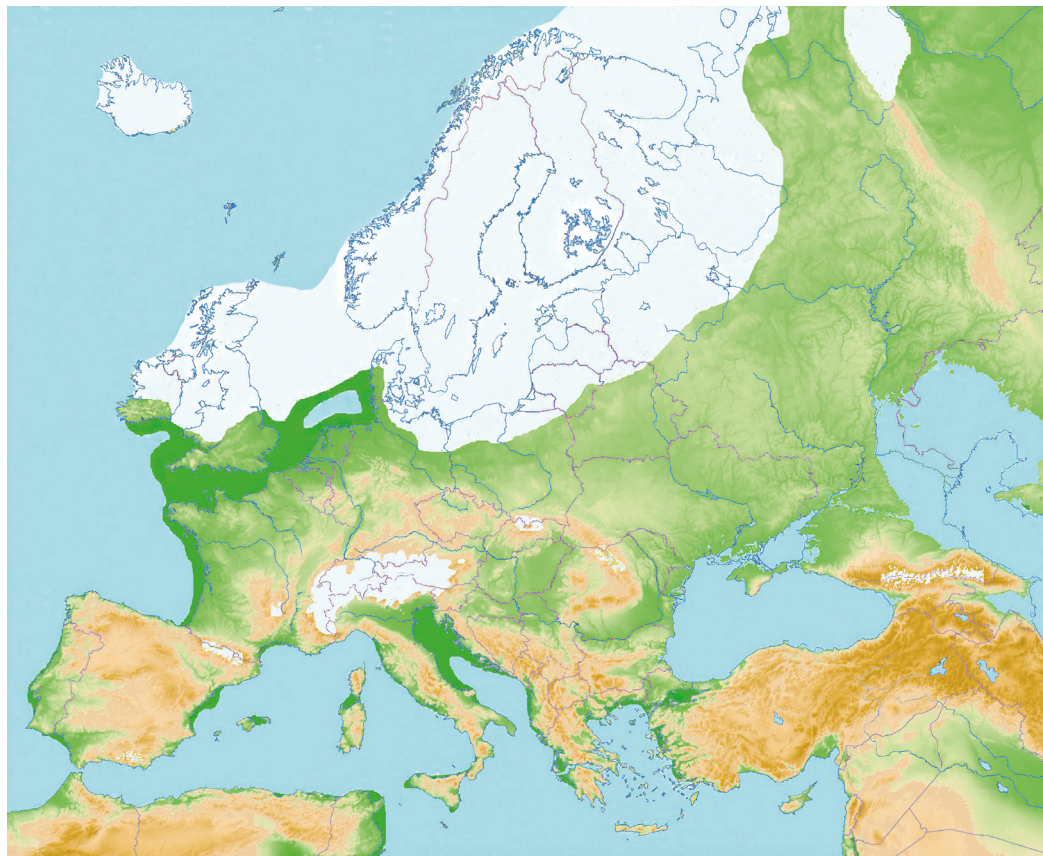
Fig. 1 - Map of the last glaciation in Europe, ~70,000-20,000 years BP (credit: Wikimedia Commons, user Ulamm; License CC-BY - https://doi.org/10.5880/SFB806.15).

In this paper, we present an overview of current knowledge regarding the structure of biological variation in Italian populations, including paleontological, genetic and linguistic evidence, with the aim of providing a synthetic view of human diversity and the proximate and remote causes that have shaped such variation from prehistory to current times.

Early human peopling

Italian territory represents a geographical area that contains evidence of the oldest human peopling in Western Europe. This event is attested by direct and indirect evidence dated between 1.8 Mya (Parés et al. 2006) and 1.2/0.8 Mya (Carbonell et al. 1995, 2008). It is difficult to assign a taxonomic identity to hominins associated with Lower Paleolithic Mode 1 (Oldowan) lithic industries due to the scarcity and fragmentary nature of their fossil skeletal remains (Bermúdez de Castro et al. 2011; Bermúdez de Castro et al. 2017).

The oldest evidence on the peninsula is exclusively archaeological (Borgia and Cristiani 2018) and concerns two sites: Pirro Nord in southern Italy and Cà Belvedere di Monte Poggiolo in North-Eastern Italy (Arzarello 2018). The former site is among the oldest in Europe with dating on a biochronological basis ranging between 1.6 and 1.3 Mya (Cheheb et al. 2019; López-García et al. 2015), while the latter is attributed to 850 Kya

(shortly after MIS22) through a combination of paleomagnetism and electron spin resonance (Muttoni et al. 2011).

The earliest occurrence in Italy of human fossils (see Alciati et al. 2005 and Buzi et al. 2021 for a detailed overview), starts after the Marine Isotope Stages (MIS) 16 and is represented by the partial shaft of a femur from the level supra-α of Venosa Notarchirico (Moncel et al. 2020), dated to 661-614 Kya (Pereira et al. 2015). It is worth mentioning that this fossil specimen represents the oldest human fossil in Europe, which is stratigraphically associated with bifaces of Mode 2 (Acheulean) technology (Moncel et al. 2020).

Slightly more recent is the tooth recovered from Level 3 of the Isernia la Pineta site that is dated at the end of MIS15 at about 583-561 Kya using 40Ar/39Ar measurements (Peretto et al. 2015). The Isernia La Pineta lithic assemblage is composed mainly of small to medium-sized flakes of local flint and limestone, with the absence of bifaces (Peretto et al. 2015). The coeval presence in Southern Italy of a Palaeolithic site with and without bifaces may reflect local and ecological diversity in subsistence strategies or a more complex peopling scenario corresponding to the arrival of bifaces in Europe from Africa through the Levant corridor after, or around, MIS 16 (Manzi et al. 2011; Moncel et al. 2020; Santagata et al. 2020; Buzi et al. 2021).

Subsequent to 500 Kya (MIS 13), Italy begins to show a more continuous peopling with an increase in sites containing human remains associated with bifaces distributed across the Peninsula. These fossil specimens share a number of morphological features with early representatives of *Homo heidelbergensis* in Europe, such as the mandibles from Mauer and Arago, and incipient Neanderthal features which indicate that a pattern of evolutionary continuity on the continent was already established during the Middle Pleistocene (Zanolli et al. 2018). The Italian specimens include cranio-dental remains from Visogliano dated via the ESR/U-series in a range between MIS 13 and MIS 10 (Falguères et al. 2008) and dental remains from Fontana Ranuccio dated via K/Ar to 460 Kya (MIS 12) (Muttoni et al. 2009).

Other coeval specimens, however, do not exhibit any Neanderthal apomorphic features in the preserved anatomical portions. Such is the case with the Ceprano calvarium, dated to MIS 11 between 430 and 385 Kya (Muttoni et al. 2009; Manzi et al. 2010; Nomade et al. 2011). However, it is possible that such morphological heterogeneity is an effect of the fragmentary nature of the recovered specimens and the loss of parts that could have been directly compared with each other. Alternatively, the archaic morphology of Ceprano and its affinity with European (Petralona and Arago 21) and African (Broken Hill 1 and Bodo) specimens, as indicated by some studies (Manzi et al. 2001; Mounier et al. 2011; Di Vincenzo et al. 2017), could indicate the persistence in Italy of representatives of an early European spread of Acheulean hunters and gatherers (Di Vincenzo et al. 2017), while in the more western regions of Europe, such as from the Sima de los Heusos site in the Sierra de Atapuerca, local populations were already beginning to evolve Neanderthal-like morphologies (Arsuaga et al. 2014).

It is likely, therefore, that in the early stages of the evolution of *Homo heidelbergensis* in Europe (roughly between MIS 13 and MIS 9), the Mediterranean, Iberian, Italian, and Balkan peninsular regions acted as ecological *refugia* from the cyclic expansion of glacial ice sheets further North. Isolation, demographic fragmentation and reduced gene flow combined with local adaptations and stochastic drift factors probably promoted a differentiation in competitive morphologies. In this regard, the accumulation of Neanderthal features during the Middle and Upper Pleistocene (Dean et al. 1998; Hublin, 2009) was probably not a phenomenon that occurred homogeneously in all European human populations, but rather it took place along a geographic, as well as chronological, gradient. Neanderthal features might have appeared early in western populations of *Homo heidelbergensis* (i.e., Sima de los Huesos sample) and then spread eastward, replacing the remaining plesiomorphic morphologies in Italy (e.g., Ceprano) and the Balkans (e.g., Petralona, Mala Balanica: Roksandic et al. 2018) (Fig. 2).
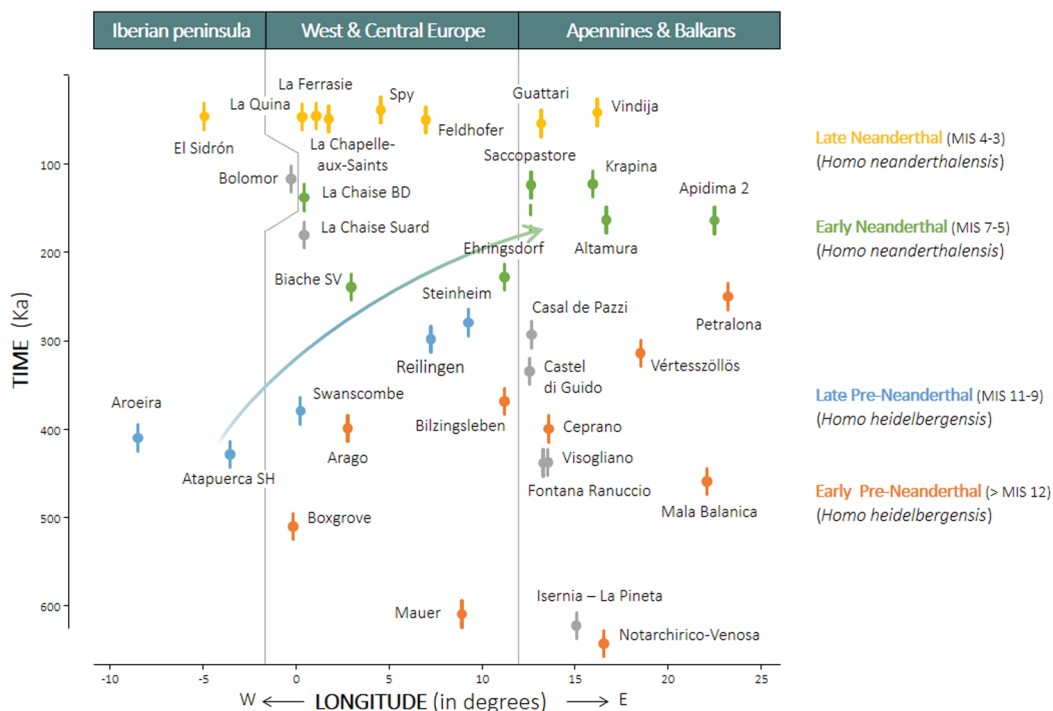
Fig. 2 – A "phylogeographic" scenario for the evolution of Homo heidelbergensis *and* Homo nean-
derthalensis *in Europe. Overall, a West-East progression of Neanderthal affinity over time is evident
(arrow), only partially in accordance with the so-called "accretion model", whose denominations are
reported in the right column in this graph (Dean et al. 1998) Specimens of uncertain or controversial
attribution are shown in gray (see color code used in the right column for the taxonomic status).*

Interestingly, in addition to human and archaeological remains, there is an ichnosite for the Middle Pleistocene in the Foresta locality at the foot of the now extinct volcano of Roccamonfina (South-Western Italy), which was active from some 650 Kya to 50 Kya. The site consists of several tracks (A-E) of human footprints dated to 345-350 Kya (cold stage MIS 10), (Panarello 2020; Panarello et al. 2020; Scaillet et al. 2008).

A set of very fragmentary human specimens dated between MIS 8 and MIS 6, such as those from the sites of Casal de'Pazzi, Ponte Mammolo, and Sedia del Diavolo in the Aniene River Valley within the Rome metropolitan area (Alciati et al. 2005; Buzi et al. 2021), marks the transition to the Middle Palaeolithic (Mode 3, or Mousterian). The specimens from these sites show more Neanderthal-like morphologies than those associated with the

Lower Palaeolithic of Mode 2 (e.g. Castel di Guido and La Polledrara di Cecanibbio in Latium and Grotta del Principe in Liguria in addition to those already considered) (Alciati et al. 2005).

Starting from the final Middle Pleistocene, Neanderthal evolution strongly characterizes the Peninsula's human fossil record. The two Neanderthal skulls from Saccopastore discovered in 1929 and 1935, respectively, come again from the Aniene Valley area, and they are associated with a few lithic tools of "archaic" Mousterian origin (Alciati et al. 2005). The Saccopastore skulls are dated to MIS 5e (approx. 125 kya) (Alciati et al. 2005), on the basis of stratigraphic surveys made at the time of discovery and before the site was completely destroyed by the urban expansion of the city of Rome. However, a date to MIS 7 (approx. 250 kya) has been proposed based on a re-examination

of the original documentary materials, faunas, sedimentological analyses and stratigraphic correlations with other areas of the Aniene Valley and the Roman countryside (Marra et al. 2015, 2017). Should this case be confirmed, those from Saccopastore would be the oldest European specimens to show a fully established Neanderthal morphology. The skulls of Saccopastore show morphological affinities with other early Neanderthals (sensu Dean et al. 1998), such as those from Krapina in Croatia dated to MIS5e (Rink et al. 1995).

Similarly archaic appears to be the Neanderthal skeleton discovered in 1993 within the Lamalunga karst complex near the town of Altamura in Apulia. U/Th dating performed on the karstic concretions in contact with the bones still embedded in the cave of discovery suggested an age for the specimen between 172 and 130 Kya (Lari et al. 2015). The arrangement of the bones does not suggest any accumulation due to water or animal transport from a long distance. Instead, it is compatible with the *in situ* death of the individual, who appears to be the only individual present within the cave, and apparently not associated with any lithic artefacts. Given the extraordinary conditions of preservation and the virtual absence of external contamination, it was possible to extract the mitochondrial DNA (mtDNA), which is compatible with Neanderthal (Lari et al. 2015). Altamura represents the oldest Italian human fossil from which it has been possible to extract endogenous DNA. An anatomical feature of the shoulder (the bisulcate/ventral pattern of the axillary border of the scapula) found among Neanderthals only in Altamura and in the Krapina sample suggests the existence of demographic contacts between Italy and the Balkan regions across a vast transit plain during glacial peaks and today completely occupied by the Adriatic Sea (Di Vincenzo et al. 2019).

Starting from MIS 4 (about 70 Kya), evidence for the presence of the so-called "classic" or Würmian morphotype of the species *Homo neanderthalensis* becomes abundant. Archaeological sites linked to the activities of Mousterian hunters and gatherers are scattered throughout mainland Italy, and include about twenty sites that have also yielded skeletal remains (Alciati et al.

2005; Buzi et al. 2021). These remains are mostly cranio-mandibular fragments (e.g., Archi and Nicotera in Calabria, Scario in Campania, Fate in Liguria, Monte Fenera in Piedmont, Spinadesco in Lombardy), postcranial fragments (e.g., Bisceglie in Apulia, Buca del Tasso in Tuscany, Calascio in Abruzzo) or more frequently isolated teeth. The most complete remains are those from the Circeo promontory, South of Rome. Along its South-Western cliff, about 30 natural caves open up to the sea. When the coastline was more distant from the present cliffs during glacial phases, many of them were frequented by humans, as evidenced by the presence of Middle and Upper Paleolithic archaeological levels (Manzi 2004). Only from three caves, namely Guattari, Fossellone and Breuil, come several Neanderthal human remains recovered from 1939 to 2021 including the almost complete skull of Guattari 1. This skull discovered in 1939 is linked to the hypothesis of ritual cannibalism formulated by Blanc soon after the discovery and later rejected based on extensive analysis of the damage on the skull, which is more plausibly attributable to scavenging by hyenas (Alciati et al. 2005).

Unfortunately, paleogenetic data on Italian Neanderthals dated between MIS 4 and MIS 3 is currently very scarce. Robust data comes only from the deciduous canine tooth from Riparo Broion (North-Eastern Italy), dated to 48 Kya, which has been shown to carry Neanderthal-like mtDNA (Romandini et al. 2020). The attribution to *Homo neanderthalensis* of some human remains from Monti Lessini (including a jaw fragment from the Riparo Mezzena), whose DNA had previously been used for studies of Neanderthal pigmentation (Lalueza-Fox et al. 2007) and hybridization with anatomically modern humans (Condemi et al. 2013), has been questioned by new direct radiocarbon dating and genetic analyses (Talamo et al. 2016).

More recently than 40 Kya, no evidence of Mousterian industries can be found throughout Italy and continental Europe (Higham et al. 2014). The causes of the apparent abrupt end of the Mousterian and demise of Neanderthals are still debated. They could be related to ecological factors of competitive exclusion with

anatomically modern humans, whose entry into Europe is dated between 56.8 Kya and 51.7 Kya (Slimak et al. 2022) or, less likely, to environmental phenomena due to rapid climatic deterioration on the entire European continent resulting from the explosion of the Campi Flegrei volcano that occurred 39 Kya (Black et al. 2015).

More stable settlements of *Homo sapiens* populations in Europe have been dated between 45 Kya and 43 Kya, figures obtained from five isolated dental remains from the Bacho Kiro site in Bulgaria (Hublin et al. 2020) and from three Italian sites respectively, Grotta Cavallo in Apulia (Benazzi et al. 2011; Moroni et al. 2018), Riparo Bombrini in Liguria and Grotta di Fumane in Veneto (Benazzi et al. 2015). Bombrini and Fumane 2 (both deciduous incisors) are archaeologically associated with the Upper Palaeolithic Protoaurignacian, which is a marker of the presence of *Homo sapiens*, while the two deciduous molars from Grotta Cavallo are associated with the Uluzzian. This latter is a so called "transitional" techno-complex (as well as Châtelperronian, Szeletian, and Lincombian-Ranisian-Jerzmanowician found elsewhere in Europe), distributed in peninsular Italy and in Greece (Hublin 2015; Moroni et al. 2018). This association in Grotta Cavallo, strongly supports the hypothesis that the Uluzzian is a lithic culture of the earliest *Homo sapiens* that arrived in South-Eastern Europe after 45 Kya (Benazzi et al. 2011). This is contrary to an alternative hypothesis that suggests this culture was a technological achievement that the last Neanderthals had acquired independently or through acculturation (imitative) processes (Hublin 2015).

A number of mtDNA sequences from the Fumane 2 tooth place the specimen at the base of the spread in Eurasia of the R haplogroup, close to the 45 Kya specimen from Ust'-Ishim in Western Siberia and other fossils from pre-Neolithic Eurasian populations (Benazzi et al. 2015).

The spread of Upper Palaeolithic human populations, particularly Epigravettian, occurred throughout Italy, including the islands of Sicily and Sardinia. Genetic data on the mtDNA of these populations are available from several sites that include (from North to South)

those of Villabruna and Riparo Tagliente in Veneto, Arene Candide in Liguria, Continenza in Abruzzo, Paglicci and Ostuni in Puglia, and San Teodoro in Sicily. Of this heterogeneous group of Palaeolithics for which there is genetic information available, those from Paglicci and Ostuni (dated to 33 Kya and 28 Kya, respectively) are associated with Gravettian and Early Epigravettian industries and show genetic affinities with Western European hunter-gatherers, the so-called "Vestonice cluster" (Fu et al. 2016; Aneli et al. 2021). Following the expansion of Alpine ice-sheets during the LGM, these populations were replaced by late Epigravettian populations with Eastern European affinities, which formed the basis of the post-glacial European genetic landscape (Fu al. 2016; Aneli et al. 2021; Modi et al. 2021). This event is the so-called "Villabruna replacement", whose oldest evidence is represented by the individual of Riparo Tagliente 2 dated at approximately 17 kya (Bortolini et al. 2021).

During the Neolithic, the Italian peninsula served as a bridge to Europe for the spread of populations of early European farmers from the regions of Anatolia. The spread took place through Apulia (where the first traces of agricultural practices in Italy are found), Northward along the Adriatic coast, and in addition through eastern Sicily going up the Tyrrhenian coast (Boattini et al. 2013; Aneli et al. 2021). In the Eneolithic period, the Alps were particularly important due to its supply of copper and other raw materials. In this period, we find metallurgical cultures of Remedello and Rinaldone in Northern and Central Italy, and Gaudo in the South (Aneli et al. 2021). This is the context of the 1991 discovery of the natural mummy of "Ötzi" at the foot of the Similaun Glacier (3213 m above sea level), on the border between Italy and Austria. He carried a copper axe of the Remedello type, which was produced in Northern Italy using minerals from Tuscany (Keller et al. 2012; Artioli et al. 2017; Aneli et al. 2021). Genetic analyses have revealed that Ötzi is related to populations living in Central and Southern Italy, particularly geographically isolated populations such as the Corsicans and

Sardinians (Keller et al. 2012). So, he was part of the migration of early European farmers who migrated from Anatolia to Europe, replacing the hunter-gatherers of earlier Europe. Subsequent Bronze Age migrations to Italy of nomadic populations from the Ponto-Caspian steppes as well as other farmers from the Middle East (Marcus et al. 2020; Fernandes et al. 2020) strongly contributed to defining the genetic profile of present-day Italy.

Digging into the past through DNA

The developments in DNA sequencing over the past two decades, with the introduction of next generation techniques, have revolutionized numerous fields of biological research. Regarding the study of human evolution, the production of an unprecedented amount of genome-wide data relating to existing and extinct human groups is providing important new insights into our past. This also applies to the reconstruction of the ancient population of Italy, as will be described later and summarized in Figure 3.

To describe the most significant results, we can start from some apparently simple evidence: the genetic variation among individuals living in the Italian peninsula, Sicily and Sardinia is one of the highest among those observed in European countries. (Capocasa et al. 2014; Fiorito et al. 2016; Ralph and Coop 2013; Raveane et al. 2019). This can be observed even when excluding Sardinian groups, which have been characterised by a different demographic history and by some degree of isolation. The underlying cause could be linked to a combination of the different impact that demographic and mixing events have had on human groups over the millennia and the lower degree of migration along the "Boot", due to the latitudinal extension of the peninsula (Diamond 2003).

For its part, the Mediterranean Sea acted more like a corridor than a barrier, as the observation of a "Mediterranean Continuum" shared between Italy, the Balkans, the Caucasus, the Middle East and North Africa suggests (Sazzini et al. 2016; Sarno et al. 2017). At least in the south

and in Sicily, some of the genetic influences from populations in North Africa and the Middle East are probably traceable to the Arab kingdoms in Southern Europe, although a detailed picture of their chronology and geographical distribution is still lacking (Botigue et al. 2013; Fiorito et al. 2016; Raveane et al. 2019, 2022; Sarno et al. 2017; Sazzini et al. 2016). However, the analysis of ancient DNA has recently shown that ancestry linked to the Middle East and the Levant was already present in Italy as early as the Roman imperial era, because of the expansion of Roman influence. (Antonio et al. 2019, 2022; Moots et al. 2022). More ancient African or Levantine contributions were also detectable in genetic material extracted from individuals associated to "Phoenician" culture, especially in Sicily and Sardinia (Fernandes et al. 2020) and also in Etruscans (Posth et al. 2021). An earlier contribution from North Africa and the Middle East has been identified in the Chalcolithic and Bronze Age groups, although caution is required in this regard due to the relatively small number of individuals analyzed (Fernandes et al. 2020; Marcus et al. 2020). In Europe, the overall pattern of genetic variation from the Iron Age (~3,000 BC) to Imperial Rome/Antiquity is similar to that generally assessed in present-day Europeans, suggesting that the last 3,000 years contributed less to the formation of genetic structure, a hypothesis supported by statistical inferences on modern data (Busby et al. 2015; Antonio et al. 2022). However, it remains unclear whether this holds for the whole continent or whether some areas had a different demographic history, as suggested by Iron Age Etruscan and Daunian genomes (Posth et al. 2021; Aneli et al. 2022).

On the other hand, a strong discontinuity has been observed both in Europe and in Italy during the Bronze Age and the Neolithic. In fact, around 5,000 years ago, groups of semi-nomadic pastoralists, associated with the so-called Yamna culture, expanded from the Pontic-Caspian Steppe area in Central and Southern-East Europe, reaching the British Isles and the Atlantic shores not later than 4,000 years ago. These Bronze age people have been described as carrying two different genetic
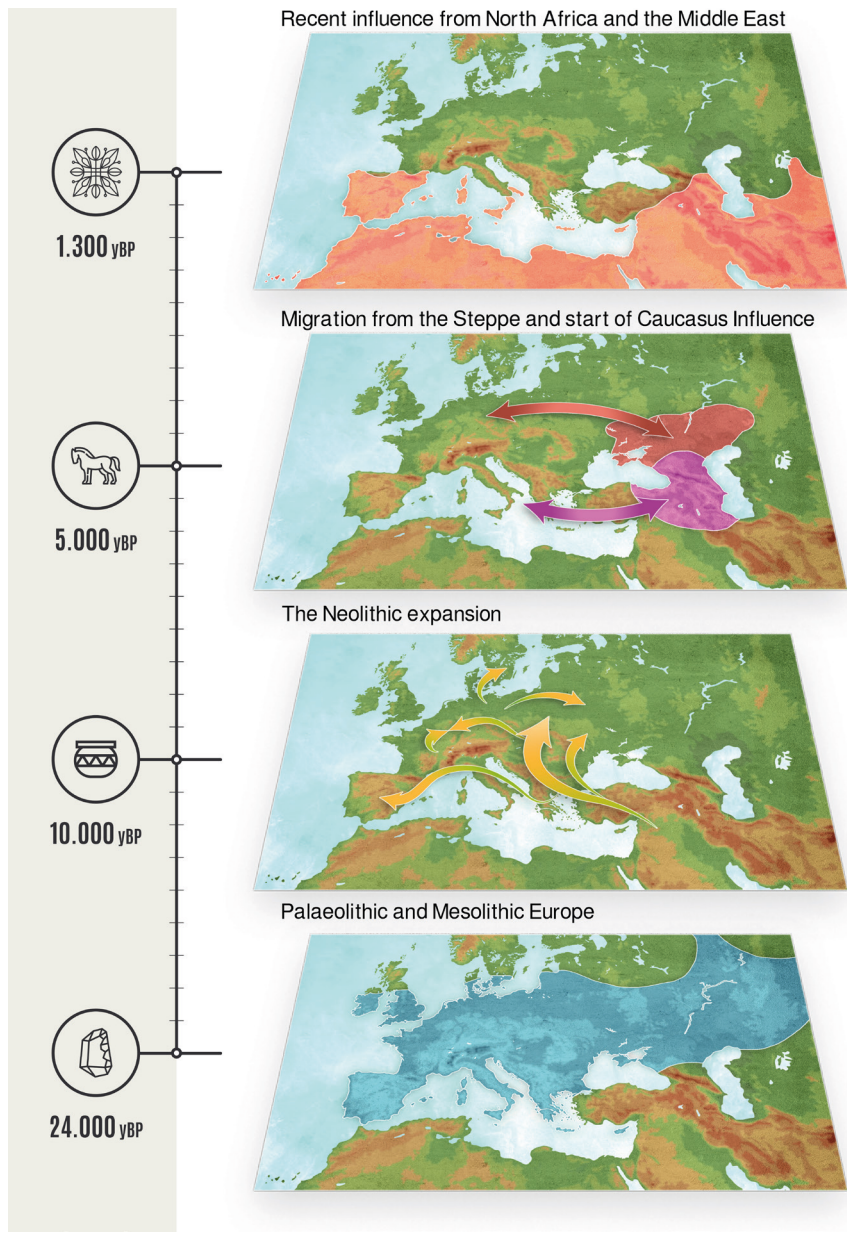
Fig. 3 - An overview of the main pre-historical chapters of Italian genome variation. From top to bottom: The influence of the Middle East and North Africa in medieval times (note the small pink areas in southern and insular Italy); the massive migration from the steppe (orange area represent a possible start of migration) and the beginning of ancient gene flow from the East (Caucasus hunter-gatherer component, light blue); the main routes of Neolithic expansion from Anatolia as indicated by archaelogical remains; Mesolithic and Palaeolithic European complex population dynamics (area where Palaeolithic and Mesolithic artifacts were found). Redrawn from https://francescomontin-aro.github.io/projects/3_project/, credits: Alessandro Corlianò.

ancestries: one similar to the typical hunter-gatherers from Eastern Europe, and the other related to hunter-gatherers from the Caucasus or Neolithic individuals from Iran (Lazaridis et al. 2016). This dispersal, which is often associated with the introduction of Indo-European languages and technological innovations, had a strong influence in Europe, and its legacy is still clearly recognizable in virtually every present-day individual of European ancestry. In Peninsular Italy, the earliest signature of the so-called "Steppe-Ancestry" has been reported in a few samples from Remedello and Grotta del Broion dated at 3.9 and 3.8 Kya, in Central Italy approx 3.4 Kya (Olalde et al. 2022), while it has already been reported in Sicily ~4.4 Kya, possibly arriving from the Iberian peninsula (Marcus et al. 2020). On the other hand, no evidence of Steppe ancestry has been observed before 3 kya in Sardinia (Marcus et al. 2020). Unfortunately, the lack of ancient samples from the southern part of the Italian peninsula during the Bronze Age prevents a full characterisation of the demographic processes and movements that allowed the expansion of the Steppe influence. In this context, it is important to stress that a non-negligible proportion of this ancestry has been observed in Mycenaean and in the Middle Bronze Age individuals from Greece. In Italy, the distribution of this ancestry, today, follows a North South cline, with proportions ranging from ~25% to < 10% (Haak et al. 2015; Raveane et al. 2022). These observations open up the possibility that it could have arrived in the Peninsula at least in part by the sea, rather than through a spread exclusively from the north. Evaluating the exact route of this ancestry by analysing several individuals from multiple Peninsular areas will make it possible to obtain a clearer picture regarding the spread of the Steppe ancestry and, combined with linguistic and archaeological data, will probably help shed light on the expansion of Indo-European languages.

The Steppe ancestry, albeit in different proportions, added to a genetic substrate that had been mostly shaped in the Neolithic. Several studies of DNA extracted from human remains associated with Neolithic culture throughout Europe have revealed a remarkable homogeneity and a strong genetic affinity with Anatolian samples dated no later than 9,000 years ago, revealing an important role of the demic diffusion of farming practices and pottery technologies (Allentoft et al. 2015; Haak et al. 2015; Skoglund et al. 2012). However, incoming groups of farmers did not completely replace the already residing hunter-gatherers. In fact, after an initial isolation, there was a "hunter-gatherer resurgence", as an increasing proportion of the so-called Villabruna (from a site close to Belluno in the Veneto region) ancestry starting from the (Middle, Late) Neolithic has been observed in many regions, including Italy (Haak et al. 2015; Fu et al. 2016). Archaeological records suggest that the Neolithic diffusion followed at least two routes, namely the "Danubian" and the "Mediterranean", although studies are continuing to add further complexity to this simplified view (Shennan et al. 2013). From a genetic point of view, recent analyses have revealed the existence of two main geographic Neolithic clusters, one including mostly individuals from the Western and the other from the Eastern part of the continent, with the latter showing a higher degree of genetic diversity. Interestingly, individuals from Sardinia and Western Europe differ from all the other Neolithic and Chalcolithic samples from Italy, confirming that the island underwent a different demographic scenario already in prehistory (Saupe et al. 2021; Marcus et al. 2020). To date, the most parsimonious interpretation of this genetic separation comes from the observation that the two groups are characterised by a different proportion of Villabruna ancestry, suggesting that admixture between farmers and foragers occurred differently depending on the geographic area. The refining of DNA extraction methods and the forthcoming increase in sample size will help better clarify the possible differences in the diffusion routes detected by archaeologists and will make it possible to test and compare expansion models.

The groups of hunter-gatherers that mixed with Neolithic farmers were not direct descendants of the first people that inhabited Europe and Italy. In fact, they arrived on the continent much later, as the strong genetic differences between foragers before and after 20,000 years

ago suggest (Skoglund et al. 2012). In detail, the groups identified as "Villabruna" are closer to Middle-Eastern populations when compared with modern Near-East individuals, suggesting an expansion from the East that might have occurred after the LGM. So far, the most ancient individuals showing Villabruna ancestry have been discovered in the Riparo Tagliente site (Veneto, Northern Italy) which was dated at approximately 17 kya (Bortolini et al. 2021). It might be possible that these foragers arrived on the Italian peninsula through a "refugium" area in the Balkans or Anatolia, and their arrival, following the Slovenian corridor, is chronologically in line with the emergence of cultural transitions, such as those between Solutrean and Magdalenian in Western Europe or between Early and Late Epigravettian material culture in a wide European area (Bortolini et al. 2021). Alternatively, it might be possible that individuals related to Riparo Tagliente were inhabiting the Italian peninsula during the LGM, and that there was a connected network of refugia in Southern Europe and Western Eurasia; this hypothesis was proposed following the discovery of an individual in Grotta Paglicci (Apulia, Southern Italy) dated at 18.5 kya which was found to have an mtDNA haplogroup within the Villabruna cluster variability (Fu et al. 2016). In modern Italians, the proportion of Villabruna ancestry is on average 8%, with a higher proportion in Sardinia, possibly due to the lower impact of some of the later demographic changes described above. Although sharing a common ancestor with all the European palaeolithic foragers discovered to date, individuals older than 17 Kya in Italy are genetically different from Villabruna and so far no evidence of admixture has been shown, although a larger sample size from different areas is needed to shed more light on the palaeolithic and mesolithic admixture of Italy (Fu et al. 2016).

Modern Italians, as virtually all non-African populations (but see also Chen et al. 2019), have a small portion of their genome that derives from admixture with Neanderthals, which is thought to have occurred approximately 50,000 years ago, possibly soon after the out-of-Africa process (Green et al. 2010). Although many DNA fragments of Neanderthal derivation were quickly purged by negative selection, some were neutral or conferred advantages in the new environment faced by *H. sapiens* populations, and today contribute to the genetic variability that underlies the variation of complex traits in Eurasia (Racimo et al. 2015).

Given the way genetic variation is structured in Italy, one would expect the archaic contribution to vary between individuals from different areas, mainly due to an uneven distribution of Neanderthal ancestry already in place over 30 Kya (Lazaridis et al. 2016). A first assessment of Neanderthal ancestry in Italians suggested that Southern Italians have significantly less Neanderthal ancestry than other Italian groups. However, this observation should be interpreted with caution, because of the possible confounding effect of an undetected and geographically different African contribution in the tested samples. The release of a second high coverage Neanderthal genome in 2017 will hopefully provide a clearer picture of Neanderthal ancestry in Europe and Italy (Prufer et al. 2017).

Languages and genes

To give evolutionary and historical significance to the genetic patterns of intra and inter-population diversity observed in human populations, it is essential to consider social and cultural aspects. Among these, language is undoubtedly the one whose variation can most easily be related to that of genetic material due to the characteristics it shares with DNA. Both are built on letters (nucleotides) and words (codons) that can be arranged to create sentences and paragraphs (pathways and networks), whose meaning can be deciphered by a specific code. Exploiting their structural analogies, languages and DNA can be analyzed in parallel to assess the extent to which linguistic diversity has been shaped by the demographic processes underlying genetic variation and to make inferences about the socio-cultural history of populations (Cavalli Sforza et al. 1988). As is to be expected, given the different dynamics by

which linguistic change can occur in human populations, studies conducted in distinct geographical areas have produced different results (Chen et al. 1995; Belle and Barbujani 2007; Matsumae et al. 2021). For example, correlation signals have been detected at global level and continental level in Europe and Africa, whereas they are lacking for Native Americans and Asians (see Belle and Barbujani 2007). Obviously the results can also be influenced by the transmission and evolution modalities of the analyzed loci. This is exemplified by investigations among European populations at continental level, which have shown a correlation between linguistic and genetic variation which is strong and significant regarding autosomes but low for Y-chromosome and substantially missing for mitochondrial diversity (Sokal et al. 1988; Sajantila et al. 1995; Rosser et al. 2000; Longobardi et al. 2015).

Focusing on Italy, there are two studies based on polymorphisms at protein level which should be mentioned despite the fact more than three decades have passed since their publication. Piazza et al. (1988; see also Piazza 1991) highlighted a parallel between the fragmentation of the spatial distribution of the genetic diversity of Italian populations with that of the languages spoken in pre-Roman times (at the end of the sixth century BC), suggesting a sort of mirroring between the diversity of local cultures already in place at the beginning of the Iron Age (ninth-eighth century BC) and the current genetic structure. Barbujani and Sokal (1991) observed a closer relationship of genetic distances with linguistic rather than geographic factors, with exceptions being represented by the polymorphisms that were subject to malarial selection. They also noticed that zones of sharp genetic variation correspond to physical barriers to gene flow and boundaries between dialect families.

Unfortunately, the above-mentioned studies could not answer a simple question that arises from an important linguistic feature of our country: diversity is greater than in other European countries, even in those with comparable demographic size and geographical extension. Thirty five different languages are spoken in Italy, compared to 27

in Germany, 23 in France, 15 in Spain and 13 in the United Kingdom (data from *ethnologist.com* SIL International) In quantitative terms, if we use the linguistic diversity index to measure the probability of randomly extracting two individuals of different mother tongue in the same group (analogous of gene diversity), we obtain a value of 47%, while other European countries do not exceed 38% (in Germany) Importantly, Italian cultural richness is testified also by the internationally recognized quantity and diversification of cultural heritage. Italy is the country with the most World Heritage sites, landmarks or areas designated by the United Nations Educational, Scientific and Cultural Organization (UNESCO, data 2022; *https://whc.unesco.org/en/list/*) for their particular cultural interest: there are 53 distributed throughout the Italian territory, followed by 48 in Germany and 45 in Spain (Fig. 4). This is the largest concentration in the world also in relative terms, reaching 16.3 sites per 100,000 km2, compared to 11.4 in the United Kingdom and 10.6 in Germany (UNESCO, 2014 date). The areas of particular value, subject to the protection constraint of the Code of Cultural Heritage and Landscape, cover almost half of the national territory (46.9%) and the properties registered by the Ministry of Cultural Heritage and Activities and Tourism (Ministry of Culture since 2021) - such as archaeological, architectural and museum sites - exceed 100,000 units (more than 33 every 100 km2*; https://www.istat.it/it/files//2014/06/09_Pascape-patrimonio-culturale-Bes2014.pdf).* There is also evidence regarding the link between nature and cultural diversity. The famous variety of Italian foods has its roots both in the extraordinary variety of living forms and in the legacy of the numerous populations that met in the country. The biodiversity present on Italian territory is in fact considered to be among the richest in the Mediterranean basin and in Europe, with an unprecedented number of endemics in Europe (Audisio 2013). The great variety of edible mushrooms, plants and animals that have evolved in fertile and different microclimates represents the starting point for the vast assortment of Italian culinary traditions.
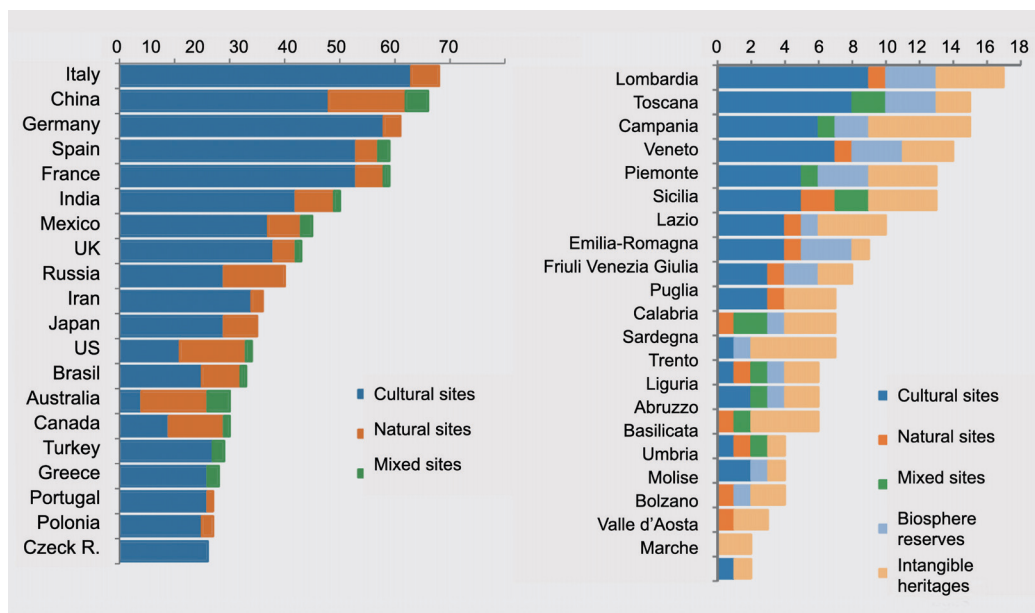
Fig. 4 - Items registered in the Unesco World Heritage List by category and country (top 20 countries by number of registered properties), year 2021, absolute values (on the left) Items registered in the Unesco World Heritage List by category and other elements recognized by UNESCO by region, year 2021, absolute values (on the right) Source: Istat, Elaboration on Unesco and Ministry of Culture data.

Ultimately, Italy can be seen as a sort of cultural microcosm that embraces an extraordinary heritage which includes material cultures, archaeological sites, languages, monuments and traditions that are reflected in everyday life. These testimonies, which range from prehistoric times (e.g., that found in the Pirro Nord site) to the nineteenth century (i.e., the last migrations by ethno-linguistic minorities), are the legacy of different peoples, some of which have also left genetic signatures such as the Etruscans, Romans, Greeks and Arabs. Obviously there has not been just a simple stratification of cultural expressions because processes of mutual mixing and contamination have created further complexity over time. The migrations to the country that occurred after the Second World War have overlapped with this background.

For all the reasons mentioned above, when looking at biodiversity from a holistic perspective it is worth asking an initial question: is the remarkable linguistic diversity observed in Italy mirrored by a comparably high genetic diversity? As anticipated in the chapter "Digging into the past through DNA", the introduction of genome-wide approaches has shed light on the remarkable genetic diversity of Italian populations, providing important insights into colonization and migration events. More in detail, Fiorito et al. (2016) argued that there was great genetic diversity in the Italian population, mainly based on the evidence that the genetic distance (in terms of Fst index) between groups from the northern and southern part of the country is comparable or even greater than that observed between individuals living in different European countries. The authors suggested that this pattern could be due to a combination of ancient and recent events: the persistence of heterogeneous ancestries of populations from the main Italian macro-areas combined with the continuous flow of ancient genes and remote isolation in recent times. Raveane et al. (2019) used a different approach but found a similar pattern to Fiorito et al. (2016). They observed that

the degree of variation between the genetic clusters in Italy (Northern Italy and Southern Italy) was significantly higher than in any other country examined and was comparable with the estimates obtained at continental level.

Although the lack of recombination makes unilinear genetic systems less informative than autosomal loci, they can however help shed light on the effects of cultural and social factors on genetic structure (Seielstad et al. 1999). A previous study we carried out (Destro Bisol and Anagnostou, unpublished data; Capocasa et al. 2014) was designed to explore the relationships between language and genes among Italian populations, using a larger dataset (a total of 46 Italian populations) than the genomic studies cited above. A strong signal was provided by mtDNA, whose diversity among Italian populations was found to be even greater than observed throughout the whole of Europe (Amova Fst 0.38% vs 0.33%). This is particularly significant if we consider the fact that genetic differences between groups tend to increase as a function of their geographical distance (which decreases the possibility of meeting and, therefore, of mixing) and that on average the Italian populations are much less distant than the European ones. However, the correlation between genetic and geographic distances seems to have a greater impact on Y chromosome polymorphisms (Amova Fst 3.19% vs 8.95%) (Capocasa et al. 2014; unpublished data).

Once the initial question has been answered using data from different genetic loci, we can try to answer a more specific one: what is the contribution to the current genetic diversity of the alloglot populations that arrived in our country before the start of the massive migratory flows in the 1960s? This question originates from the fact that in addition to Italian, a neo-Latin language spoken by about 55 million people, there are linguistic minorities of German, Occitan, French and Slavic derivation in the north, Croatian in the centre, and then again Greek and Albanian in the south and on the islands (Toso 2008). These groups amount to about 3 million people and are an important part of the aforementioned primacy of Italian linguistic diversity in Europe. Including

them in the study allowed us to go beyond the search for parallels of genetic and linguistic landscapes, by exploring the occurrence of divergences which, for example, may arise from barriers to admixture that may be generated by linguistic barriers. With this more inclusive sampling scheme, we obtained increased diversity estimates (Amova Fst for mtDNA from 0.38% to 1.89%; Y chromosome from 3.19 to 6.89%) that were higher than or close to those obtained in a wide European dataset also including ethno-linguistic minorities (mtDNA from 0.33% to 1.52%; Y chromosome 8.95% from to 10.60%).

How can we interpret all of this? Zoologists and botanists have extensively documented the fact that the animal and plant biodiversity of our territory is among the largest in the Mediterranean and in Europe. This is largely linked to the geographical location and longitudinal extension of Italy described at the beginning of this paper. It is plausible that this same characteristic also conditioned the ancient processes of peopling described in the chapter "Digging into the past through DNA" (see also Boattini et al. 2013), and more recent phenomena (from the Middle Ages onwards), making our territory a zone of convergence, and also of mixing, between migratory flows from different parts of Europe. However, by including ethno-linguistic minorities in the study, we were able to depict a more complex scenario, where local isolation phenomena have determined a notable differentiation of migrant communities from both their original groups and the neighbouring populations. In fact, some of these minorities stand out genetically due to the combination of linguistic (and, more in general, cultural) isolation from the surrounding populations and physical barriers (often mountainous environments) which have acted as a further barrier to gene flow. This is, for example, the case of the German-speaking groups of Sappada and Sauris in the Eastern Alps, whose signature of isolation are among the strongest observed in Europe, a finding confirmed by analyses at genomic level (Destro Bisol and Capocasa 2016; Anagnostou et al. 2017).

Another benefit of studying linguistic minorities concerns the search for possible parallels or divergences between genetic and cultural patterns.

Tab 1 - Main syntactic and lexical features of languages spoken in the linguistic islands of the eastern Alps.

| PLACE	SYNTAX	LEXICON
Velo Veronese (Cimbrians)	Independent from the original Germanic model, recreated on an Italian or Veneto-Trentino basis	Numerous casts or novel borrowings adapted to the Cimbrian pronunciation and introduced to describe objects, situations or expressions absent at the time of the first settlers.
Timau	Evident influences of the Friulian or Italian novel model	Conservative but with casts or novel borrowings, which refer in particular to the plant, animal world or economic activities
Sappada	Preservation of the original German syntactic structure, with some tenses lacking	A low percentage of novel loans
Sauris	In principle, in line with the Germanic model, with a strong degree of archaicity associated with the maintenance of typical metaphonic elements of the Bavarian dialects.	Numerous loans, casts and neologisms on a neo-Latin basis, born out of the need to describe objects or socio-economic situations unknown at the time of colonization.
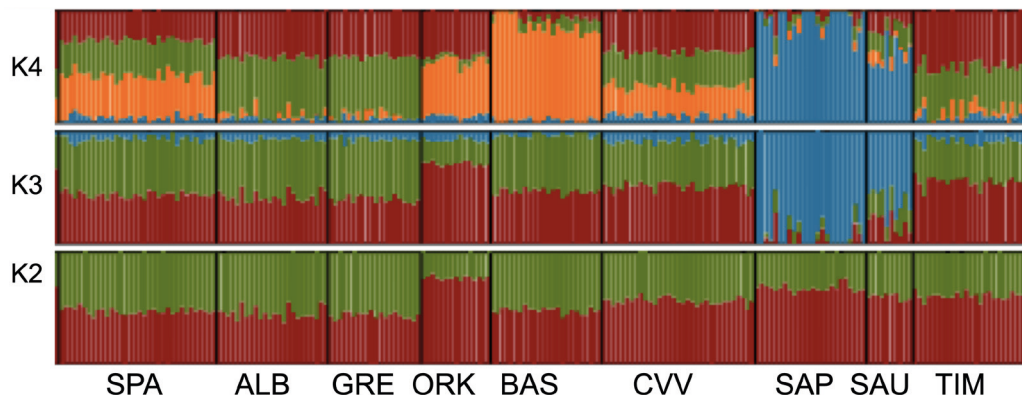
Fig. 5 - Maximum likelihood estimation of individual ancestries for K= 2-4 (see Anagnostou et al. 2019 for further details) Abbreviations: SPA, Spain; ALB, Albania; GRE, Greece; ORK, Orkney islands; CVV, Cimbrians, Velo Veronese; SAP, Sappada; SAU, Sauris; TIM, Timau. The term "K" indicates the number of clusters (individual ancestries) assumed in each estimation. Each bar represents an individual sample and colors code membership of each individual with the assigned cluster.

In our case, the question to ask is: are there analogies between the genetic and linguistic differences that ethno-linguistic minorities have accumulated from their parents' populations? It should be noted that the widely used approach of estimating the correlations between genetic and linguistic distances could not be applied in the case of ethno-linguistic minorities due to the inflation of the former parameter in small isolated populations. However, we were able to compare the maximum likelihood estimates of individual ancestries of the linguistic islands of the eastern Italian Alps (Sauris, Sappada,

Timau and Cimbri) with their linguistic characteristics (Anagnostou et al. 2017, 2019; Caria 2019). Notably, thanks to the sampling scheme adopted for the genetic study (grandfather rule, only unrelated individuals with father and grandfather born in the village were investigated), the possible effects of recent admixture were minimized.

Among Cimbrians, who were subject to the most pronounced linguistic replacement, the proportion and heterogeneity of ancestral components across the different numbers of clusters (K) observed is similar to north Italy and other

European groups (Tab. 1, Fig. 5). The likely ancestral component (blue) is well represented in Sauris (at K = 3 and 4), where there seems to be a greater persistence of archaic elements, and in Sappada where the original German syntactic structure is well preserved. Also worthy of note is the high heterogeneity of intra-group admixture estimates found in Sauris, where the linguistic continuity with the founder group is associated with a noticeable introgression of neo-latin linguistic elements. Timau, where the conservation of ancient linguistic features was found to be lower than Sauris and Sappada, shows a pattern close to north Italy and other European groups up to K=3 with a lower heterogeneity of intra-group admixture estimates than in the other two alloglot groups and less maintenance of the original ancestral component (visible only at K=5). Although it is difficult to infer cause-and-effect relationships between linguistic diversity and genetic structure (also due to the coexistence of linguistic and cultural geographical barriers), it is interesting to note that we were able to observe some interesting parallels. The most significant is that languages and genomes appear to have retained archaic or ancestral characteristics along with features resulting from relatively recent introgression events, despite the diminishing effect of drift on genetic diversity.

Environment, genes and diseases

The availability of genome-wide data is also having an important impact on our understanding of the effects of selective pressures on the genome and their possible significance for the health of extant groups. In this perspective, the latitudinal cline of genetic variation observable for the Italian population, which tightly mirrors the gradient along which the population is geographically distributed, merits further investigation not only in the light of the multitude of prehistoric and historical demographic processes that shaped the heterogeneous gene pool of the Italians' ancestors, but also by considering the tangled mosaic of bioclimatic

and ecological settings that characterizes the peninsula and the neighbouring islands (Rivas-Martínez et al. 2006). Since prehistoric times, the different human groups that have inhabited the geographical area, which is nowadays ascribable to the Italian territory, have indeed had to cope with diversified environmental conditions. Accordingly, it can be hypothesized that appreciably different selective pressures have played a role in shaping the genetic and biological profiles of the ancient populations that occupied the most ecologically diverging regions of this multifaceted territory, such as those belonging to the temperate bioclimatic zones and those instead characterized by a Mediterranean climate. This has arguably led to the evolution and/or maintenance of different biological adaptations, whose genetic determinants further contribute to making the Italians' gene pool very heterogeneous.

Parolo and colleagues (2015) conducted one of the first studies that provided genomic evidence regarding a diversified action of natural selection on the different human groups distributed along the peninsula. In detail, this work implemented a gene-enrichment approach to identify the main biological functions associated with the genetic loci that correlate with the latitudinal gradient of Italian variation. In doing so, the authors pointed to variants involved in immune functions as the most differentiated in terms of allele frequencies, in addition to others (e.g. *LCT*, *HERC2/OCA2*, *HLA*; see Table 2 for abbreviations, function and possible adaptive role) that have already been demonstrated to have contributed to the European North-South cline of variation (Prugnolle et al. 2005; Anagnostou et al. 2009; Donnelly et al. 2012; De Fanti et al. 2015). For instance, genes belonging to the Toll-like receptors cluster, *CD79A* encoding for a subunit of the B-cell antigen receptor, malaria-associated *HBB*, *CR1* and *FCGR2B* loci, as well as genes participating in the Nf-kB signaling pathway have been proposed to have considerably differentiated within the Italian population due to the action of natural selection in response to pathogens such as *Yersinia pestis*,

Tab. 2 - *Genes showing variation patterns plausibly shaped by natural selection in Italian populations, along with the main biological functions they are involved in and the adaptive processes they have contributed to mediate.*

GENE	ACRONYM	FUNCTION	ADAPTATION
Adenylate cyclases	ADCY	Modulation of adiposity	Improved thermogenesis (high-fat diets)
Aldehyde dehydrogenases	ALDH	Glycolysis/gluconeogenesis	Improved thermogenesis (high-calorie diets)
BAG Cochaperone 6	BAG6	Formation of B-cells/antigen complex	Response to pathogens
B-Cell Antigen Receptor Complex-Associated Protein α	CD79A	B cell differentiation	Response to pathogens
Complement C3b/C4b Receptor 1	CR1	Erythrocytes binding to immune complexes	Protection against malaria
Deleted In Lymphocytic Leukemia 1	DLEU1	B-cell maturation	Response to pathogens
Fc Gamma Receptor IIb	FCGR2B	Phagocytosis of immune complexes	Protection against malaria
Frizzled Class Receptor	FZD	Melanogenesis	Response to UV radiation
Glucose-6-Phosphate Dehydrogenase	G6PD	NADPH production	Protection against malaria
Haemoglobin Subunit Beta	HBB	Polypeptide chain in adult haemoglobin	Protection against malaria
HECT and RLD Domain Containing E3 Ubiquitin Protein Ligase 2	HERC2	Hair/skin pigmentation	Response to UV radiation
Human Leukocyte Antigen	HLA	Self-cell recognition	Response to pathogens
Interleukin 23 Receptor	IL23R	Modulation of inflammation	Protection against tuberculosis/leprosy
Lactase	LCT	Digestion of lactose	Milk consumption in adulthood
Lymphocyte Antigen 6 Family Member G6C	LY6G6C	Formation of B-cells/antigen complex	Response to pathogens
Membrane Spanning 4-Domains A2	MS4A2	Clearance of antigen-antibody complexes	Protection against malaria
MRM3 Pseudogene 2	RNMTL1P2	Regulation of high-density lipoprotein levels	Improved thermogenesis (high-fat diets)
OCA2 Melanosomal Transmembrane Protein	OCA2	Eye/skin pigmentation	Response to UV radiation
Phospholipases C Beta	PLCB	Regulation of glucose homeostasis	Improved thermogenesis (high-calorie diets)
Phospholipases C Gamma	PLCG	Regulation of glucose homeostasis	Improved thermogenesis (high-calorie diets)
Polypeptide N-acetylgalactosaminyltransferases	GALNT	Mucin biogenesis	Response to pathogens
Polypeptide N-Acetylgalactosaminyltransferase Like	GALNTL	Mucin biogenesis	Response to pathogens
Protein Kinases C	PRKC	Regulation of glucose homeostasis	Improved thermogenesis (high-calorie diets)
R3H Domain Containing 1	R3HDM1	Regulation of triglyceride levels	Improved thermogenesis (high-fat diets)
RAB3 GTPase Activating Protein Catalytic Subunit 1	RAB3GAP1	Regulation of cholesterol levels	Improved thermogenesis (high-fat diets)
Tankyrase	TNKS	Immunoglobulin secretion	Response to pathogens
Thrombospondin 1	THBS1	Erythrocyte adhesion to blood vessels	Protection against malaria
Toll-Like Receptor cluster	TLR10-TLR1-TLR6	Modulation of inflammation	Protection against tuberculosis/leprosy
Transmembrane Protein 163	TMEM163	Cell sensibility to insulin	Improved thermogenesis (high-calorie diets)
WD Repeat Containing Planar Cell Polarity Effector	WDPCP	Adipogenesis	Improved thermogenesis (high-fat diets)
Wnt Family Members	WNT	Melanogenesis	Response to UV radiation

Vibrio cholera, smallpox virus and *Plasmodium falciparum*.

Some of these findings were replicated in a subsequent study that further suggested how mycobacteria responsible for tuberculosis and leprosy might have represented a strong selective pressure for millennia, especially for populations from the Central-Southern regions of the peninsula (Sazzini et al. 2016). In fact, these human groups showed genomic signatures left by the action of natural selection that are not evident in groups from Northern Italy and that encompassed the *TLR10-TLR1-TLR6* gene cluster and the *IL23R* interleukin receptor locus, which are known to modulate inflammatory responses and to be associated with reduced susceptibility to the above-mentioned infectious diseases. Unfortunately, some of the variants of these genes that have been hypothesized to have exerted an adaptive role during the evolutionary history of Central-Southern Italian populations are nowadays responsible for their increased risk in developing inflammatory conditions (e.g., inflammatory bowel disease, Crohn's disease, etc.) due to the remarkable shifts in dietary habits experienced by these human groups in the last century (Sazzini et al. 2016). An analogous process of dis-adaptation has been described for variants at loci involved in B-cell maturation (*DLEU1*), immunoglobulin secretion (*TNKS*), and the proper formation of the B-cell/antigen complex (*BAG6*, *LY6G6C*), which past selective pressures brought to an appreciable frequency in Italian populations from Mediterranean regions due to their role in improving adaptive immunity against pathogens, but that in the modern era are found to negatively impact on the susceptibility to autoimmune disorders (e.g. systemic lupus erythematosus) (Sazzini et al. 2016).

Moreover, the same study identified a series of biological adaptations that characterize human groups from Northern Italian regions, which seem to have modulated the metabolism of the adipose tissue, body heat production and thermoregulation processes, as well as cell responses to insulin release, plausibly in response to high-calorie and high-fat diets (Sazzini et al. 2016).

Ancestral populations settled in this geographical area have been indeed exposed to environmental conditions similar (albeit less intense) to those experienced by groups for Central-Northern Europe, thus having long-maintained dietary habits that are useful to cope with energy-demanding climates. In particular, differently from what happened along the peninsula, the climate in the Alpine mountains range and on the neighbouring plains remained characterized by abrupt changes and relatively long and cold winter seasons for thousands of years after the LGM (Kaniewski et al. 2013; Quagliariello et al. 2017). Therefore, despite the multiple demographic changes that occurred in the last 20 Kya, natural selection has probably had enough time to operate on genes that regulate adipogenesis (*WDPCP*), HDL concentration (*RNMTL1P2*), cholesterol and triglyceride levels (*RAB3GAP1* and *R3HDM1*), as well as the sensibility of cells to insulin (*TMEM163*). Interestingly, derived adaptive alleles identified at these loci have been found to be associated with a reduced risk of developing coronary artery disease, insulin resistance and type 2 diabetes (T2D) in populations of European ancestry (Sazzini et al. 2016). This might be explained by the fact natural selection optimized the allocation of energy provided by high-fat foods for thermogenesis and thermoregulation processes, thus increasing individuals' survival in a harsh climate and indirectly reducing long-term health challenges related to such a dietary regimen.

Conversely, the disappearance of these selective pressures in the Central-Southern regions of the peninsula soon after the LGM, coupled with a more intense gene flow from populations across the Mediterranean Basin since the Neolithic, determined the maintenance at an appreciable frequency in the gene pool of these groups of ancestral *RAB3GAP1*, *R3HDM1* and *TMEM163* alleles, which have the potential to increase the susceptibility to the above-mentioned diseases. Accordingly, when the diets and lifestyles of these people changed considerably in the modern era due to industrialization and globalization processes, such genetic profiles

suddenly turned into risk factors for the development of metabolic diseases (Sazzini et al. 2016).

Another study confirmed this overall picture, also providing additional evidence which expands the investigation of biological adaptations evolved by the ancestors of present-day Italians to selective events involving complex traits (Sazzini et al. 2020). In fact, this work used high-coverage whole genome sequence data to test a model of polygenic adaptation and was also able to trace back to the Late Glacial period the earliest signatures ascribable to the formation of a latitudinal gradient of variation along the peninsula. This corroborated the hypothesis that selective pressures imposed by cold climate and high-calorie diets acted predominantly on the ancestors of human groups from Northern Italy, especially in the light of polygenic selective events found to be specific to these populations and to have targeted signalling pathways that regulate thermogenesis and adiposity (*ADCY* genes), glycolysis and gluconeogenesis (*ALDH* genes), as well as key steps of glucose homeostasis (*PRKC*, *PLCG*, and *PLCB* genes). Once again, the observed adaptive haplotypes have been demonstrated to be associated with reduced susceptibility to insulin resistance, T2D and obesity, thus representing protective factors for present-day Northern Italians (Sazzini et al. 2020).

Likewise, pathogen-related selective pressures have been confirmed to be pivotal triggers for the adaptive evolution of the ancestors of Italian people from Mediterranean regions. Indeed, these groups presented genomic signatures attributable to the pervasive action of natural selection on complex networks of loci belonging to the *GALNT* and *GALNTL* gene clusters, which encode for mucins that prevent pathogens from binding on mucosal surfaces. For instance, microorganisms such as *Pseudomonas aeruginosa*, *Entamoeba histolytica*, and *Burkholderia cepacia* are known to be able to elude mucosal/cellular barriers by inactivating mucins and show geographical distributions along the peninsula that positively correlate with environmental temperatures. That being so, they have been proposed as the most plausible selective pressures responsible for selective events regarding mucin biogenesis

pathways (Sazzini et al. 2020). Moreover, polygenic adaptations have been inferred from the genomes of Southern Italians also in relation to the observation of combinations of multiple variants of the *FZD* and *WNT* genes, which positively regulate the expression of several loci that play a role in melanogenesis. These adaptive events might have evolved in response to the elevated annual solar radiation that characterizes Italian Mediterranean regions, enabling their inhabitants to prevent skin micronutrient photodegradation due to UV damage and indirectly conferring them with reduced susceptibility to several skin malignancies (Sazzini et al. 2020).

Finally, it has been long demonstrated that peculiar adaptations have evolved in the Sardinian population, especially to cope with infection by *Plasmodium falciparum*, which was endemic to the island until a few decades ago. These were mediated by selective events at the β-globin gene (*HBB*), which are associated with both β-Thalassemias and less severe malaria symptoms, or at the *G6PD* locus, which catalyzes the production of NADPH to avoid oxidative damage in cells, and whose activity is reduced by alleles that lead to glucose-6-phosphate dehydrogenase deficiency, but at the same time protecting against infection by the malaria parasite (Siniscalco et al. 1966). Recent genome-wide scans identified additional loci involved in the adhesion of infected erythrocytes to blood vessels (*THBS1*), in the clearance of antigen-antibody complexes within them (*CR1*), or in modulating the production of pro-inflammatory and oxidative metabolites (*MS4A2*), which are differently associated with reduced malaria severity and/or progression in the Sardinian population (Kosoy et al. 2011; Piras et al. 2012 ; Parolo et al. 2015; Sazzini et al. 2016).

Conclusions

In this paper, we have overviewed the relationships between the structure of genetic variation of Italian populations and geographical, environmental and cultural factors. We hope that what we have discussed here (schematized in
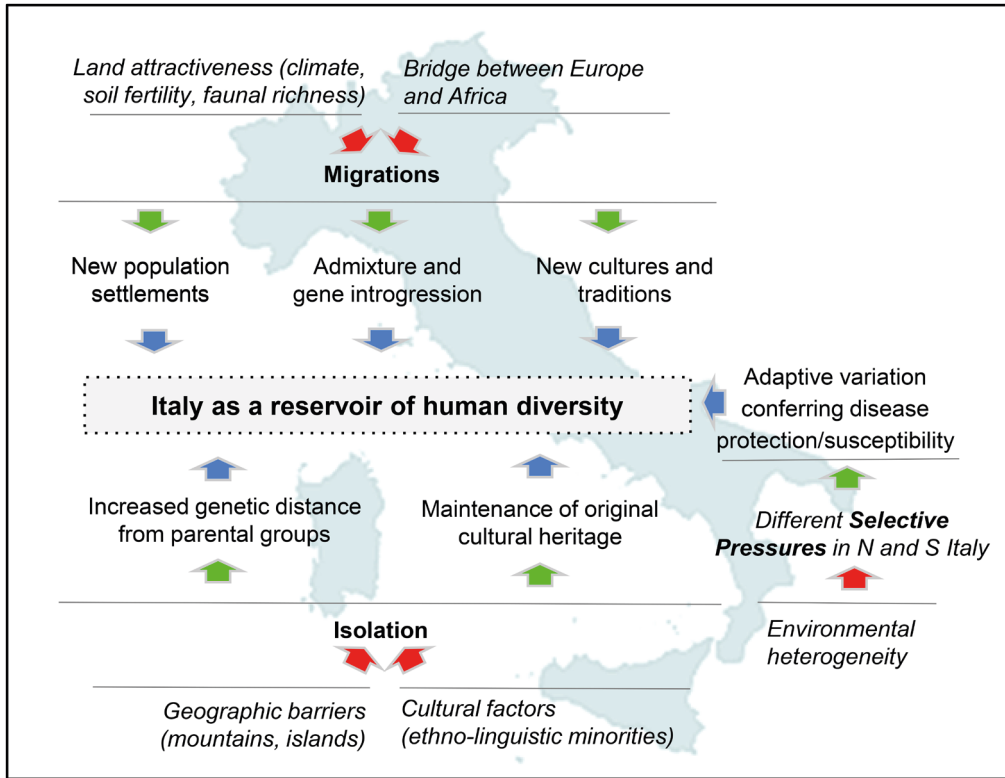
Fig. 6 - Schematic representation of the factors underlying the diversity (biological and cultural) of Italian populations.

Figure 6) will help make sense of an often over-used term, complexity, which actually seems to well fit our description of the diversity of Italians and the different factors that have influenced it.

As a first step, we looked into the remote past. The peopling of Italy by the genus *Homo* can be placed far back in time thanks to some of the earliest lithic industries discovered in Europe, whose technological characteristics are comparable with the earliest material cultures, found in Africa and attributed to the Oldowan. Even the fossil evidence of *Homo sapiens* is among the most ancient found in Europe, pointing to the central role of our country in any reconstruction of the upper Paleolithic on the continent. Then, we discussed how the advent of genomics and the increasingly complete characterization of ancient DNA are radically changing our understanding of the

human past. What we managed to shed light on regarding the ancient migratory processes towards Italy was probably unthinkable just ten years ago. Although important questions remain open, delving into the ancient genetic history of our country is a unique opportunity to better understand how some of the most significant population processes in Europe, Africa and Asia Minor have combined to create the background upon which the genetic structure of today's Italian population has developed. Taking into consideration the Italian ethno-linguistic minorities and the interactions of gene pools with different environmental contexts, we have shown how it becomes possible to better appreciate the role of isolation and selection in Italy and how this has produced considerable genetic diversity which is unique in Europe. The extent of this diversity and cultural heritage also

goes hand in hand with the vast animal and plant biodiversity found in our country.

Although this may appear heterodox, we would like to close this text by moving away from scientific arguments for a moment. Let's go back to Henry James, the author of the quote at the beginning of this paper, an American-British writer considered one of the greatest English-language novelists. He met and fell in love with Italy, which he portrayed extensively in his travel writings. Our quote is from "Roderick Hudson", a novel that James published as a serial in 1875 in The *Atlantic Monthly* (a well-known American magazine now renamed *The Atlantic*), which tells the vicissitudes of Roderick Hudson, a young law student and amateur sculptor during his stay in Europe. In the tale, the apparently extravagant concept "impossible beauty" that seems to have taken possession of Roderick Hudson himself arises from a series of events in which hopes, youth and love are indissolubly mixed.

Putting romanticism to one side for a moment, it seems to us that the use of this apparently extravagant concept can make sense if we think of Italy as a place with extremely different environments where distant peoples met through the ages, bringing and sharing their genes and ideas. Being able to grasp the extraordinary variety of cultural, historical and artistic manifestations that derive from such a history means inevitably being attracted to a particular form of beauty which is difficult, perhaps impossible, to grasp in all its entirety but can undoubtedly exercise a sort of invincible charm.

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