The multiple histories of Western Asia: Perspectives from ancient, and modern genomes

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Abstract:

Anthropological genetics has revolutionized the way we study variation in human populations, their relationships with each other and with past populations. Since the very early days of the discipline, Western Asia has been a major focus (Menozzi et al. 1978). After all, it is the geographical focal point where Africa, Asia, and Europe meet and it is the hotbed of cultural innovation, most notably the emergence of settled Neolithic communities (Gordon Childe 1936; Mellaart 1967; Barker 2009). As such, it has been central to most major Eurasian civilizations (Kuhrt 1995; Gregory 2010), and, more recently, a dynamic mix of tribal and ethnic units, religious sects, and national identities. Some questions emerge as central within the broader framework of Western Asian genetic variation: Who are the ancestors of Western Asian populations? How did contemporary and ancient Western Asians contribute to the peopling of the rest of Eurasia? Which routes in Western Asia did the first migrants out of Africa take? Who were the first farmers? Where, when, and to what extent did Neanderthals contribute to the gene pools of Eurasian ancestors? In this paper, we review the latest genetics research tackling these questions, with special emphasis on the recently available ancient genomics datasets, as well as the emerging notion that ancient interactions among human populations are more important than previously thought.

Western Asia:

Western Asia has been the geographical center of history of Eurasian peoples, first as an ancestral homeland, and later as a center and crossroads of civilizations (**Figure 1**). The area is informally defined, but is often understood as comprising the contemporary national boundaries

of Turkey, the Arabian peninsula, Iran, Armenia, Azerbaijan and south Caucasus (Knapp 1988). The region was first populated by early human species as early as 1.5 Million years ago, starting with the migrations of hominins into the region and later populated by Neanderthals and anatomically modern humans (McCown and Keith 1939; Bar-Yosef and Belfer-Cohen 2001; Kappelman et al. 2008; Hershkovitz et al. 2015). Fossil records are notoriously patchy and, due to occasional inconsistencies in dating and interpretation, specific conclusions derived from them are often hotly debated among anthropologists. Regardless, it is clear that modern human ancestors, whether they are direct ancestors or not, have lived in Western Asia since at least 500,000 years before present, if not earlier. In fact, it is plausible that multiple hominin species inhabited the region simultaneously and exchanged genetic material. Introgression from such related species to the modern human gene pool is now actively being discussed to explain some of the unusually divergent haplotypes among human genomes (Pääbo 2015). For example, the current genetic data suggests that all Eurasians carry 1-4% of Neanderthal alleles in their genomes, due to an introgression event that happened in western Asia approximately 60,000 years ago (Green et al. 2010; Prüfer et al. 2014).

Since the first inhabitation of Western Asia, the region has played multiple pivotal roles in human history. Arguably the most important of those is the emergence of settled human societies. Thanks to amazing discoveries in archaeological sites, such as Catalhoyuk, Gobeklitepe, Atlit Yam, Ali Kosh, Jericho, among others, there is now a fascinating debate about how humans transition into sedentary life (Bellwood et al. 2007). While previous work focused on economic and demographic trends when explaining this transition (Bocquet-Appel and Bar-Yosef 2008), the work in Gobeklitepe potentially adds a symbolic perspective where religious identities may have led a group of people to settle, predating agriculture (Gosden 2004). Regardless of the reasons, after being hunter-gatherers for more than 100,000 years, humans who settled in Western Asia started engaging in agriculture, dramatically increasing their population and rapidly increasing the complexity of the societies that they lived in (Bocquet-Appel and Bar-Yosef 2008). This cultural transition has since shaped human history, where both peoples and their cultures spread across the world, significantly shaping the contemporary genetic variation of Eurasia (Skoglund et al. 2012; Lazaridis et al. 2013; Allentoft et al. 2015).

The first agricultural village emerged in Western Asia roughly 12,000 years before present (Barker 2009). Since then, the region's history has been defined by wars, migrations, trade, religious and ethnic connections and segregations, and, perhaps most importantly, kinship connections among extended families (Lewis 1995; Mansfield 2013). Very few genetic studies have explored the complex population interactions, which somehow transformed the inhabitants of the few farming villages of Western Asia into the large and diverse populations of the bronze and iron age cosmopolites (Cinnioğlu et al. 2004; Gokcumen et al. 2011; Rodriguez-Flores et al. 2016; Scott et al. 2016). The genetic impact of the invading peoples also remains unknown, from the Indo-European speaking Hittites to Alexander's armies. The genetic impact of over two thousand years of social and political complexities of The Roman and Byzantine periods, and later the Islamic Ottoman empire remains unknown. Overall, multiple histories of Western Asia pose a fascinating set of questions, which the recently available genetic tools are beginning to address.

Contemporary human genomics, what changed?

Genetic information has been used to inform us about human movements for decades, especially by looking at genetic variation in mitochondrial genomes and certain non-recombining regions of the Y-chromosome (Comas et al. 1996; Di Benedetto et al. 2001; Cinnioğlu et al. 2004). However, today human genomics is applied to investigate the human past with unprecedented empirical power. Data from whole genomes now enables an in-depth look at multiple ancestors of each genome, allowing researchers to ask precise questions. In parallel, with the availability of thousands of samples from hundreds of modern and ancient populations, we have a broader look at the human genetic variation across geography and time (Veeramah and Hammer 2014). It is worthwhile to emphasize two recent breakthroughs that allow us to conduct our analyses with unprecedented power and accuracy.

The first of these breakthroughs is our recent ability to afford the sequencing of thousands of entire genomes with previously impossible speed (Schuster 2008). This allowed us to parse the genome into haplotype blocks, each telling different stories of our ancestors (Veeramah and Hammer 2014). The random inheritance of maternal and paternal chromosomes combined with the effect of recombination makes our genome a mosaic of pieces, each coming from a different ancestor. With next generation sequencing and sophisticated computational approaches, we are able to study the history of each of these genomic mosaic pieces affording us a glimpse into thousands of ancestral lineages, rather than tracing a single ancestral line (Harris and Nielsen 2013). Such a comprehensive view of the genome has allowed us to look at the contribution from our ancestors at different time scales (Schiffels and Durbin 2014). For example, we can determine which of the pieces in Western Asian genomes were inherited from Neanderthal ancestors some 50,000 years ago (Vernot and Akey 2014), while measuring the East Asian component of Western Asian genomes, likely a relic from migrations of Turkic speaking groups into the region only one to two thousand years ago (Alkan et al. 2014).

The second breakthrough comes in the form of sequencing entire ancient genomes, which allows us to study the genetic variation of ancestral populations directly (Green et al. 2010). A decade ago building entire variation maps of whole genomes from extremely fragmented DNA of ancient human remains was thought to be impossible. The surprising compatibility of next generation platforms to short fragments of ancient remains, combined with ingenious bioinformatics techniques (that leverage the consistent and predictable chemical damage that ancient DNA undergoes), allows for the accurate resequencing of entire genomes that are as old as **700,000** years (Orlando et al. 2013). With these trailblazing achievements in methodologies in the last decade, we now have genome-wide sequencing data from hundreds of ancient human genomes from different periods and geographies (Reich et al. 2010; Prüfer et al. 2014; Allentoft et al. 2015; Gallego Llorente et al. 2015; Kılınç et al. 2016; Siska et al. 2017).

The far-reaching impact of these two breakthroughs has especially challenged two previously-held beliefs about human history. First, the discovery that modern humans interbred with Neanderthals, as well as Denisovans (a distinct hominin species), contradicts the previously held single-origin model (Green et al. 2010; Reich et al. 2010). Second, it is clear that contemporary human genetic variation is a product of complex interactions in past populations, most of which

are now gone (Prüfer et al. 2014; Sankararaman et al. 2014; Lin et al. 2015; Racimo et al. 2015; Hsieh et al. 2016; Kuhlwilm et al. 2016; Vernot et al. 2016). For example, contemporary Europeans are not necessarily descendant of the Europeans from 10,000 years ago, but rather a product of complex admixtures among multiple ancient populations (Lazaridis et al. 2013). In sum, ancient population genomics heralds a new era, where we can directly test hypotheses with regard to genetic variation of past populations and their relationships to contemporary humans.

The global context of genetic variation in Western Asian populations

There are only a few studies that document genetic variation among Western Asian populations at a whole-genome level (Behar et al. 2010; Alkan et al. 2014; Reich et al. 2015), particularly when compared to wide-reaching datasets detailing European genomic variation. Nevertheless, even in the data from these few studies, certain patterns emerge. As a whole, the contemporary Western Asian genomic variation looks most similar to genomic variation of South European populations, *e.g.,* Southern Italians (Alkan et al. 2014). This seems to be true for Arabian, Turkish and Jewish variation, and, to a lesser extent, Iranian genetic variation (Scott et al. 2016). From a bird's-eye view, the contemporary genetic variation in Western Asia appears to be shaped by geography.

However, it is important to note some caveats when interpreting this data. First, there is evidence for different ethnic, religious, and kinship groups (*e.g.*, extended tribes) contributing to the genetic structure in this region, likely in a higher degree than in European populations (Gokcumen et al. 2011; Scott et al. 2016). As such, it would not be surprising to see enclaves of genetic variation that have very distinct genetic characteristics in the region. In fact, such genetic structuring was recently reported for the Bedouin population in Qatar (Rodriguez-Flores et al. 2016). Second, the genetic variation in Central Asian populations that neighbor Western Asia has been poorly characterized. We have little or no genome-wide data from Azerbaijan, Turkmenistan, and Afghanistan. As such, it is likely that Western Asian populations are also closely related to populations in the east, but Central Asian populations are yet to be comprehensively sampled for genome-wide analyses.

Third, the origins of contemporary genetic variation are not clear and this creates some level of confusion. For example, the most likely explanation for the genetic similarity between contemporary Western Asia and Eastern European populations is from the very recent effect of *isolation-by-distance*, *i.e.*, populations that are geographically close share genetic variation with each other (Wright 1943). As demonstrated beautifully in the landmark paper by Novembre et al. for European populations, this effect creates *clines* of genetic variation where the allele frequencies gradually increase or decrease across geographies (Novembre et al. 2008). However, recent studies have shown that genetic continuity in a given geography over time is not a universal trend. For example, there are reports that while Neolithic Chinese population seem to genetically resemble contemporary Han Chinese (Siska et al. 2017), the Neolithic populations of Western Asia were observably different genetically from contemporary populations living in the same geography (Kılınç et al. 2016). As such, contemporary genetic variation data do not necessarily reveal the genetic variation of the past populations living in these geographies or vice versa,

New insights into the contemporary genetic structure within Western Asian populations

The first genome-wide glimpses into genetic variation of Western Asian populations revealed a surprising genetic structuring both within and among national boundaries. This contrasts what is found in Western Europe and, to some degree, Eastern Asia, where the genetic variation is mostly continuous, superseding national boundaries (Novembre et al. 2008). As mentioned before, Western Asian populations seem to have the highest genetic similarities to their geographic neighbors. Nevertheless, when looking at the genetic variation with a finer lens, a more complicated picture emerges. One of the major quantitative tools for visualizing the variation among genomes is principal component analysis, which, very simply put, identifies correlated genetic variants among genomes and converts them to singular *principal components.* This statistical procedure essentially summarizes the multidimensional data (*i.e.* hundreds of thousands of single nucleotide variants in this case) into a smaller number of dimensions, with the first principal component carrying the highest amount of variance stemming from correlated variants the data. In genetic anthropological analyses, generally the first two (sometimes also the third and fourth) principal components are shown (Reich et al. 2008). These principal components show the separation of individual genomes from each other based on a small portion of the genetic variation analysed, which maximizes the separation.

Principal component analyses of Western Asian populations, for which comparable genetic data are available, showed that no clear genetic boundaries can be drawn between populations (Hodoğlugil and Mahley 2012; Scott et al. 2016). Even though this has not specifically been tested, two apparent trends have emerged from multiple recent studies (Alkan et al. 2014; Rodriguez-Flores et al. 2016; Scott et al. 2016). One, contemporary populations in Iran and Turkey are more related to each other than they are to populations living in the Arabian peninsula. Second, these two populations also seem to have higher levels of genetic affinities to southern European populations as compared to populations speaking semitic languages.

These are interesting observations and several cultural and historical factors can be considered to explain them. One possible such explanation is that the contemporary population of Iran is Indo-European speaking and, as such, has a linguistic affinity to European populations that date back 8-9 thousand years before present (Gray and Atkinson 2003). However, the more likely explanation is that relatively recent interactions of different groups in the region, including Kurdish and Turkic speakers, transgressed national, and possibly linguistic borders. For answering such questions from a more targeted approach, anthropologically and historically contextualized sampling is essential. For example, the genetic variation within Kurdish and Turkic speakers that populate the border areas between modern-day Turkey and Iran remains unexplored. It should be noted here that all of these historical and linguistic inferences have not been tested by data and it is possible that other explanations for the genetic structure among Western Asian populations will be put forward as our understanding of the cultural and genetic diversity of the region increases.

Even with that caveat, one of the major trends that emerges within Western Asia is the level of local genetic structure independent of national boundaries. We have previously discussed how Western Asian villages have created extended patrilineal kinship groups that lead to a clear separation of Y-chromosome variation between neighboring villages, while maintaining a high level of homogeneity within the villages (Gokcumen et al. 2011). This leads to an overall trend where the genetic variation is high in the region as a whole and within ethnic groups, while inbreeding is higher than what is observed in western European and Eastern Asian populations (Scott et al. 2016). The genetic variation of the Jewish population, which has been extensively studied, exemplify this trend. Briefly, most Jewish genomes cluster with other Western Asian genomes, especially with those of the Druze. However, within the Jewish population, significant structure exists that corresponds to the geographic origin of the sampling (e.g., Ashkenazi, Sephardic or Ethiopian origins) (Behar et al. 2010). For example, a recent study has connected some genetic elements found in contemporary Ashkenazi genomes to genetic variation observed in Eastern Turkey (Das et al. 2016). The interpretation of this finding is up for debate, relative confinement of religious, ethnic, linguistic and political groups remains a major factor shaping the overall structuring of genetic variation in the region.

Ancestors of contemporary Western Asians

Recent data from ancient Western Asian genomes has revitalized the field and provided a first direct empirical glimpse of the complex genetic past in the region that had previously only been predicted from historical and archaeological evidence. Early attempts to get ancient DNA from the region were limited to fragments of mtDNA sequences with interesting, yet inconclusive, information gained (Matney et al. 2012). In the last two years, several studies provided genome-wide data from hundreds of human remains, coming from multiple regions. These include: contemporary Europe, but also Turkey, Iran, Jordan, Israel, as well as Caucasus and Central Asia, and span the Paleolithic, early and late Neolithic, and into the Bronze Age (Keller et al. 2012; Skoglund et al. 2012; Skoglund et al. 2014; Allentoft et al. 2015; Jones et al. 2015; Mathieson et al. 2015; Hofmanová et al. 2016; Kılınç et al. 2016; Lazaridis et al. 2016; Omrak et al. 2016).

One unexpected finding from this data is that the early farmers in Iran, Anatolia (the area that is covered by modern Turkey) and the Levant (Israel/Jordan area) are genetically different from each other, as well as from the contemporary populations living in those areas (Kılınç et al. 2016). This contrasts with previous thinking where researchers often considered the expansion of a single ancestral Neolithic population in Western Asia. Instead, we are faced with an unexpected diversity in Neolithic Western Asia, which was populated by distinct agricultural populations that later admixed into each other to contribute to the genetic pool of contemporary Western Asians.

These early agricultural populations affected the genetic variation in the rest of Eurasia. Based on this data, it is now widely accepted that farming arrived to Europe via the migration of Western Asian farmers and their genomic contribution constitutes the majority of genetic variation of contemporary Europeans (Skoglund et al. 2012; Lazaridis et al. 2013). In fact, contemporary South Europeans cluster better with this ancient population than do contemporary Turkish populations (Kılınç et al. 2016). In addition, there is evidence, albeit less conclusive, that early

Iranian farmers contributed to the genetic variation of contemporary Central Asians and South Asians, while early farmers in the Levant contributed to the genetic variation of contemporary East Africans (Lazaridis et al. 2016). We now know that contemporary Western Asian genomes have been greatly influenced by these early inhabitants, as well as by the contribution of later population movements, including migrations of Turkic speakers into the region. It is now an exciting time to investigate the origins of contemporary genetic variation in the region.

FUTURE

Western Asia has been the focus of anthropologists, archaeologists, historians, and geneticists for a long time (Renfrew 1990; Gordon Childe 2014). Several major hypotheses ranging from the origins of all Eurasians to underlying reasons behind the transition to agriculture have been put forward within the geographic context of western Asia. As such, the incredible increase in the number of modern and ancient genomes has not necessarily changed the questions that we have been asking. Instead, they have allowed us to tackle these old questions with an unprecedented empirical rigor. For example, multiple studies in the last two years, have generally solidified the Neolithic Anatolian population as the ancestral population that give rise to the European Neolithic population, which in turn contributed greatly to contemporary genetic variation. Similar to this resolution of the issue of European Neolithic origins, we argue that the next phase in Western Asian genomics will tackle three exciting new avenues of research.

First is the question of the nature, extent and origins of Neanderthal admixture into Eurasian ancestors. Recent studies now convincingly argue that all Western and Eastern Eurasians share genetic variation with Neanderthals, likely because of a common introgression event that happened in Western Asia after modern human ancestors crossed the Sahara desert but before they migrated out of Western Asia (Green et al. 2010; Prüfer et al. 2014; Vernot and Akey 2014). The current model, based on the currently available data mostly from modern human genomes, posits that a single introgression introduced Neanderthal haplotypes to a singular ancestral western Asian population. However, there is accumulating evidence that the interactions between Neanderthals and modern humans in Western Asia was more complicated. A ~40,000 year old human genome from Romania (Peştera cu Oase, Figure 1), which borders Western Asia, shows substantial Neanderthal ancestry, suggesting a direct Neanderthal ancestor for this human only 4-6 generations back (Fu et al. 2015). However, it seems that this genome does not contribute to contemporary genetic variation of Eurasia, raising the possibility that multiple Western Asian populations have differential levels of Neanderthal admixture, and only a few contributed to the genetic variation of contemporary populations. Indeed, a recent study showed that Bedouin populations from Qatar are not only distinct from other Western Asian populations, but they aslo carry lower amounts of Neanderthal DNA than their neighbors (Rodriguez-Flores et al. 2016) (Figure 1). This is consistent with the notion that at least some of the ancestry of indigenous Arabs can be traced back to distinct Western Asian populations that have diverged from other Eurasian lineages shortly after the out-of-Africa migration. The time is ripe for a systematic study reconstructing the genetic variation of paleolithic populations in Western Asia and specifically to determine the timing and extent of Neanderthal introgression into these populations.

A second question concerns the routes the first migrants took when they travelled out of Africa. There is some level of consensus that Western Asia was the stepping stone for Paleolithic African migrants on their way to populate Eurasia. When exactly did the first modern humans arrive in Western Asia? Were there multiple migrations out-of-Africa or did a single ancestral population cross the Sahara (Drake et al. 2011)? Which route did they take? Did they establish multiple isolated populations during their time there? Which of these peoples populated Europe, Asia, South Asia, Australia? Two recent studies have argued that a single ancestral population from Africa populated all of Eurasia and Australia (Malaspinas et al. 2016; Mallick et al. 2016), whereas another study showed evidence for a distinct out-of-Africa ancestry in a modern day Australian that is not present in any other Eurasian genome (Pagani et al. 2016). If the latter study is accurate, it is plausible that isolated Western Asian populations may carry signatures of such distinct ancestry. In fact, the genetic variation of the Qatari population (Rodriguez-Flores et al. 2016), as well as that of ancient Western Eurasian populations (Lazaridis et al. 2016), show the presence of a *basal* Eurasian lineage that is distinct from the ancestral lineages that later populated the rest of Eurasia. Another unknown with regards to early migrants out of Africa is the exact route through which they took to reach Western Asia and later the rest of Eurasia. While paleo-archaeological evidence suggests a "Southern" route through the Arabian Peninsula (Armitage et al. 2011), at least one genetic inference argues for a "Northern" route through Egypt (Pagani et al. 2015). There is a lively discussion in the field with regards to the exact route(s) (Boivin et al. 2013; Nasab et al. 2013; Bosch et al. 2015; Douka et al. 2015; Winder et al. 2015), as well as the genetic variation within the population(s) that left Africa (Hershkovitz et al. 2015; Malaspinas et al. 2016; Mallick et al. 2016; Pagani et al. 2016). Ancient genomes from the region may allow for the direct testing of these different models. Overall, we argue that with the increasing number of genomes available, the currently blurry picture of population dynamics in Paleolithic Western Asia will become clearer in the near future.

The Neolithic transition, which has changed multiple aspects of human life from diet to social dynamics, first happened in Western Asia less than 12,000 years before the present - a flicker in the evolutionary timeline. Nevertheless, this transition may be the single most important event that adaptively shaped human genetic variation. Some of the best-known examples of selection in the human genome are of variants that are linked to the agricultural lifestyle. For example, lactase persistence has evolved recurrently and been selected for in multiple agricultural populations (Tishkoff et al. 2007; Romero et al. 2011). Similarly, the copy number of salivary amylase is strongly associated with increased starch consumption, which is a hallmark of agricultural societies (Perry et al. 2007). Now with more genomes across geographies and time (Mathieson et al. 2015), as well as a better understanding of the signatures of adaptive evolution in human genomes (Key et al. 2016), the next decade will surely witness a major increase in our understanding of how our bodies adapt to amazing diversity of ecologies that modern humans settled in the last hundred thousand years.

One major challenge to all these exciting prospects is sampling. We believe that three major biases exist in current samples. First, the majority of samples have been collected in a medical setting to search for rare diseases (Scott et al. 2016). As such, it is plausible that there is a bias in selecting families with a history of inbreeding, which also translates into sampling from certain

geographies where such in-family marriages are more common than others. Second, because of national politics, there are major differences in the number of samples collected and the amount of genetic data available from different geographical regions. For example, there are 18 full Turkish genomes and hundreds of genomes from Israel available for analyses, whereas to our knowledge there are no genomes from Iraq, Syria, or Azerbaijan. It is possible that more ancient than contemporary genomes were sequenced from some Western Asian geographies. The third bias is the lack of proper background information with regard to samples. This is partly also due to complicated politics. For example, ethnic, religious and ancestral backgrounds could be lost because donors may be stigmatized precisely because of their background. Further, collecting such information may be illegal, as is the case for Turkey. These factors may also bias the degree of inbreeding observed in Western Asia. We believe, however, that the ongoing studies from multiple groups will bridge the gaps in geography, time, and historical connections to establish a clearer and finer-scale picture of the genetic history of the region.

Conclusion

In this paper, we highlight some of the current research on the population genomics of Western Asia. This region stands at the crossroads of Africa, Asia, and Europe. As such, it has been a hotspot of human interaction and activity. Moreover, it is the place where arguably the most important cultural shift in human evolution, conversion to a sedentary lifestyle, emerged. Despite its importance, sampling from the region has always been problematic due to contemporary social and political realities. Nevertheless, the emerging picture from multiple genome-wide inferences into the region's history has revealed a fascinating complexity. We believe that the next years will witness an explosion of new insights into the history of the region, and a better understanding of human genomic variation as a whole.

Acknowledgments

Figure 1.

A general view of Western Asia. The green area represents the area we considered Western Asia. We also highlighted the locations of samples and archaeological sites we mention in the manuscript. Please note that these are by no means exhaustive. At the bottom of the graph, is a basic time-scale with regards to major demographic events affecting the populations of the region.

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