Chapter 11
Global Landscapes of Human Phenotypic Variation in Inherited Traits

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Abstract Modern humans exhibit phenotypic variation among individuals, and phenotypes in some physical and physiological traits are highly differentiated between populations. This chapter focuses on genetic polymorphisms related to phenotypes that show interpopulation differentiation, which have traditionally attracted the attention of both anthropologists and human geneticists. Owing to the recent development of DNA technology, we have obtained powerful tools for use in identifying the genetic polymorphisms associated with phenotypes. In addition, the availability of genome diversity data associated with global populations has enabled us to identify the signatures of the local genetic adaptations that are engraved in our genomes. Using data associated with current phenotypic variation in humans, we can elucidate the history of human adaptation in response to the selective pressures of various environments.

Keywords Phenotypic variation · Genetic differentiation · Genetic adaptation · Selective sweep · Genome-wide association study · Physical and physiological traits

11.1 Introduction

The physical and physiological traits of humans vary among individuals. Some traits, such as skin color, hair morphology, and facial features, clearly differ between populations. While the study of human diversity is well established, exploration into the genetic basis of human phenotypic variation has only just

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begun. This chapter, which introduces the genetic factors that affect certain traits, focuses on how and why human phenotypic variations are formed.

Over the past 100,000 years, anatomically modern humans have spread from Africa throughout the rest of the world and have occupied a variety of habitats with different environmental conditions. During the early stages of human expansion, adjustments to life in new environments were likely achieved by behavioral and physiological changes at the individual level, while genetic adaptations would have gradually occurred over successive generations within populations. Climatic and physical conditions, such as UV radiation, temperature, precipitation, humidity, and altitude, likely acted as selective forces shaping human phenotypic variation. Lifestyle, including diet and labor, could also have modified both genotypes and phenotypes over the course of generations. Epidemics could have resulted in strong positive selection for specific alleles related to disease tolerance. Potential selective pressures such as these indicate that the phenotypic variation in some inherited traits could have arisen as the result of recent adaptive evolution. The recent availability of genome-wide single nucleotide polymorphism (SNP) and sequence data for many human populations has enabled us to examine which genetic and phenotypic traits are the targets of natural selection and which are affected by neutral evolution.

11.2 What Drives Phenotypic Differentiation Between Human Populations?

Theoretical studies in population genetics have yielded a significant body of knowledge regarding patterns of genetic variation in human populations. Throughout the history of modern humans, divergence times between populations have been relatively short, which has resulted in ancestrally shared polymorphisms typically being observed among different populations (Fig. 11.1a, b). When a single genetic locus is examined, the gene tree associated with that particular locus typically differs from the average phylogenetic relationship and genetic closeness between populations. This discrepancy between gene trees and population trees is known as "incomplete lineage sorting." When examining unrelated individuals from a randomly mating population, the average tree developed using whole genome data exhibits a "star phylogeny," since each pair of unrelated individuals would be expected to have the same genetic distance (Fig. 11.1c). In humans, the average genetic distance between individuals from different populations is only slightly larger than the genetic distance between individuals from the same population.

Degrees of genetic differentiation, which are usually evaluated by a statistic F_{ST}, depend on the time since divergence and the migration rate between the populations. Because only a relatively short time has passed since human populations have diverged from one another, complete or nearly complete genetic differentiation has rarely been observed in human populations under neutral conditions. For example, Fig. 11.2 shows the distribution of F_{ST} values between three populations used for the HapMap project, and majority of SNP loci show very small

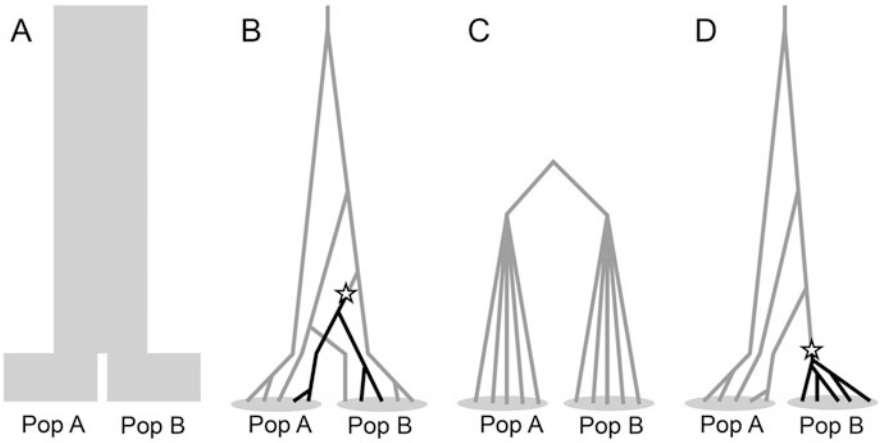

Fig. 11.1 Gene phylogeny versus population phylogeny. (**a**) Assumed population phylogeny of two populations. (**b**) Gene phylogeny of a single locus. Human populations generally do not have a monophyletic gene tree. A mutation (☆) causes a shared polymorphism between populations. (**c**) Dendrogram constructed from the expected average genetic distance. Analysis of the whole nuclear genome demonstrates that all unrelated individuals from a randomly mating population are expected to possess equal genetic closeness to one another. (**d**) Monophyletic gene tree in a population. Recent positive selection can result in a star phylogeny. A mutation (☆) creates a differentiated polymorphism between populations

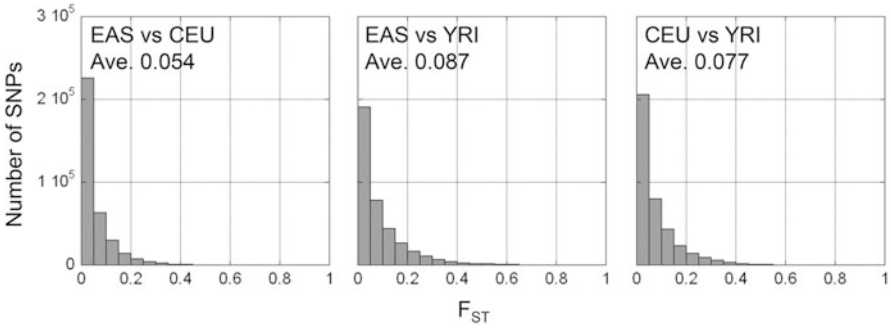

Fig. 11.2 F_{ST} between human populations determined using HapMap data (Chinese Han in Beijing, CHB; Japanese in Tokyo, JPT; Yorba in Ibadan, YRI; Utah residents with ancestry from northern and western Europe, CEU). EAS represents CHB+JPT

F_{ST} values. Therefore, in humans, loci exhibiting extremely large differentiation between populations can be identified as candidates for positively selected loci in one population (Fig. 11.1d). While phenotypic differentiation can be caused by neutral evolution, monogenic traits that are highly differentiated between human populations have likely been affected by some selective pressure. It is worth noting that positively selected loci can serve as population markers in humans although it is a typically held belief that neutral loci are more suitable for studying relationships between populations.

Polygenetic traits can result in large phenotypic differentiation between populations due to the summation of relatively small genetic differentiations at multiple loci (Fig. 11.3); however, even in the case of polygenetic traits, it is difficult for neutral evolution to result in large phenotypic differentiation, since changes in allele frequency occur in random directions under genetic drift. In contrast, selection acting on a phenotype can rapidly shift genotype distributions of multiple loci so that phenotype-related alleles increase within a given population. Therefore, large phenotypic differentiation in a polygenic trait can indicate the existence of some selective pressure; Q_{ST} is a metric of the degree of genetic differentiation indicated by quantitative traits, and Q_{ST}/F_{ST} comparisons provide a means to detect non-neutral differentiation in polygenic traits (Leinonen et al.

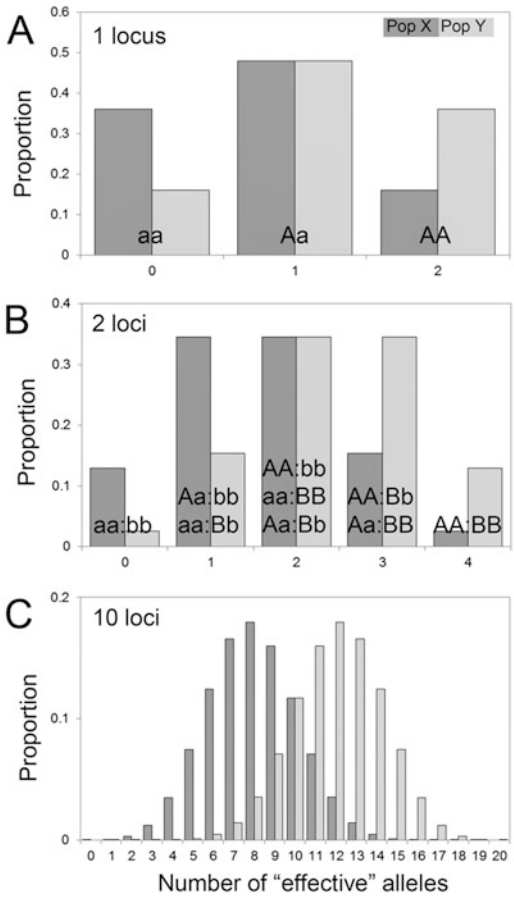

Fig. 11.3 Phenotypic distribution and differentiation in a polygenic quantitative trait. It is assumed that, at all loci associated with the trait, frequencies of the "effective" allele are 40% and 60% in populations A and B, respectively. (**a**) 1 locus. (**b**) 2 loci. (**c**) 10 loci

2013; Whitlock 2008). However, since phenotypes are also affected by environmental factors, it is difficult to isolate the effects of genetic factors in many cases.

11.3 Identification of Signatures of Adaptive Evolution in the Human Genome

Adaptive evolution occurs over a long time period and cannot be experimentally reproduced. Direct evidence of adaptive evolution could be obtained by observing differences in fitness between phenotypes, but proving that adaptive evolution occurred is usually impossible. Therefore, it is difficult to verify that a given phenotype is actually adaptive to an environment. In order to determine whether or not a phenotype is adaptive to a particular environment, one must accumulate indirect evidence by any means available, such as collecting information that can be gleaned from data regarding genetic diversity.

As described above, the extent of the differences in allele frequency between populations can act as a signature of positive selection. Another signature of positive selection is a reduction of long-ranged haplotype diversity, called "selective sweep." When a mutation occurs in a haplotype and that haplotype increases in a given population, alleles of surrounding sites that are tightly linked to the mutation also increase their frequencies. In this process, the links between the mutation and surrounding alleles are gradually broken over time through recombinations. Therefore, haplotype diversity can serve as an index for how rapidly a mutation proliferated in a given population, which would also serve as a measure of strength of positive selection (Fig. 11.4). Many studies have been undertaken regarding the methods and practical applications of using genome-wide data to identify signatures of selection (Grossman et al. 2010, 2013; Kimura et al. 2007; Pickrell et al. 2009; Sabeti et al. 2007; Tang et al. 2007; Voight et al. 2006; Wang et al. 2006; Williamson et al. 2007); however, previous approaches have not been adequate for the detection of selection on standing variation, known as "soft sweep" (Huang et al. 2009). When attempting to provide evidence of polygenic selection, gene set enrichment tests can prove useful, a point illustrated by Daub et al. (2013),

Fig. 11.4 Selective sweep. Rapid increase of a beneficial mutation results in a reduction in haplotype diversity in the region around the selected locus

who determined that the genes involved in immune-response pathways are enriched for signals of genetic adaptation.

Another strategy to obtain evidence for selection is to observe spatial patterns of allele frequencies. In heat and cold tolerance, genes involved in energy metabolism play a significant role, and Bergmann's and Allen's rules also assert the importance of both body mass and body proportion (Roberts 1953). Therefore, examining correlations between allele frequencies and climatic variables is one way to provide evidence for climatic adaptation in human populations. Studies examining these correlations have suggested that genetic variants associated with common metabolic disorders such as obesity, diabetes, and hypertension have been subjected to climate-mediated selective pressures (Hancock et al. 2011, 2008).

Genome-wide association studies (GWASs) have proven to be a powerful tool in the identification of genotype-phenotype correspondence and have been used to elucidate the genetic bases of medical and nonmedical traits in recent years (McCarthy et al. 2008; Plomin et al. 2009; Rosenberg et al. 2010). Some strong signatures of selection have been identified on phenotype-associated polymorphisms. The subsequent section provides a brief overview of the genetic bases of phenotypic variation that have attracted the interest of anthropologists.

11.4 Genes Associated with Common Phenotypic Variations I: Visible Traits

11.4.1 Height

Height is a highly heritable trait (heritability 70–90%). To date, GWASs have identified approximately 700 variants that have an association with height at a genome-wide significance level of $P < 5 \times 10^{-8}$. These include *ADAMTSL3*, *CDK6*, *DLEU7*, *GDF5*, *HHIP*, *HMGA2*, *LCORL*, and *ZBTB38* (Berndt et al. 2013; Lango Allen et al. 2010; Wood et al. 2014). Lango Allen et al. (2010) demonstrated that 180 loci explain approximately 10% of all phenotypic variation in height. More recently, Wood et al. (2014) estimated that 697 variants clustered in 423 loci explain one-fifth of the heritability, and all common variants in the genome together capture 60% of heritability. This suggests that the independent effects of common genetic variants cannot explain the majority of the contribution of genetic factors to variation in height. Studies targeting rare variants and epistasis effects are required in order to account for the "missing" heritability.

Average height varies among human populations, with African pygmies exhibiting particularly short statures, a feature believed to reflect past adaptation to a tropical environment. A genomic region on chromosome 3, which harbors a cluster of selection and association signals and includes genes such as *DOCK3* and *CISH*, could potentially explain, in part, the short stature observed in pygmy populations (Boyko 2011; Jarvis et al. 2012).

11.4.2 Obesity

Heritability of body mass index (BMI: weight kg/height m^2) is 40–70% (Maes et al. 1997; Stunkard et al. 1986). GWASs have detected a number of obesity-related polymorphisms, with strong association signals in *FTO*, *TMEM18*, *MC4R*, and *GNPDA2* (Berndt et al. 2013; Willer et al. 2009).

An ethnic difference exists in the prevalence of obesity, with Pima Indians and Polynesians being famous examples of exhibiting particularly high levels of obesity. The genetic backgrounds of these ethnic differences have not yet been determined, since the effects of currently identified polymorphisms are considerably smaller than the ethnic differences that have been observed. The "thrifty gene" hypothesis first proposed by Neel (1962) states that a genotype that efficiently stores energy would have been advantageous during times when food resources were scarce. Genome-wide scans for selection have nominated several candidates for "thrifty gene" in Polynesians (Kimura et al. 2008); however, further validation of phenotype-genotype association with respect to obesity in this population is required before any conclusions can be made. In studies on the Greenlandic Inuit and native Siberians, strong signatures of selective sweep were found on genes related with glucose uptake and fatty acid metabolism such as *TBC1D*, *CPT1A*, and *FADSs*, which is evidence for genetic adaptation to cold climates and specialized diets rich in protein and fatty acids (Clemente et al. 2014; Fumagalli et al. 2015; Moltke et al. 2014).

The risk of developing lifestyle diseases such as diabetes, hypertension, and heart disease increases along with increasing BMI. There is also strong evidence suggesting that at any given BMI, these risks are higher in some ethnic groups than they are in others (Shai et al. 2006; Wen et al. 2009). Hancock et al. (2008) identified significant correlations between climatic variables and the frequencies of genetic variants associated with metabolic disorders including obesity.

11.4.3 Pigmentation

It has been well established that skin, hair, and eye color vary among human populations with geographic gradation from low to high latitudes, a pattern that clearly reflects the strength of UV radiation. Genes involved in melanogenesis are well known from numerous studies involving either animal models or human pigmentation disorders (Rees 2003). Furthermore, GWASs have identified many genetic variants that explain variation in pigmentation-related traits. These variants are located in the cording and regulatory regions of melanogenesis-related genes—*ASIP*, *IRF4*, *KITLG*, *MC1R*, *OCA2*, *SLC24A4*, *SLC24A5*, *TYR*, *TYRP1*, etc. (Eriksson et al. 2010; Han et al. 2008; Nan et al. 2009; Stokowski et al. 2007; Sulem et al. 2007, 2008); however, since the majority of studies on pigmentation-related traits have focused on populations of European ancestry, genetic bases regarding global patterns of pigmentation-related traits are not fully understood.

To date, only a few studies examining East Asian populations with respect to pigmentation have been undertaken, with these studies having demonstrated that *MC1R* and *OCA*2 were associated with skin color variation in the Asian populations examined (Akey et al. 2001; Edwards et al. 2010; Yamaguchi et al. 2012). In a study on the Melanesian Solomon Islanders, Kenny et al. (2012) demonstrated that their blond hair is associated with a nonsynonymous variant in *TYRP1*, which is independent of the genetic basis of blond hair in Europeans. Genetic variations in melanogenesis-related genes often have pleiotropic effects, resulting in correlations between skin, hair, and eye color; however, some genes exhibit a tissue-specific effect.

Genome scans for positive selection have indicated that positive selection clearly acted on variants associated with low pigmentation in non-African populations (Lao et al. 2007; Norton et al. 2007; Sturm and Duffy 2012; Williamson et al. 2007). For example, *SLC24A5* and *SLC45A2* have signatures of hard selective sweeps in European populations, whereas *KITLG* and *OCA2* show evidence for selection in both European and East Asian populations. This means that the relaxation of the evolutionary constraint of damage due to the effects of solar UV radiation alone cannot explain the global pattern of human pigmentation. Possible selective pressures acting on skin pigmentation are the need for vitamin D synthesis and protection from photolysis of folate (Jablonski and Chaplin 2000). Alternatively, sexual selection is a potential explanation for positive selection on human pigmentation traits (Aoki 2002).

11.4.4 Morphology of Hair, Teeth, and Other Skin Appendages

Along with skin pigmentation, hair morphology is one of the traits exhibiting a high degree of differentiation between populations on different continents. African and Melanesian populations typically possess frizzled hair, while European populations typically exhibit wavy/curly hair or straight hair with a much lower frequency of frizzled hair. The majority of East Asian populations exhibit straight, thick hair (Franbourg et al. 2003).

One variant associated with hair morphology is located in *EDAR* and partly explains Asian-specific thick hair (Fujimoto et al. 2008). The nonsynonymous variant 370Val>Ala is found almost exclusively in Asian and Native American populations and has been shown to be a target of strong positive selection. GWASs examining individuals with European ancestry have identified variants associated with hair curliness in *TCHH* and *WNT10A* (Eriksson et al. 2010; Medland et al. 2009).

The *EDAR* variant has also been linked to tooth morphology. This variant is associated with the grade of shovel-shape in the incisors, a well-known Asian-specific phenotype (Fig. 11.5) (Kimura et al. 2009; Scott and Turner 1997). Along with the grade of shovel-shaped incisors, tooth size and the number of cusps in the second molars have been shown to increase due to the Asian-specific *EDAR* variant

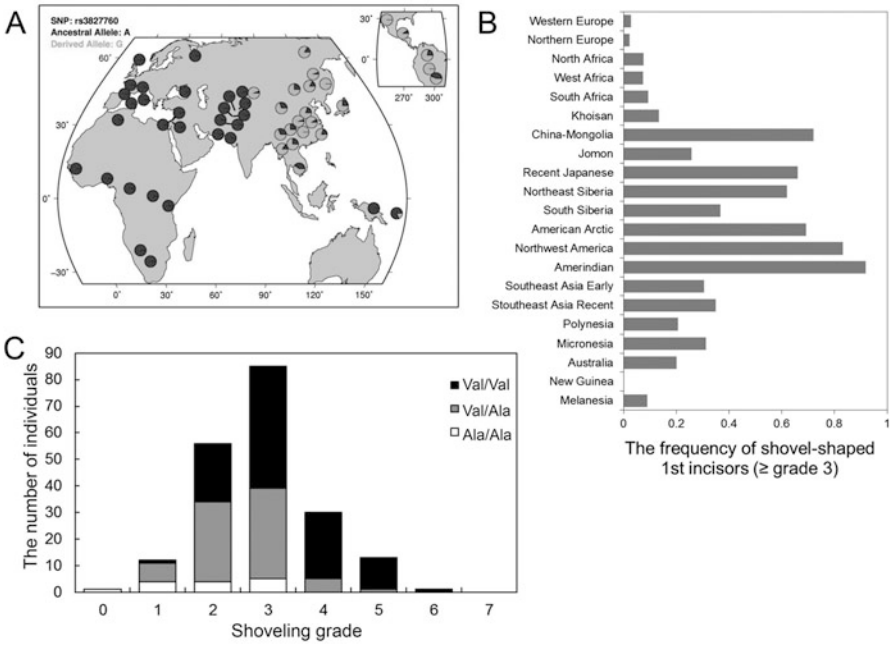

Fig. 11.5 *EDAR* 370Val>Ala and shovel-shaped incisors. (**a**) Global distribution of *EDAR* 370Val (ancestral) and 370Ala (derived) (rs3827760) (http://hgdp.uchicago.edu/cgi-bin/gbrowse/HGDP/). (**b**) The prevalence of strong, shovel-shaped incisors (≥ grade 3) in world populations (Scott and Turner 1997). (**c**) The association of *EDAR* 370Val>Ala with shoveling of first incisors in the Japanese population (Kimura et al. 2009)

(Park et al. 2012). An animal experiment using knock-in mice expressing the human *EDAR* variant determined that the variant increases branch density of eccrine sweat glands and mammary glands, with the association of the variant and eccrine sweat gland density having also been confirmed in humans (Kamberov et al. 2013). Another study has shown that *EDAR* variants are associated with ear morphology (Adhikari et al. 2015).

The selective pressure that acted on the *EDAR* variant in Asia remains unclear, due in part to the pleiotropic effects of this variant. It is likely that only one of these phenotypes would have been under selective pressure, while the other phenotypic traits were seemingly selected for increased only as a by-product of this selection. Situations such as this indicate the importance of identifying genetic bases to aid in our understanding of phenotypic evolution.

11.4.5 Baldness

Androgenetic alopecia is the most common type of baldness and is characterized by progressive thinning and loss of hair on the scalp. Interpopulation differences in the

prevalence of androgenetic alopecia exist, with populations of European ancestry exhibiting a greater prevalence of androgenetic alopecia than populations of both Asian and African ancestry (Hamilton 1951; Wang et al. 2010).

The *EDAR2-AR* region on X chromosome has been shown to be associated with androgenetic alopecia (Ellis et al. 2001), a finding confirmed by more recent GWAS investigations (Li et al. 2012). Recent GWASs have also identified genomic regions such as *PAX1* on chromosome 20, *HDAC4* on chromosome 2, and *HDAC9* on chromosome 7 as baldness-associated loci (Brockschmidt et al. 2011; Hillmer et al. 2008; Li et al. 2012; Richards et al. 2008).

In East Asian populations, a signature of selective sweep has been observed in the *EDAR2-AR* region, as most SNPs are fixed and genetic diversity is remarkably low (Hillmer et al. 2009). Since the region exhibiting low genetic diversity is very long and includes many genes, the identity of the selected gene and the selected phenotype remains unclear. Furthermore, this region alone cannot explain the observed differences between populations in prevalence of androgenetic alopecia.

11.4.6 Facial Morphology

Craniofacial shape is one of the most distinctive traits among humans. Facial morphology is highly heritable as we know that monozygotic twins have almost identical faces. Although numerous genes involved in craniofacial development have been identified through studies employing animal experiments or examining human genetic disorders, the search for the genetic factors responsible for common variation in human craniofacial morphology has only just begun. Recent advances in imaging technology as well as DNA technology have accelerated genetic studies regarding craniofacial morphology. A GWAS in Europeans identified SNPs associated with facial morphology on *PRDM16*, *PAX3*, *TP63*, *C5orf50*, and *COL17A1* (Liu et al. 2012). An association between *PAX3* variants and the shape of the nasal root was also detected in a separate GWAS study (Paternoster et al. 2012). In addition, new morphometric methods have enabled us to establish high-density semi-landmarks, instead of only using the limited number of anthropologically defined landmarks. Using these methods, a candidate gene study examining individuals of Chinese ancestry found that a genetic variant on *IRF6*, which is also a well-known risk factor associated with non-syndrome cleft lip, strongly affected mouth shape (Peng et al. 2013). Studies such as these could eventually allow for predictive modeling of faces based on sex, ancestry, and genes (Claes et al. 2014).

Some researchers have reported that either natural/sexual selection or assortative mating, rather than genetic drift, was responsible for facial differences between populations (Hubbe et al. 2009; Roseman and Weaver 2004; Roseman 2004; Guo et al. 2014). Identification of the genes associated with facial morphology will aid in our understanding of the selective pressures affecting facial shape in humans.

11.5 Genes Associated with Common Phenotypic Variations II: Physiological Traits

11.5.1 Lactase Persistence

Lactase persistence, the persistence of lactase activity from childhood into adulthood, is one of the most famous examples of genetic adaptation to a human dietary culture. The causal SNP for lactase persistence/nonpersistence in Europeans is located roughly 14 kb upstream from the *LCT* gene locus (Enattah et al. 2002). This genetic locus shows a strong signal for selective sweep in the European population (Bersaglieri et al. 2004). Pastoralism originated around 10,000 years ago, which resulted in lactase persistence becoming advantageous due to the availability of milk from domesticated animals as a food source for adults. A study based on approximate Bayesian computation has inferred that the lactase persistence allele first underwent selection among dairying farmers around 7500 years ago in a region between the central Balkans and Central Europe, possibly in association with the dissemination of the Neolithic Linearbandkeramik culture over Central Europe (Itan et al. 2009). Beja-Pereira et al. (2003) demonstrated geographic coincidence between distribution of the lactase persistence allele in contemporary Europeans, the increased genetic diversity in cattle milk genes, and locations of European Neolithic sites of cattle pastoralists. Although lactase persistence is also found in African populations, the causal SNPs differ from those of European populations (Ranciaro et al. 2014; Tishkoff et al. 2007). This indicates that multiple independent variants have allowed human populations to quickly modify *LCT* expression and that these variants have been strongly adaptive in adult milk-consuming populations.

11.5.2 Alcohol Intolerance

Harada et al. (1980) first demonstrated that a genetic variant in *ALDH2* responsible for aldehyde dehydrogenase deficiency is commonly found in Japanese populations. This variant, 504Glu>Lys, is strongly associated with the reduced alcohol tolerance commonly observed in Asian populations. In individuals with the deficiency variant, drinking a small amount of alcohol results in facial flushing, light-headedness, palpitations, and nausea. Homozygotes for the deficiency variant have an extremely reduced ability to metabolize alcohol and are likely to suffer from acute alcoholism. Instead, individuals with the deficiency variant have a lower risk of developing alcohol-related problems such as alcohol dependence and alcoholic liver disease due to their inability to consume alcoholic drinks (Goedde et al. 1983; Macgregor et al. 2009; Shibuya and Yoshida 1988). In East Asian populations, 30–40% of individuals carry at least one copy of *ALDH2*-deficient

allele (Oota et al. 2004); however, the allele is extremely rare in people who are not of Asian descent.

The enzyme encoded by *ADH1B*, cytosolic alcohol dehydrogenase, also has functional variants. In East Asian populations, a nonsynonymous variant, 48His>Arg, can be observed at a frequency of approximately 75%, while this variant is almost never found in populations of African and European descent. In addition, a signature of selective sweep on the variant provides obvious evidence for positive selection acting on Asian populations. Another variant, 370Arg>Cys, is found almost exclusively in populations of African descent (Li et al. 2007; Osier et al. 2002; Peng et al. 2010). These two variants are known to metabolize ethanol at rates 100 times higher than the ancestral allele (Edenberg 2000; Hurley et al. 1994). It has also been reported that individuals possessing the 48His>Arg variant exhibit lower blood alcohol concentrations one day after a period of heavy drinking than individuals without the variant (Yokoyama et al. 2007). Recent GWASs have demonstrated strong evidence for the association of *ADH1B* polymorphisms with alcohol consumption, alcohol dependence, and other alcohol-mediated diseases (Frank et al. 2012; Kapoor et al. 2013; Park et al. 2013).

It is intriguing that the Asian-specific variants, *ALDH2* 504Glu>Lys and *ADH1B* 48His>Arg, are both associated with alcohol intolerance. One hypothetical explanation for positive selection on these genes could be that a high acetaldehyde concentration in blood may have antiprotozoal effects (Goldman and Enoch 1990).

11.5.3 Apocrine Gland Secretion

Wet/dry earwax types are a classical Mendelian trait (Matsunaga 1962); however, the genetic basis of these traits, a polymorphism on *ABCC11*, has been discovered relatively recently (Yoshiura et al. 2006). The ancestral allele, which is dominantly associated with wet earwax, is highly prevalent in African and European populations. On the other hand, in Asian populations, a variant, 180 Gly>Arg, which is recessively associated with dry earwax, is observed with a frequency of approximately 80%. In addition, it has been shown that the wet-type allele has a strong association with axillary osmidrosis (Matsunaga 1962; Nakano et al. 2009) and that dry-type earwax is associated with a lack of colostrum secretion from the mammary glands in women on the first postpartum day (Miura et al. 2007). Human *ABCC11* is thought to play a central role in the secretion of steroid metabolites from the apocrine glands.

Genetic diversity data show strong evidence for positive selection acting on the *ABCC11* variant in Asian populations. Since *ABCC11* is involved in the apocrine sweat function, the genetic adaptation may be toward Asian-specific climates. A simulation study has estimated that 180 Gly>Arg originated approximately 50,000 years ago (Ohashi et al. 2011).

11.5.4 Blood Types

Yamamoto et al. (1990) elucidated the molecular genetic basis of the ABO blood group system long after its discovery at the beginning of the twentieth century. The ABO gene encodes a glycosyltransferase that catalyzes the transfer of carbohydrates on the extracellular surface of red blood cell membranes. The proteins encoded by the A and B alleles transfer different carbohydrates, either N-acetylgalactosamine or galactose, into the H antigen to form either A or B antigens. The O allele is dysfunctional and produces neither the A nor the B antigen. ABH antigens are also highly expressed on a variety of cells and tissues other than red blood cells, such as platelets, the epithelium, the vascular endothelium, and sensory neurons (Eastlund 1998).

It has long been known that the ABO blood groups are associated with the plasma levels of the blood glycoprotein von Willebrand factor and factor VIII, which are involved in hemostasis (Moeller et al. 2001; O'Donnell and Laffan 2001; Preston and Barr 1964). A number of clinical and experimental studies have assessed the effects the ABO blood group on the risk factors for arterial or venous thrombotic events (Liumbruno and Franchini 2013). Recent GWASs have confirmed the association of non-O blood groups with a variety of vascular disorders including coronary heart disease, ischemic stroke, and venous thromboembolism (Dichgans et al. 2014; Heit et al. 2012; Reilly et al. 2011; Schunkert et al. 2011; Tang et al. 2012, 2013; Tregouet et al. 2009; Williams et al. 2013). It has also been shown that the *ABO* locus is associated with the levels of several biomarkers including cholesterols (Kim et al. 2011; Teslovich et al. 2010; Willer et al. 2013; Zhou et al. 2013), alkaline phosphatase (Chambers et al. 2011; Kamatani et al. 2010; Li et al. 2013; Yuan et al. 2008), and soluble adhesion molecules such as ICAM-1, E-selectin and P-selectin (Barbalic et al. 2010; Pare et al. 2008, 2011; Paterson et al. 2009; Qi et al. 2010).

The O allele has a reduced susceptibility to severe malaria caused by *Plasmodium falciparum* due to a reduced adhesion of red blood cells to the vascular endothelium (Band et al. 2013; Timmann et al. 2012). Decreased risks of gastric and pancreatic cancers related to the O allele due to its association with infection and activation of *Helicobacter pylori* have also been reported (Amundadottir et al. 2009; Edgren et al. 2010; Iodice et al. 2010; Risch et al. 2010; Wang et al. 2012; Wolpin et al. 2009). On the other hand, individuals possessing the O allele are more susceptible to severe infections caused by cholera (*Vibrio cholerae*) (Clemens et al. 1989; Glass et al. 1985; Harris et al. 2005) and *Escherichia coli* O157 (Blackwell et al. 2002; van Loon et al. 1991). It is hypothesized that the presence of A, B, and O alleles in human populations is maintained by balancing selection (Calafell et al. 2008), even though the distribution of these alleles varies among populations (Roychoudhury and Nei 1988). It is possible that the ABO blood group system is associated with susceptibility to many other infectious diseases, since bacterial and viral antigens have epitopes similar to ABH antigens and since the ABH antigens can be a receptor for binding by pathogens.

FUT2, which is classically known as the secretor factor locus (*Se*), encodes alpha-(1,2) fucosyltransferase (Rouquier et al. 1995). This enzyme regulates the secretion status of the ABH and Lewis (Le) antigens in tissues and body fluids other than blood cells (Oriol et al. 1981). Individuals with active *FUT2* express ABH and Le^b antigens, whereas individuals with inactive *FUT2* express only Le^a antigens. To date, several nonsynonymous variants that result in the nonsecretor phenotype have been identified (Kelly et al. 1995; Koda et al. 1996, 2000a; Kudo et al. 1996). Interestingly, different nonsecretor variants are found in Western and Eastern populations (Fig. 11.6). The frequency distribution of the *FUT2* variants is believed to be the result of balancing selection (Ferrer-Admetlla et al. 2009; Koda et al. 2000b, 2001). There are advantages and disadvantages associated with both secretor and nonsecretor alleles.

Lindesmith et al. (2003) reported that individuals possessing the nonsecretor allele are completely resistant to Norwalk virus infection; however, it has also been suggested that individuals possessing the nonsecretor allele are more susceptible to infections caused by *Haemophilus influenzae* (Blackwell et al. 1986a), *Neisseria meningitidis*, *Streptococcus pneumoniae* (Blackwell et al. 1986b), *V. cholerae* (Arifuzzaman et al. 2011), and *E. coli* (Sheinfeld et al. 1989). Recent GWASs revealed that the nonsecretor allele is associated with an increased risk of Crohn's disease (Franke et al. 2010; Jostins et al. 2012; McGovern et al. 2010) as well as increased plasma levels of vitamin B12 (Hazra et al. 2008, 2009; Lin et al. 2012; Tanaka et al. 2009). A recent study hypothesized that the FUT2 secretor variant may decrease plasma levels of B12 by influencing secretion of gastric intrinsic factor, a fucosylated glycoprotein that is required for the ileal uptake of vitamin B12 (Chery et al. 2013).

11.6 Closing Remarks

Recent studies examining the human genome have provided information regarding local genetic adaptations that have resulted in phenotypic differentiation between populations; however, determining what constitutes a true selective pressure remains difficult. Lifestyles, as well as climatic and physical conditions, could serve as selective pressures, and as we have learned from the study of blood types, one of the strongest selective forces could be infectious diseases. There exist many classical examples of malaria-resistant variants in *HBB*, *G6PD*, *DARC*, and other genes (Currat et al. 2002; Hamblin and Di Rienzo 2000; Ohashi et al. 2004; Sabeti et al. 2002; Zimmerman et al. 1999). Furthermore, HLAs have been well documented as targets of both positive and balancing selection (Hedrick et al. 1991; Hughes and Nei 1988; Prugnolle et al. 2005; Takahata et al. 1992). Recently, Fumagalli et al. (2011) suggested that pathogenic environments play a more important role in local adaptation than do climatic factors. It has also been supposed that autoimmune diseases in humans, such as celiac disease, type 1 diabetes, and multiple sclerosis, may have emerged as a by-product of adaptations that

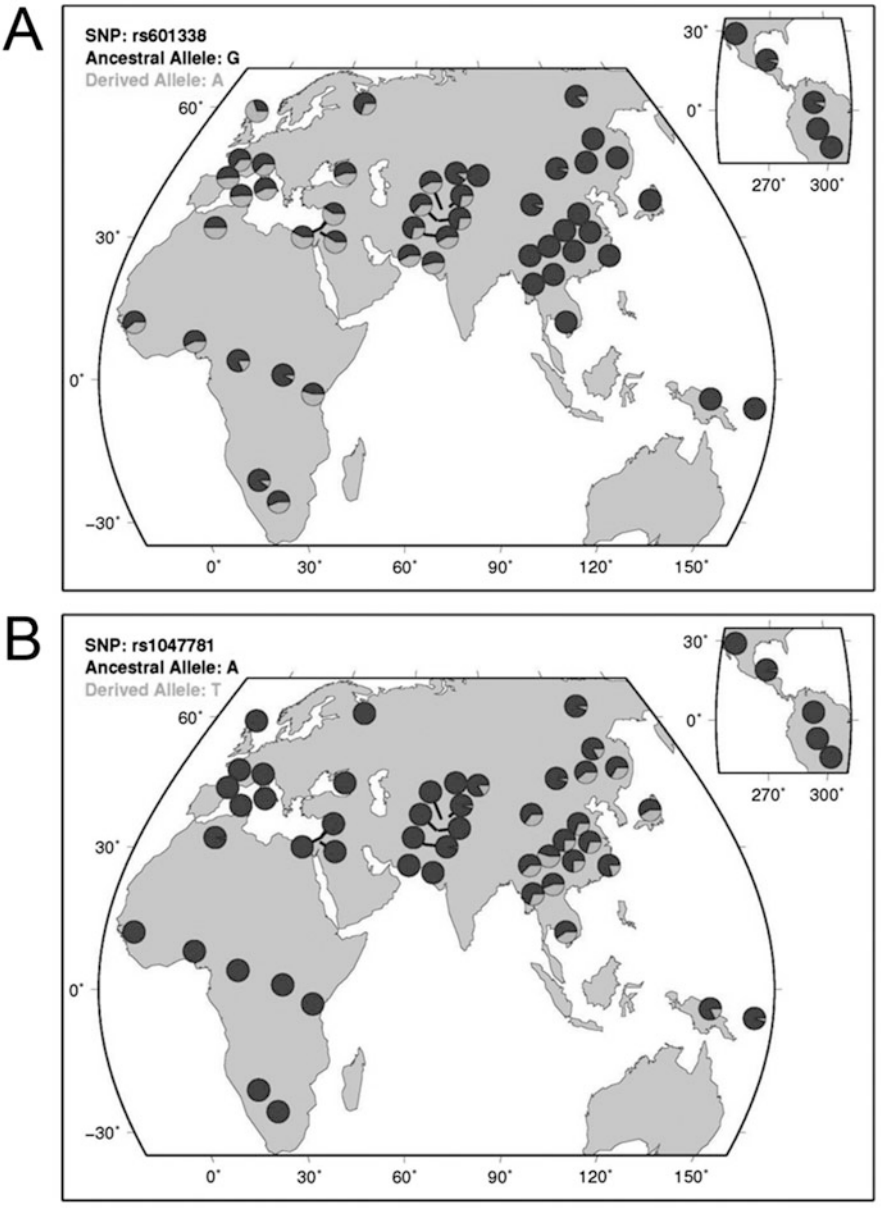

Fig. 11.6 Global distribution of nonsecretor variants in *FUT2*. (**a**) 154Trp>Ter (rs601338). (**b**) 140Ile>Phe (rs1047781) (http://hgdp.uchicago.edu/cgi-bin/gbrowse/HGDP/)

resulted from past pandemics of infectious diseases (Skoglund et al. 2011; Young et al. 2010). Recent genome scans for selective sweeps have detected a number of signatures on immunity-related genes. Together with the results of GWASs examining infectious diseases and immune functions, the findings outlined previously indicate that past endemics experienced by human populations and how those populations overcame them must be understood in greater detail. Further study of the phenotypes of modern humans will allow us to develop a greater understanding of the history of human conquests against the environments in which we have lived.

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