

DETAILED CONTENTS

CHAPTER 1 AN INTRODUCTION TO HUMAN EVOLUTIONARY GENETICS

1.1 WHAT IS HUMAN EVOLUTIONARY GENETICS?

1.2 INSIGHTS INTO PHENOTYPES AND DISEASES

A shared evolutionary history underpins our understanding of biology

Understanding evolutionary history is essential to understanding human biology today

Understanding evolutionary history shapes our expectations about the future

1.3 COMPLEMENTARY RECORDS OF THE HUMAN PAST

Understanding chronology allows comparison of evidence from different scientific approaches

It is important to synthesize different records of the past

None of the different records represents an unbiased picture of the past

1.4 WHAT CAN WE KNOW ABOUT THE PAST?

1.5 THE ETHICS OF STUDYING HUMAN POPULATIONS

SUMMARY

REFERENCES

CHAPTER 2 ORGANIZATION AND INHERITANCE OF THE HUMAN GENOME

2.1 THE BIG PICTURE: AN OVERVIEW OF THE HUMAN GENOME

2.2 STRUCTURE OF DNA

2.3 GENES, TRANSCRIPTION, AND TRANSLATION

Genes are made up of introns and exons, and include elements to initiate and regulate transcription

The genetic code allows nucleotide sequences to be translated into amino acid sequences

Gene expression is highly regulated in time and space

2.4 NONCODING DNA

Some DNA sequences in the genome are repeated in multiple copies

2.5 HUMAN CHROMOSOMES AND THE HUMAN KARYOTYPE

The human genome is divided into 46 chromosomes

Size, centromere position, and staining methods allow chromosomes to be distinguished

2.6 MITOSIS, MEIOSIS, AND THE INHERITANCE OF THE GENOME

2.7 RECOMBINATION—THE GREAT RESHUFFLER

2.8 NONRECOMBINING SEGMENTS OF THE GENOME

The male-specific Y chromosome escapes crossing over for most of its length

Maternally inherited mtDNA escapes from recombination

SUMMARY

QUESTIONS

REFERENCES

CHAPTER 3 HUMAN GENOME VARIATION

3.1 GENETIC VARIATION AND THE PHENOTYPE

Some DNA sequence variation causes Mendelian genetic disease

The relationship between genotype and phenotype is usually complex

Mutations are diverse and have different rates and mechanisms

3.2 SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) IN THE NUCLEAR GENOME

Base substitutions can occur through base misincorporation during DNA replication

Base substitutions can be caused by chemical and physical mutagens

Sophisticated DNA repair processes can fix much genome damage

The rate of base substitution can be estimated indirectly or directly

Because of their low mutation rate, SNPs usually show identity by descent

The CpG dinucleotide is a hotspot for mutation

Base substitutions and indels can affect the functions of genes

Synonymous base substitutions

Nonsynonymous base substitutions

Indels within genes

Base substitutions outside ORFs

Whole-genome resequencing provides an unbiased picture of SNP diversity

3.3 SEQUENCE VARIATION IN MITOCHONDRIAL DNA

mtDNA has a high mutation rate

The transmission of mtDNA mutations between generations is complex	64	Primer extension and detection by mass spectrometry is a medium-throughput method	109
3.4 VARIATION IN TANDEMLY REPEATED DNA SEQUENCES	65	High throughput SNP chips simultaneously analyze more than 1 million SNPs	110
Microsatellites have short repeat units and repeat arrays, and mutate through replication slippage	66	Whole-genome SNP chips are based on a tag SNP design	110
<i>Microsatellite mutation rates and processes</i>	67	4.6 DATABASES OF SEQUENCE VARIATION	112
Minisatellites have longer repeat units and arrays, and mutate through recombination mechanisms	69	4.7 DISCOVERING AND ASSAYING VARIATION AT MICROSATELLITES	112
<i>Minisatellite diversity and mutation</i>	70	4.8 DISCOVERING AND ASSAYING STRUCTURAL VARIATION ON DIFFERENT SCALES	114
Telomeres contain specialized and functionally important repeat arrays	71	Discovering and assaying variation at minisatellites	114
Satellites are large, sometimes functionally important, repeat arrays	72	Discovering and assaying variation at well-defined indels, including <i>Alu</i> /LINE polymorphisms	115
3.5 TRANSPOSABLE ELEMENT INSERTIONS	73	Discovering and assaying structural polymorphisms and copy-number variants	115
3.6 STRUCTURAL VARIATION IN THE GENOME	75	4.9 PHASING: FROM GENOTYPES TO HAPLOTYPES	119
Some genomic disorders arise from recombination between segmental duplications	76	Haplotypes can be determined by physical separation	120
Copy-number variation is widespread in the human genome	77	Haplotypes can be determined by statistical methods	120
Cytogenetic examination of chromosomes can reveal large-scale structural variants	78	Haplotypes can be determined by pedigree analysis	122
3.7 THE EFFECTS OF AGE AND SEX ON MUTATION RATE	78	4.10 STUDYING GENETIC VARIATION IN ANCIENT SAMPLES	123
3.8 THE EFFECTS OF RECOMBINATION ON GENOME VARIATION	81	DNA is degraded after death	123
Genomewide haplotype structure reveals past recombination behavior	84	Contamination is a major problem	125
Recombination behavior can be revealed by direct studies in pedigrees and sperm DNA	87	Application of next-generation sequencing to aDNA analysis	127
The process of gene conversion results in nonreciprocal exchange between DNA sequences	88	SUMMARY	129
SUMMARY	90	QUESTIONS	130
QUESTIONS	91	REFERENCES	130
REFERENCES	92	CHAPTER 5 PROCESSES SHAPING DIVERSITY	133
CHAPTER 4 FINDING AND ASSAYING GENOME DIVERSITY	95	5.1 BASIC CONCEPTS IN POPULATION GENETICS	133
4.1 FIRST, FIND YOUR DNA	96	Why do we need evolutionary models?	133
4.2 THE POLYMERASE CHAIN REACTION (PCR)	98	The Hardy–Weinberg equilibrium is a simple model in population genetics	134
4.3 SANGER SEQUENCING, THE HUMAN REFERENCE SEQUENCE, AND SNP DISCOVERY	100	5.2 GENERATING DIVERSITY BY MUTATION AND RECOMBINATION	136
4.4 A QUANTUM LEAP IN VARIATION STUDIES: NEXT-GENERATION SEQUENCING	101	Mutation changes allele frequencies	137
Illumina sequencing is a widely used NGS method	102	Mutation can be modeled in different ways	137
Sequencing can be targeted to regions of specific interest or the exome	105	Meiotic recombination generates new combinations of alleles	139
NGS data have to be processed and interpreted	106	Linkage disequilibrium is a measure of recombination at the population level	140
Third-generation methods use original, unamplified DNA	107	Recombination results in either crossing over or gene conversion, and is not uniform across the genome	140
4.5 SNP TYPING: LOW-, MEDIUM-, AND HIGH-THROUGHPUT METHODS FOR ASSAYING VARIATION	108	5.3 ELIMINATING DIVERSITY BY GENETIC DRIFT	141
PCR-RFLP typing is a simple low-throughput method	108	The effective population size is a key concept in population genetics	142

Different parts of the genome have different effective population sizes	143	Genomewide data allow calculation of genetic distances between individuals	176
Genetic drift causes the fixation and elimination of new alleles	143	Complex population structure can be analyzed statistically	177
Variation in census population size and reproductive success influence effective population size	144	Population structure can be analyzed using genomic data	178
Population subdivision can influence effective population size	147	Genetic distance and population structure can be represented using multivariate analyses	179
Mate choice can influence effective population size	148	6.4 PHYLOGENETICS	182
Genetic drift influences the disease heritages of isolated populations	149	Phylogenetic trees have their own distinctive terminology	182
5.4 THE EFFECT OF SELECTION ON DIVERSITY	149	There are several different ways to reconstruct phylogenies	184
Mate choice can affect allele frequencies by sexual selection	153	Trees can be constructed from matrices of genetic distances	184
5.5 MIGRATION	154	Trees can be generated using character-based methods	185
There are several models of migration	154	How confident can we be of a particular phylogenetic tree?	188
There can be sex-specific differences in migration	155	Networks are methods for displaying multiple equivalent trees	188
5.6 INTERPLAY AMONG THE DIFFERENT FORCES OF EVOLUTION	156	6.5 COALESCENT APPROACHES TO RECONSTRUCTING POPULATION HISTORY	190
There are important equilibria in population genetics	157	The genealogy of a DNA sequence can be described mathematically	191
<i>Mutation–drift balance</i>	157	Neutral mutations can be modeled on the gene genealogy using Poisson statistics	192
<i>Recombination–drift balance</i>	157	Coalescent analysis can be a simulation tool for hypothesis testing	193
<i>Mutation–selection balance</i>	158	Coalescent analysis uses ancestral graphs to model selection and recombination	193
Does selection or drift determine the future of an allele?	159	Coalescent models of large datasets are approximate	194
5.7 THE NEUTRAL THEORY OF MOLECULAR EVOLUTION	160	6.6 DATING EVOLUTIONARY EVENTS USING GENETIC DATA	194
The molecular clock assumes a constant rate of mutation and can allow dating of speciation	160	Dating population splits using F_{ST} and Nei's D statistics is possible, but requires a naive view of human evolution	195
There are problems with the assumptions of the molecular clock	161	Evolutionary models can include the timing of evolutionary events as parameters	195
SUMMARY	163	<i>Evolutionary models and effective population size</i>	196
QUESTIONS	164	An allele can be dated using diversity at linked loci	197
REFERENCES	164	<i>Interpreting TMRCA</i>	198
CHAPTER 6 MAKING INFERENCES FROM DIVERSITY	167	Estimations of mutation rate can be derived from direct measurements in families or indirect comparisons of species	198
6.1 WHAT DATA CAN WE USE?	167	An estimate of generation time is required to convert some genetic date estimates into years	198
6.2 SUMMARIZING GENETIC VARIATION	168	6.7 HAS SELECTION BEEN ACTING?	200
Heterozygosity is commonly used to measure genetic diversity	168	Differences in gene sequences between species can be used to detect selection	203
Nucleotide diversity can be measured using the population mutation parameter θ	169	Comparing variation <i>between</i> species with variation <i>within</i> a species can detect selection	207
The mismatch distribution can be used to represent genetic diversity	172	Selection tests can be based on the analysis of allele frequencies at variant sites	208
6.3 MEASURING GENETIC DISTANCE	173		
Genetic distances between populations can be measured using F_{ST} or Nei's D statistics	173		
Distances between alleles can be calculated using models of mutation	175		

Comparing haplotype frequency and haplotype diversity can reveal positive selection	209	Intraspecific diversity in great apes is greater than in humans	247
Analysis of frequency differences between populations can indicate positive selection	209	Signatures of lineage-specific selection can be detected in ape genomes	250
Other methods can be used to detect ongoing or very recent positive selection	214	SUMMARY	254
How can we combine information from different statistical tests?	214	QUESTIONS	254
Tests for positive selection have severe limitations	215	REFERENCES	254
6.8 ANALYZING GENETIC DATA IN A GEOGRAPHICAL CONTEXT	216	CHAPTER 8 WHAT GENETIC CHANGES HAVE MADE US HUMAN?	257
Genetic data can be displayed on maps	217	8.1 MORPHOLOGICAL AND BEHAVIORAL CHANGES EN ROUTE TO <i>HOMO SAPIENS</i>	258
Genetic boundary analysis identifies the zones of greatest allele frequency change within a genetic landscape	219	Some human traits evolved early in hominin history	260
Spatial autocorrelation quantifies the relationship of allele frequency with geography	219	The human mind is unique	263
Mantel testing is an alternative approach to examining a relationship between genetic distance and other distance measures	220	Only a few phenotypes are unique to modern humans	265
SUMMARY	220	8.2 GENETIC UNIQUENESS OF HUMANS AND HOMININS	265
QUESTIONS	221	The sequence and structural differences between humans and other great apes can be cataloged	265
REFERENCES	222	Humans have gained and lost a few genes compared with other great apes	266
CHAPTER 7 HUMANS AS APES	225	Humans differ in the sequence of genes compared with other great apes	269
Which nonhuman animals are the closest living relatives of humans?	225	Humans differ from other apes in the expression levels of genes	270
Are humans typical apes?	225	Genome sequencing has revealed a small number of fixed genetic differences between humans and both Neanderthals and Denisovans	272
7.1 EVIDENCE FROM MORPHOLOGY	226	8.3 GENETIC BASIS OF PHENOTYPIC DIFFERENCES BETWEEN APES AND HUMANS	273
Primates are an Order of mammals	226	Mutations causing neoteny have contributed to the evolution of the human brain	273
Hominoids share a number of phenotypic features with other anthropoids	228	The genetic basis for laterality and language remains unclear	275
Ancestral relationships of hominoids are difficult to resolve on morphological evidence	230	What next?	278
7.2 EVIDENCE FROM CHROMOSOMES	232	SUMMARY	278
Human and great ape karyotypes look similar, but not identical	232	QUESTIONS	279
Molecular cytogenetic analyses support the picture from karyotype comparisons	233	REFERENCES	279
7.3 EVIDENCE FROM MOLECULES	236	CHAPTER 9 ORIGINS OF MODERN HUMANS	283
Molecular data support a recent date of the ape-human divergence	237	9.1 EVIDENCE FROM FOSSILS AND MORPHOLOGY	284
Genetic data have resolved the gorilla-chimpanzee-human trichotomy	237	Some fossils that may represent early hominins from 4–7 MYA are known from Africa	285
Sequence divergence is different among great apes across genetic loci	239	Fossils of australopithecines and their contemporaries are known from Africa	287
Great apes differ by gains and losses of genetic material	241	The genus <i>Homo</i> arose in Africa	290
The DNA sequence divergence rates differ in hominoid lineages	241	The earliest anatomically modern human fossils are found in Africa	294
7.4 GENETIC DIVERSITY AMONG THE GREAT APES	242	The morphology of current populations suggests an origin in Africa	295
How many genera, species, and subspecies are there?	247	9.2 EVIDENCE FROM ARCHAEOLOGY AND LINGUISTICS	295
		Paleolithic archaeology has been studied extensively	298

Evidence from linguistics suggests an origin of language in Africa	299	Low differentiation can result from balancing selection	334
9.3 HYPOTHESES TO EXPLAIN THE ORIGIN OF MODERN HUMANS	300	High differentiation can result from directional selection	335
9.4 EVIDENCE FROM THE GENETICS OF PRESENT-DAY POPULATIONS	301	<i>Positive selection at EDAR</i>	336
Genetic diversity is highest in Africa	301	SUMMARY	338
Genetic phylogenies mostly root in Africa	304	QUESTIONS	339
<i>Mitochondrial DNA phylogeny</i>	304	REFERENCES	339
<i>Y-chromosomal phylogeny</i>	305		
<i>Other phylogenies</i>	305		
Insights can be obtained from demographic models	306		
9.5 EVIDENCE FROM ANCIENT DNA	307		
Ancient mtDNA sequences of Neanderthals and Denisovans are distinct from modern human variation	308		
A Neanderthal draft genome sequence has been generated	309		
A Denisovan genome sequence has been generated	310		
SUMMARY	313		
QUESTIONS	315		
REFERENCES	315		
CHAPTER 10 THE DISTRIBUTION OF DIVERSITY	319		
10.1 STUDYING HUMAN DIVERSITY	319		
The history and ethics of studying diversity are complex	319		
<i>Linnaeus' classification of human diversity</i>	320		
<i>Galton's "Comparative worth of different races"</i>	320		
<i>Modern attitudes to studying diversity</i>	320		
Who should be studied?	323		
A few large-scale studies of human genetic variation have made major contributions to human evolutionary genetics	323		
What is a population?	326		
How many people should be analyzed?	327		
10.2 APPORTIONMENT OF HUMAN DIVERSITY	328		
The apportionment of diversity shows that most variation is found within populations	328		
The apportionment of diversity can differ between segments of the genome	329		
Patterns of diversity generally change gradually from place to place	330		
The origin of an individual can be determined surprisingly precisely from their genotype	331		
The distribution of rare variants differs from that of common variants	332		
10.3 THE INFLUENCE OF SELECTION ON THE APPORTIONMENT OF DIVERSITY	333		
The distribution of levels of differentiation has been studied empirically	334		
		CHAPTER 11 THE COLONIZATION OF THE OLD WORLD AND AUSTRALIA	341
		11.1 A COLDER AND MORE VARIABLE ENVIRONMENT 15–100 KYA	341
		11.2 FOSSIL AND ARCHAEOLOGICAL EVIDENCE FOR TWO EXPANSIONS OF ANATOMICALLY MODERN HUMANS OUT OF AFRICA IN THE LAST ~130 KY	344
		Anatomically modern, behaviorally pre-modern humans expanded transiently into the Middle East ~90–120 KYA	345
		Modern human behavior first appeared in Africa after 100 KYA	346
		Fully modern humans expanded into the Old World and Australia ~50–70 KYA	347
		<i>Modern human fossils in Asia, Australia, and Europe</i>	347
		<i>Initial colonization of Australia</i>	349
		<i>Upper Paleolithic transition in Europe and Asia</i>	352
		11.3 A SINGLE MAJOR MIGRATION OUT OF AFRICA 50–70 KYA	353
		Populations outside Africa carry a shared subset of African genetic diversity with minor Neanderthal admixture	353
		mtDNA and Y-chromosomal studies show the descent of all non-African lineages from a single ancestor for each who lived 55–75 KYA	355
		11.4 EARLY POPULATION DIVERGENCE BETWEEN AUSTRALIANS AND EURASIANS	357
		SUMMARY	360
		QUESTIONS	361
		REFERENCES	361
		CHAPTER 12 AGRICULTURAL EXPANSIONS	363
		12.1 DEFINING AGRICULTURE	363
		12.2 THE WHERE, WHEN, AND WHY OF AGRICULTURE	365
		Where and when did agriculture develop?	365
		Why did agriculture develop?	366
		Which domesticates were chosen?	368
		12.3 OUTCOMES OF AGRICULTURE	369
		Agriculture had major impacts on demography and disease	369
		<i>Rapid demographic growth</i>	369

<i>Malnutrition and infectious disease</i>	369	CHAPTER 13 INTO NEW-FOUND LANDS	409
<i>Agriculture led to major societal changes</i>	371	13.1 SETTLEMENT OF THE NEW TERRITORIES	409
12.4 THE FARMING–LANGUAGE CO-DISPERSAL HYPOTHESIS	372	Sea levels have changed since the out-of-Africa migration	409
Some language families have spread widely and rapidly	372	What drives new settlement of uninhabited lands?	411
Linguistic dating and construction of proto-languages have been used to test the hypothesis	373	13.2 PEOPLING OF THE AMERICAS	412
What are the genetic implications of language spreads?	373	The changing environment has provided several opportunities for the peopling of the New World	413
12.5 OUT OF THE NEAR EAST INTO EUROPE	374	Fossil and archaeological evidence provide a range of dates for the settlement of the New World	415
Nongenetic evidence provides dates for the European Neolithic	374	<i>Fossils</i>	415
Different models of expansion give different expectations for genetic patterns	377	<i>Archaeological remains</i>	416
<i>Models are oversimplifications of reality</i>	378	<i>Clovis and the Paleoindians</i>	416
Principal component analysis of classical genetic polymorphisms was influential	379	<i>Pre-Clovis sites</i>	416
<i>Interpreting synthetic maps</i>	379	<i>Unresolved issues</i>	417
mtDNA evidence has been controversial, but ancient DNA data are transforming the field	380	Did the first settlers go extinct?	418
<i>Data from ancient mtDNA</i>	382	A three-migration hypothesis has been suggested on linguistic grounds	419
Y-chromosomal data show strong clines in Europe	384	Genetic evidence has been used to test the single- and the three-wave migration scenarios	419
<i>New developments for the Y chromosome</i>	384	<i>Mitochondrial DNA evidence</i>	420
Biparentally inherited nuclear DNA has not yet contributed much, but important ancient DNA data are now emerging	386	<i>Interpretation of the mtDNA data</i>	422
<i>Ancient DNA data</i>	387	<i>Evidence from the Y chromosome</i>	422
What developments will shape debate in the future?	388	<i>Evidence from the autosomes</i>	424
12.6 OUT OF TROPICAL WEST AFRICA INTO SUB-EQUATORIAL AFRICA	388	<i>Conclusions from the genetic data</i>	425
There is broad agreement on the background to African agricultural expansion	388	13.3 PEOPLING OF THE PACIFIC	425
<i>Rapid spread of farming economies</i>	389	Fossil and archaeological evidence suggest that Remote Oceania was settled more recently than Near Oceania	427
Bantu languages spread far and rapidly	390	Two groups of languages are spoken in Oceania	428
Genetic evidence is broadly consistent, though ancient DNA data are lacking	392	Several models have been proposed to explain the spread of Austronesian speakers	430
<i>Genomewide evidence</i>	392	Austronesian dispersal models have been tested with genetic evidence	431
<i>Evidence from mtDNA and the Y chromosome</i>	393	<i>Classical polymorphisms</i>	431
12.7 GENETIC ANALYSIS OF DOMESTICATED ANIMALS AND PLANTS	394	<i>Globin gene mutations</i>	432
Selective regimes had a massive impact on phenotypes and genetic diversity	395	<i>Mitochondrial DNA</i>	433
<i>Key domestication changes in crops</i>	396	<i>The Y chromosome</i>	436
<i>Effects on crop genetic diversity</i>	398	<i>Autosomal evidence</i>	437
<i>Phenotypic and genetic change in animals</i>	399	Evidence from other species has been used to test the Austronesian dispersal models	438
How have the origins of domesticated plants been identified?	400	SUMMARY	440
How have the origins of domesticated animals been identified?	401	QUESTIONS	441
<i>Cattle domestication</i>	403	REFERENCES	441
SUMMARY	404	CHAPTER 14 WHAT HAPPENS WHEN POPULATIONS MEET	443
QUESTIONS	405	14.1 WHAT IS GENETIC ADMIXTURE?	443
REFERENCES	405	Admixture has distinct effects on genetic diversity	445
		14.2 THE IMPACT OF ADMIXTURE	447
		Different sources of evidence can inform us about admixture	447

<i>Consequences of admixture for language</i>	447	15.3 SKIN PIGMENTATION AS AN ADAPTATION TO ULTRAVIOLET LIGHT	485
<i>Archaeological evidence for admixture</i>	448	Melanin is the most important pigment influencing skin color	486
<i>The biological impact of admixture</i>	449	Variable ultraviolet light exposure is an adaptive explanation for skin color variation	486
14.3 DETECTING ADMIXTURE	450	Several genes that affect human pigmentation are known	489
Methods based on allele frequency can be used to detect admixture	450	Genetic variation in human pigmentation genes is consistent with natural selection	492
Admixture proportions vary among individuals and populations	453	Does sexual selection have a role in human phenotypic variation?	493
<i>Calculating individual admixture levels using multiple loci</i>	453	15.4 LIFE AT HIGH ALTITUDE AND ADAPTATION TO HYPOXIA	495
<i>Calculating individual admixture levels using genomewide data</i>	454	Natural selection has influenced the overproduction of red blood cells	495
<i>Calculating admixture levels from estimated ancestry components</i>	456	High-altitude populations differ in their adaptation to altitude	496
<i>Problems of measuring admixture</i>	457	15.5 VARIATION IN THE SENSE OF TASTE	496
Natural selection can affect the admixture proportions of individual genes	458	Variation in tasting phenylthiocarbamide is mostly due to alleles of the <i>TAS2R38</i> gene	498
14.4 LOCAL ADMIXTURE AND LINKAGE DISEQUILIBRIUM	460	There is extensive diversity of bitter taste receptors in humans	499
How does admixture generate linkage disequilibrium?	461	Sweet, umami, and sour tastes may show genetic polymorphism	499
<i>Admixture mapping</i>	462	15.6 ADAPTING TO A CHANGING DIET BY DIGESTING MILK AND STARCH	500
<i>Admixture dating</i>	463	There are several adaptive hypotheses to explain lactase persistence	501
14.5 SEX-BIASED ADMIXTURE	464	Lactase persistence is caused by SNPs within an enhancer of the lactase gene	502
What is sex-biased admixture?	464	Increased copy number of the amylase gene reflects an adaptation to a high-starch diet	504
<i>Detecting sex-biased admixture</i>	465	15.7 THE FUTURE OF HUMAN EVOLUTION	506
<i>Sex-biased admixture resulting from directional mating</i>	465	Have we stopped evolving?	506
<i>The effect of admixture on our genealogical ancestry</i>	467	Natural selection acts on modern humans	506
14.6 TRANSNATIONAL ISOLATES	467	Can we predict the role of natural selection in the future?	507
Roma and Jews are examples of widely spread transnational isolates	468	<i>Climate change</i>	507
<i>European Roma</i>	468	<i>Dietary change</i>	507
<i>The Jews</i>	469	<i>Infectious disease</i>	507
SUMMARY	471	What will be the effects of future demographic changes?	508
QUESTIONS	472	<i>Increasing population size</i>	509
REFERENCES	473	<i>Increased mobility</i>	510
CHAPTER 15 UNDERSTANDING THE PAST, PRESENT, AND FUTURE OF PHENOTYPIC VARIATION	477	<i>Differential fertility</i>	510
15.1 NORMAL AND PATHOGENIC VARIATION IN AN EVOLUTIONARY CONTEXT	477	<i>Differential generation time</i>	511
15.2 KNOWN VARIATION IN HUMAN PHENOTYPES	478	Will the mutation rate change?	512
What is known about human phenotypic variation?	478	SUMMARY	512
<i>Morphology and temperature adaptation</i>	479	QUESTIONS	513
<i>Facial features</i>	479	REFERENCES	513
<i>Tooth morphology and cranial proportions</i>	480		
<i>Behavioral differences</i>	481		
How do we uncover genotypes underlying phenotypes?	483		
What have we discovered about genotypes underlying phenotypes?	485		

CHAPTER 16 EVOLUTIONARY INSIGHTS INTO SIMPLE GENETIC DISEASES

16.1 GENETIC DISEASE AND MUTATION—SELECTION BALANCE

Variation in the strength of purifying selection can affect incidence of genetic disease 520

Variation in the deleterious mutation rate can affect incidence of genetic disease 522

16.2 GENETIC DRIFT, FOUNDER EFFECTS, AND CONSANGUINITY

Jewish populations have a particular disease heritage 524

Finns have a disease heritage very distinct from other Europeans 525

Consanguinity can lead to increased rates of genetic disease 526

16.3 EVOLUTIONARY CAUSES OF GENOMIC DISORDERS

Segmental duplications allow genomic rearrangements with disease consequences 527

Duplications accumulated in ancestral primates 529

16.4 GENETIC DISEASES AND SELECTION BY MALARIA

Sickle-cell anemia is frequent in certain populations due to balancing selection 531

α -Thalassemias are frequent in certain populations due to balancing selection 534

Glucose-6-phosphate dehydrogenase deficiency alleles are maintained at high frequency in malaria-endemic populations 535

What can these examples tell us about natural selection? 537

SUMMARY 538

QUESTIONS 538

REFERENCES 539

CHAPTER 17 EVOLUTION AND COMPLEX DISEASES

17.1 DEFINING COMPLEX DISEASE

The genetic contribution to variation in disease risk varies between diseases 544

Infectious diseases are complex diseases 544

17.2 THE GLOBAL DISTRIBUTION OF COMPLEX DISEASES

Is diabetes a consequence of a post-agricultural change in diet? 546

The drift gene hypothesis 547

Evidence from genome-wide studies 548

The thrifty phenotype hypothesis 549

17.3 IDENTIFYING ALLELES INVOLVED IN COMPLEX DISEASE

Genetic association studies are more powerful than linkage studies for detecting small genetic effects 549

Candidate gene association studies have not generally been successful in identifying susceptibility alleles for complex disease 552

Genomewide association studies can reliably identify susceptibility alleles to complex disease 552

GWAS data have been used for evolutionary genetic analysis 556

17.4 WHAT COMPLEX DISEASE ALLELES DO WE EXPECT TO FIND IN THE POPULATION?

Negative selection acts on disease susceptibility alleles 557

Positive selection acts on disease resistance alleles 560

Severe sepsis and CASP12 560

Malaria and the Duffy antigen 560

HIV-1 and CCR5 Δ 32 562

Unexpectedly, some disease susceptibility alleles with large effects are observed at high frequency 562

Susceptibility to kidney disease, APOL1, and resistance to sleeping sickness 562

Implications for other GWAS results 563

17.5 GENETIC INFLUENCE ON VARIABLE RESPONSE TO DRUGS

Population differences in drug-response genes exist, but are not well understood 564

SUMMARY 567

QUESTIONS 568

REFERENCES 569

CHAPTER 18 IDENTITY AND IDENTIFICATION

18.1 INDIVIDUAL IDENTIFICATION

The first DNA fingerprinting and profiling methods relied on minisatellites 573

PCR-based microsatellite profiling superseded minisatellite analysis 574

How do we interpret matching DNA profiles? 574

Complications from related individuals, and DNA mixtures 576

Large forensic identification databases are powerful tools in crime-fighting 577

Controversial aspects of identification databases 577

The Y chromosome and mtDNA are useful in specialized cases 578

Y chromosomes in individual identification 579

mtDNA in individual identification 580

18.2 WHAT DNA CAN TELL US ABOUT JOHN OR JANE DOE

DNA-based sex testing is widely used and generally reliable 580

Sex reversal 581

Deletions of the AMELY locus in normal males 582

Some other phenotypic characteristics are predictable from DNA 582

Reliability of predicting population of origin depends on what DNA variants are analyzed	583	What genes are encoded within the mitochondrial genome?	602
Prediction from forensic microsatellite multiplexes	583	What diseases are caused by mutations within mtDNA?	602
Prediction from other systems	584	How has the study of mtDNA diversity developed?	602
The problem of admixed populations	584	How is information from the mtDNA variants in an individual combined?	603
18.3 DEDUCING FAMILY AND GENEALOGICAL RELATIONSHIPS	585	Why are all the deep-rooting clades called L?	603
The probability of paternity can be estimated confidently	586	Why is mtDNA so useful for exploring the human past?	603
Other aspects of kinship analysis	588	What about possible selection pressures?	605
The Y chromosome and mtDNA are useful in genealogical studies	588	THE Y CHROMOSOME	605
The Thomas Jefferson paternity case	588	How has it evolved?	605
DNA-based identification of the Romanovs	590	What does the chromosome contain?	605
Y-chromosomal DNA has been used to trace modern diasporas	591	How similar are Y chromosomes within and between species?	606
Y-chromosomal haplotypes tend to correlate with patrilineal surnames	592	What molecular polymorphisms are found on the Y chromosome?	606
18.4 THE PERSONAL GENOMICS REVOLUTION	593	How should the polymorphic information from different variants be combined?	606
The first personal genetic analysis involved the Y chromosome and mtDNA	593	What are the applications of studying Y-chromosomal diversity?	608
Personal genomewide SNP analysis is used for ancestry and health testing	593	Is there any evidence of selection on the Y chromosome?	608
Personal genome sequencing provides the ultimate resolution	593	REFERENCES	608
Personal genomics offers both promise and problems	596	GLOSSARY	609
SUMMARY	597	INDEX	641
QUESTIONS	597		
REFERENCES	598		
APPENDIX	601		
HAPLOGROUP NOMENCLATURE	601		
THE MITOCHONDRIAL GENOME	602		
What are its origins?	602		