SCIENCE AND SOCIETY

A genetic profile of contemporary Jewish populations

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The Jews are an ancient people with a history spanning several millennia. Genetic studies over the past 50 years have shed light on Jewish origins, the relatedness of Jewish communities and the genetic basis of Mendelian disorders among Jewish peoples. In turn, these observations have been used to develop genetic testing programmes and, more recently, to attempt to discover new genes for susceptibility to common diseases.

The Jewish people originated in the Middle East during the Bronze Age[1]. For more than 2,000 years, Jews have been a migratory people, establishing communities throughout the Middle East and the Mediterranean basin[2]. Some of these communities retained their continuity over long periods of time; in those communities, Jews were linked by religion, language (often a Jewish dialect of a local language), customs and marriage. The designation of who was a Jew was prescribed by religious law as one whose mother was a Jew. Entry into the community was possible through religious conversion, but was probably a rare event. As a result, Jewish identity has been continuous up to the present. Contemporary Jewish groups are delineated on the basis of the long-term place of residence of the members of the community. Three groups of Jews — Middle Eastern (or Oriental) Jews, Sephardic Jews and Ashkenazi Jews — have been defined on the basis of their three main regions of residence, with further refinement based on countries within these regions (BOX 1).

Contemporary Jewry is comprised of ~13 million people, of whom 5.7 million reside in the United States and 4.7 million reside in Israel, with the remainder living throughout the world[3]. Among the Jews of the United States, ~90% are of Ashkenazi origin. Among the Jews of Israel, 47% are of Ashkenazi, 30% of Sephardic and 23% of Oriental origin. Contemporary Jews are predominantly an urban people, with 70% living in 20 cities or their metropolitan areas.

A genetic link among Jewish groups

The idea of a link among Jews is supported by genetic polymorphism studies. Although by religious law Jewishness is a maternally transmitted trait, studies of mitochondrial and Y-chromosomal polymorphisms provide strong evidence for both matrilineal and patrilineal transmission, and many generations of ENDOGAMY in this population[4–7]. Both types of study anchor the origin of the Jews to the Middle East. Older, single-locus studies, involving blood groups, enzymes, serum markers, immunoglobulins and HUMAN LEUKOCYTE ANTIGEN types have been divided on the issue of whether Jews have had significant ADMIXTURE with non-Jewish populations, including possible mass conversions (reviewed in REFS 8,9). These studies are limited by the fact that some of these marker systems have a low frequency of polymorphism and that their alleles might have been subject to selection, causing alteration in allele frequencies compared with the founder population.

Studies of Y-chromosomal markers have provided an opportunity to assess GENE FLOW into Jewish populations from non-Jewish males. Contemporary Jews and Middle Eastern Arabs have 13 common Y-chromosomal HAPLOTYPES that are shared both within and across groups, indicating that the original Jews might have arisen from local peoples and are not the offspring of a single patriarch[7]. The most common Y-chromosomal haplotypes are thought to be of Middle Eastern and North African origin, and the less common haplotypes of Asian origin, indicating that gene flow had a role in the formation of the Jewish people. The rate of admixture is estimated to be 0.5% per generation over the 80 generations since the founding of the Ashkenazi Jews, indicating that this group might have remained endogamous throughout much of its history and that the offspring of those who married outside were lost as members of the community[10].

A specific Y-chromosomal haplotype defined by biallelic and MICROSATELLITE markers was found among a high proportion of Kohanim — men from the priestly group — numbering 10% of the total contemporary Jewish male population[11]. Among Ashkenazi and Sephardic Kohanim, 61–69% have this haplotype or variations thereof, thereby defining it as the 'Kohen modal haplotype'[12]. By examining the decay of the microsatellite markers, this haplotype was estimated to have originated ~2,000–3,000 years ago. The upper estimate COALESCENCE time coincides with the First Temple period in Jewish history, when male descendants of the Biblical Aaron were assigned a priestly role with special responsibilities. The plausible lower limit of the coalescence time is 1,000 years later — after the destruction of the Second Temple.

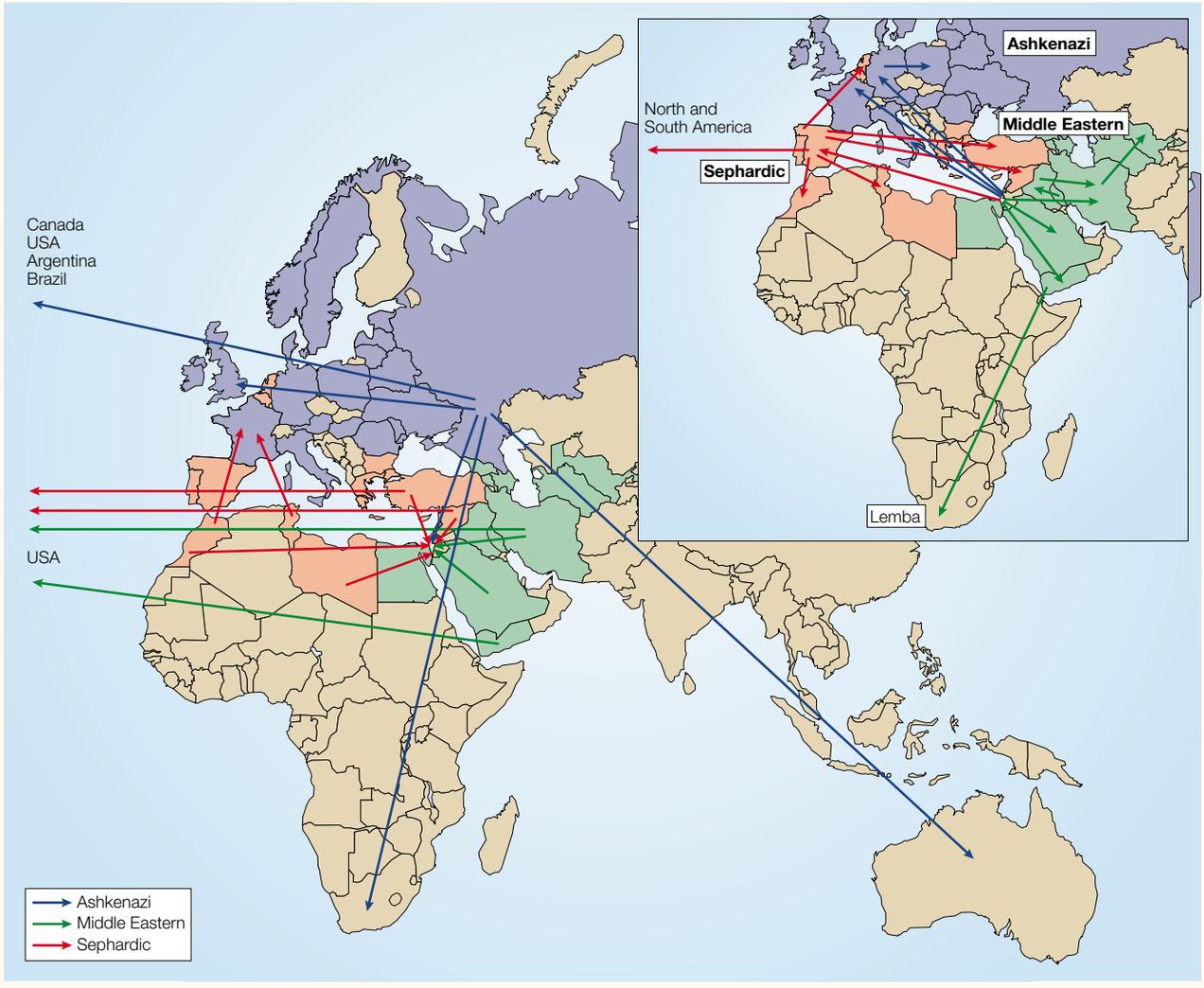
The presence of the Kohen modal haplotype has been used as a marker for Jewish ancestry among other groups; specifically, among the Lemba, a black South African tribe that claimed to have Jewish ancestry. Analysis of Y-chromosomal haplotypes from different clans showed mixed Semitic and

Box 1 | **Jewish population history**

An early history of the Jewish people is found in the Bible, although the accuracy of Biblical sources has been called into question by contemporary historians[66]. Most now believe that a Jewish identity can be ascribed only from the time of the Greek Hasmoneans, in the second century before the COMMON ERA (C.E.). According to their area of long-term residence, contemporary Jewish populations are divided into three groups (inset figure). Middle Eastern (or Oriental) Jews lived in contemporary Israel and Palestine, as well as in Iran, Iraq, Central Asia and the Arabian Peninsula. Sephardic Jews (from the Hebrew word for Spanish) resided in Spain and Portugal up to the Spanish Inquisition in the late fifteenth century, during which time Jews were persecuted by the Catholic Church, and then migrated to North Africa, Italy, the Balkans, Turkey, Lebanon, Syria and the Americas[67]. Ashkenazi Jews (from the Hebrew word for German) moved north of the Alps, probably from Italy, during the first millennium of the common era[34]. During the ninth century, the ancestors of Ashkenazi Jews settled in the cities of the Rhineland and developed their own language, Yiddish (a form of middle-high German with words also derived from Hebrew and Slavic languages). In the twelfth and thirteenth centuries, Ashkenazi Jews were expelled from the countries of Western Europe and were granted charters to settle in Poland and Lithuania. As a result, the centre of Ashkenazi Jewry shifted to the East, where it remained for the following five centuries.

Jews refer to themselves as a 'people' because this is an inclusive term that reflects a common religion, and, to some extent, a shared culture, historic experience and language. The term is deemed preferable to 'race', because Jews do not share characteristic physical features across groups[68]. In addition, the term 'race' was discredited by the pseudoscientific nature of PHRENOLOGY and racial hygiene studies that led to disastrous eugenic practices in the early and mid-twentieth century[69]. The term 'people' is deemed preferable to 'nation' because throughout most of their history Jews have not shared a common political or governing authority.

In the late nineteenth and early twentieth centuries, the centre of Ashkenazi Jewry shifted westwards (main figure), with large migration to the Americas, Western Europe, Australia and South Africa. In the twentieth century, three important events influenced Jewish demography — the Jewish Holocaust of the Second World War, leading to the death of six million people, the immigration of Jews from many of the countries of the diaspora to Israel, and the intermarriage of Jews, either with partners coming from different Jewish groups or with one partner being non-Jewish[10].



South African ancestry. The Kohen modal haplotype has been found among 8.8% of Lemba males, and at much higher frequency among the male members of the senior Lemba clan, the Buba[13]. These show that certain oral traditions can be validated by analysis of genetic ancestry.

Some contemporary Jewish groups share genetic markers with their historical non-Jewish neighbours. Ethiopian Jews share a set of Y-chromosomal haplotypes with non-Jewish Ethiopians. Cochin Jews share a significant number of serum markers with non-Jewish south Indians[4,7,14,15]. These findings indicate that these groups might have had significant admixture or that the presence of Jewish groups in these regions resulted from the religious conversion of local people.

Genetic diseases of Jewish groups

At least 40 genetic conditions with Mendelian patterns of transmission have been described in different Jewish groups (reviewed in REFS 16,17). The molecular basis for almost all of these conditions has been described (TABLES 1 and 2). In every case, one or two prevalent founder mutations and, frequently, several minor mutations have been identified. For some of these conditions, many other mutations have been found in non-Jewish populations. These conditions vary in their severity and age of onset, and can affect virtually any organ system. Several classes of disease have occurred more than once, including lysosomal storage diseases (Tay–Sachs disease, Niemann–Pick disease, Gaucher disease and mucolipidosis IV), glycogen storage disease (types I and III), clotting factor disorders (factor XI deficiency, factor VII deficiency and combined factors V and VIII deficiency), disorders of adrenal steroid biosynthesis (21-hydroxylase deficiency, 11-hydroxylase deficiency and corticosterone methyl oxidase II deficiency) and disorders of DNA repair with increased susceptibility to cancer (*BRCA1*, *BRCA2*, Bloom syndrome and Fanconi anaemia).

Some of these conditions are found in single Jewish groups, whereas others are found in several Jewish groups, or among Jews and non-Jews. An analysis of linked polymorphisms for most conditions that are shared across groups have identified the same genetic backgrounds, confirming the hypothesis of common origins. Some exceptions are cystic fibrosis, β-thalassaemia, Tay–Sachs disease (in Ashkenazi and Moroccan Jews) and the prevalent 30delG mutation in the *GJB2* (gap junction protein, β2) gene that is associated with autosomal-recessive non-syndromic hearing loss[18–21]. The latter condition is known to result from mutations at a hot-spot site in the *GJB2* gene.

Conditions for which mutations are shared between Jewish and non-Jewish groups tended to arise in the ancient world and to be disseminated around the Mediterranean basin, before the time that Jews were organized as a people. So, 167delT, the more prevalent mutation in the *GJB2* gene among Ashkenazi Jews, is observed on the same genetic background among Roman Jews, Palestinians, Italians, Spaniards and Greeks[18,22,23]. The phenomenon of shared mutations on the same genetic background is also observed for the common mutations in the *MEFV* gene that cause familial Mediterranean fever, the ΔF508 mutation (a deletion of Phe508) in the protein encoded by the *CFTR* gene that causes cystic fibrosis, and the factor V Leiden mutation[24–26].

Origins of mutations

Some mutations arose during the period of Jewish life in ancient Palestine, before the diaspora, and now are shared across Jewish

Table 1 | **Diseases with mutations shared among Jewish groups**

Disease (OMIM number)	Gene	Major biochemical effect	Heterozygote frequency	Jewish groups with which mutation sharing occurs	Ref
α-thalassaemia (141800)	*HBA1*	Decreased red-cell survival	1/100–1/5	Ashkenazi, Georgian, Iraqi, Kurdish, Moroccan, Yemeni	20
Ataxia telangiectasia (208900)	*ATM*	DNA repair	1/83	Moroccan, Tunisian	70
β-thalassaemia (141900)	*HBB*	Decreased red-cell survival	1/100–1/5	Ashkenazi, Indian, Kurdish, Moroccan, Turkish, Yemeni	19
Combined factors V and VIII deficiency (227300)	*LMAN1*	Molecular chaperone from ER to Golgi	1/158 (?)	Tunisian, Iranian	30
Creutzfeldt–Jakob disease (123400)	*PRNP*	Signal transduction	1/24,000	Libyan, Tunisian	36
Cystic fibrosis (219700)	*CFTR*	Chloride ion transport	1/99–1/25	Ashkenazi, Georgian, Greek, Iranian, Iraqi, Moroccan, Roman, Yemeni	21
Factor VII deficiency (227500)	*F7*	Blood clotting	1/40	Iranian, Moroccan	71
Factor XI deficiency, type II (264900)	*F11*	Blood clotting	1/30–1/23	Ashkenazi, Iraqi	27
Familial breast and ovarian cancer I (113705)	*BRCA1*	DNA repair	1/100	Ashkenazi, Iraqi, Moroccan	29
Familial Mediterranean fever (249100)	*MEFV*	Leukocyte inflammatory response protein	1/10–1/5	Ashkenazi, Iranian, Iraqi, Roman, Libyan, Moroccan	72
Non-syndromic recessive deafness (220290)	*GJB2*	Gap junction formation	1/44–1/20	Ashkenazi, Roman	18

ATM, ataxia telangiectasia mutated (includes complementation groups A, C and D); *BRCA1*, breast cancer 1, early onset; *CFTR*, cystic fibrosis transmembrane conductance regulator, ATP-binding cassette (sub-family C, member 7); ER, endoplasmic reticulum; *F7*, coagulation factor VII (serum prothrombin conversion accelerator); *F11*, coagulation factor XI (plasma thromboplastin antecedent); *GJB2*, gap junction protein, β2, 26 kDa (connexin 26); *HBA1*, haemoglobin, α1; *HBB*, haemoglobin, β; *LMAN1*, lectin, mannose-binding, 1; *MEFV*, Mediterranean fever; *PRNP*, prion protein (p27–30) (Creutzfeldt–Jakob disease, Gerstmann–Strausler–Scheinker syndrome, fatal familial insomnia).

groups (TABLE 1). The type III mutation in the factor XI gene, associated with clotting factor deficiency, is found on the same genetic background among Ashkenazi and Iraqi Jews[27]. The coalescence time for this mutation between these two groups is estimated to be 120 generations ago, a time frame that would fit the period of Jewish residence in Palestine[28]. The common mutation in the *BRCA1* gene (185delAG) is found in Ashkenazi, Iraqi and Moroccan Jews[29]. The common mutation in the *LMAN1* (lectin, mannose-binding, 1) gene associated with combined factors V and VIII deficiency is found in Tunisian and Iranian Jews[30]. In both cases, the mutation is likely to have had an ancient origin, although migration between groups is possible. If the origins of these mutations were ancient, then GENETIC DRIFT could account for their absence in other Jewish groups — mutation carriers either were not part of the founder population of these groups or did not transmit their mutations in subsequent generations.

Table 2 | **Diseases prevalent in specific Jewish groups**

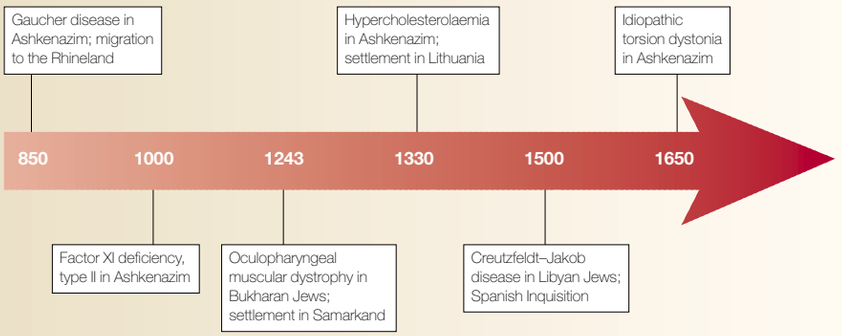
Disease (OMIM number)	Gene	Major biochemical effect	Heterozygote frequency	Refs
Predominantly Ashkenazi Jewish diseases				
Bloom syndrome (210900)	*BLM*	DNA repair	1/107	38
Canavan disease (271900)	*ASPA*	Amino-acid metabolism	1/41	73
Congenital adrenal hyperplasia, non-classical (210910)	*CYP21A2*	Steroid hormone biosynthesis	1/3	74
Crohn disease (266600)	*NOD2*	Intracellular receptor for bacterial products	1/6	75
Factor XI deficiency, type III (264900)	*F11*	Blood clotting	1/20	27
Familial breast and ovarian cancer II (600185)	*BRCA2*	DNA repair	1/100	76
Familial colon cancer (175100)	*APC*	Cell adhesion	1/16	77
Familial dysautonomia (223900)	*IKBKAP*	Transcription regulation (?)	1/36	78,79
Familial hypercholesterolaemia (143890)	*LDLR*	Cholesterol transport	1/56	33
Familial hyperinsulinism (256450)	*ABCC8*	Glucose transport	1/89	80
Fanconi anemia, complementation group C (227645)	*FANCC*	DNA repair	1/80	81
Gaucher disease (230800)	*GBA*	Lysosomal hydrolase	1/13	32
Glycogen storage disease, type I (232200)	*G6PC*	Carbohydrate and amino-acid metabolism	?	82
Idiopathic torsion dystonia (128100)	*DYT1*	Unknown	1/2000	83
Lipoamide dehydrogenase deficiency (246900)	*DLD*	Carbohydrate and amino-acid metabolism	1/94	84
Mucolipidosis type IV (252650)	*MCOLN1*	Endocytosis	1/100	85
Niemann–Pick disease 257200	*SMPD1*	Lysosomal hydrolase	1/90	86
Tay–Sachs disease (272800)	*HEXA*	Lysosomal hydrolase	1/25	87
Predominantly Bukharan Jewish diseases				
Oculopharyngeal muscular dystrophy (164300)	*PABPN1*	mRNA polyadenylation	~1/7	35
Predominantly Habbanite Jewish diseases				
Metachromatic leukodystrophy (250100)	*ARSA*	Lysosomal hydrolase	1/5	88
Predominantly Iranian Jewish diseases				
Autoimmune polyglandular disease I (240300)	*AIRE*	Transcriptional activation	1/40 (?)	89
Corticosterone methyl oxidase II deficiency (124080)	*CYP11B2*	Steroid biosynthesis	?	90
Congenital myastenia gravis	Unknown	Unknown	?	91
Hereditary inclusion body myopathy	*GNE*	Unknown	~1/20	92
Predominantly Iraqi Jewish diseases				
Glanzmann thrombasthenia (273800)	*ITGA2B*	Platelet aggregation	1/98	93
Predominantly Libyan Jewish diseases				
Cystinuria (220100)	*SLC7A9*	Amino-acid transport	?	94
Predominantly Moroccan Jewish diseases				
Cerebrotendinous xanthomatosis (213700)	*CYP27A1*	Oxidation of sterols that form bile acids	1/47	95
Complement C7 deficiency (217070)	*C7*	Bacterial infection resistance	1/46	96
11-β hydroxylase deficiency (202010)	*CYP11B1*	Steroid hormone biosynthesis	1/36 (?)	90
Glycogen storage disease III (232400)	*AGL*	Glucose metabolism	1/35	97
Tay–Sachs disease (272800)	*HEXA*	Lysosomal hydrolase	1/45	98
Predominantly Yemenite Jewish diseases				
Limb-girdle muscular dystrophy with inflammation (253601)	*DYSF*	Unknown	?	99
Phenylketonuria (261600)	*PAH*	Amino-acid metabolism	1/35	100

ABCC8, ATP-binding cassette, sub-family C (CFTR/MRP), member 8; *AGL*, amylo-1,6-glucosidase, 4-α-glucanotransferase (glycogen-debranching enzyme, glycogen storage disease type III); *AIRE*, autoimmune regulator (automimmune polyendocrinopathy candidiasis ectodermal dystrophy); *APC*, adenomatosis polyposis coli; *ARSA*, arylsulfatase A; *ASPA*, aspartoacylase (aminoacylase 2, Canavan disease); *BLM*, Bloom syndrome; *BRCA2*, breast cancer 2, early onset; *C7*, complement component 7; *CYP11B1/2*, cytochrome P450, subfamily XIB (steroid 11-β-hydroxylase), polypeptide 1/2; *CYP21A2*, cytochrome P450, subfamily XXIA (steroid 21-hydroxylase, congenital adrenal hyperplasia), polypeptide 2; *CYP27A1*, cytochrome P450, subfamily XXVIIA (steroid 27-hydroxylase, cerebrotendinous xanthomatosis), polypeptide 1; *DLD*, dihydrolipoamide dehydrogenase (E3 component of pyruvate dehydrogenase complex, 2-oxo-glutarate complex, branched chain keto acid dehydrogenase complex); *DYSF*, dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive); *DYT1*, dystonia 1, torsion (autosomal dominant; torsin A); *F11*, coagulation factor XI (plasma thromboplastin antecedent); ER, endoplasmic reticulum; *FANCC*, Fanconi anaemia, complementation group C; *G6PC*, glucose-6-phosphatase, catalytic (glycogen storage disease type I, von Gierke disease); *GBA*, glucosidase, β, acid (includes glucosylceramidase); *GNE*, UDP-*N*-acetylglucosamine-2-epimerase/*N*-acetylmannosamine kinase; *HEXA*, hexosaminidase A (α-polypeptide); *IKBKAP*, inhibitor of κ light polypeptide gene enhancer in B cells, kinase complex-associated protein; *ITGA2B*, integrin, α-2b (platelet glycoprotein IIb of IIb/IIIa complex, antigen CD41B); *LDLR*, low-density lipoprotein receptor (familial hypercholesterolaemia); *MCOLN1*, mucolipin 1; *NOD2*, NOD2 protein; *PABPN1*, poly(A)-binding protein, nuclear 1; *PAH*, phenylalanine hydroxylase; *SLC7A9*, solute carrier family 7 (cationic amino-acid transporter, y+ system), member 9; *SMPD1*, sphingomyelin phosphodiesterase 1, acid lysosomal (acid sphingomyelinase).

Many disease mutations are unique to specific Jewish groups and are likely to have arisen in the diaspora (TABLE 2). Familial dysautonomia is a disease that occurs only among Ashkenazi Jews — in fact, Ashkenazi Jewish ancestry is a criterion for diagnosis[31]. Coalescence times have been determined for several disease mutations (see TIMELINE). In some cases, these coincide with the founding of the population, although the confidence intervals are broad enough so that some founder carriers could have originated or migrated into the population after its founding. In other cases, the founder of the mutation clearly originated in the population. Two mutations in the glucocerebrosidase locus, Asn370Ser and 84GG (insertion of a second guanine in position 84), are prevalent in Ashkenazi Jews and the Asn370Ser mutation is also found among non-Jews. The coalescence time for both mutations among Ashkenazi Jews is ~50 generations ago, a time that coincides with the migration of Jews into the Rhineland and the founding of the Ashkenazi Jewish group[32]. The delGly197 mutation in the low-density-lipoprotein receptor (LDL receptor) gene is found among Ashkenazi Jews whose ancestors resided in Lithuania. The coalescence time for this mutation is 20 generations ago, which coincides with the time when Jews were granted charters by the King of Poland to reside in Lithuania[33]. The coalescence time for the common mutation in the *DYT1* gene that causes idiopathic torsion dystonia has been calculated as 12–13 generations ago, which places the origin of this mutation into more recent diaspora times and to a time when important upheavals, such as the Chmielnicki massacres in Eastern Europe in 1648–1649, might have affected the dynamics of this population by creating a bottleneck[34].

This identification of coalescence times for mutations that seem to coincide with key events of the diaspora, a phenomenon that is not confined to Ashkenazi Jews. The coalescence time for the common mutation in the *OCMD* gene that causes oculopharyngeal muscular dystrophy among Bukharan Jews is 1243 C.E., which coincides with the migration of Jews from Iraq to Samarkand and the establishment of this community[35]. The coalescence time for the common Glu200Lys mutation, caused by a point mutation in the *PRNP* (prion protein) gene that causes Creutzfeldt–Jakob disease among Libyan Jews, is 23 generations ago. This corresponds to the time of expulsion of Jews from Spain during the Spanish Inquisition and their subsequent migration across the Mediterranean. This mutation has been observed on the same background among affected non-Jewish individuals in Spain and Chile[36].

Timeline | **Timing of mutations in Jewish populations**



Coalescence times for common founder mutations were calculated from analysis of the divergence of microsatellite markers surrounding the disease locus. The population in which the mutation occurred, a mean coalescence time, and a proximal, key historic event (if known) are shown.

Mutation analysis has found evidence of Jewish ancestry among contemporary non-Jewish groups. The 185delAG *BRCA1* gene mutation common among Ashkenazi, Iraqi and Moroccan Jews has been observed among the gypsies of Spain, indicating gene flow into that group[37]. The unusual 6-bp deletion/7-bp insertion *BLM* mutation that causes Bloom syndrome has been found in affected individuals in New Mexico, Mexico and El Salvador, despite no recollection of Jewish ancestry in the families of the affected[38]. A mutation in the growth hormone receptor gene that produces Laron dwarfism in a cohort of individuals in southern Ecuador had been previously described in a Moroccan Jew[39]. These observations are compatible with known migrations from Spain and Portugal to Latin America. Following the Spanish Inquisition, large numbers of Conversos, or secret Jews, moved to the New World. In sixteenth century Brazil, up to one-third of the population might have consisted of Conversos[40].

The prevalence of these disease mutations after they had been introduced into Jewish groups can be explained by various factors[41]. For all Jewish groups, genetic drift is likely to have influenced contemporary gene frequencies. Many populations went through bottlenecks as the result of wars, pogroms and epidemics. In turn, these were followed by rapid population growth, as virtually all groups had large family sizes. The Ashkenazi Jewish population in Eastern Europe expanded rapidly, growing from an estimated 10,000–15,000 people in 1500 to 2 million in 1800 and 8 million in 1939 (REF. 34). For certain conditions, selection is likely to have influenced gene frequencies. The high prevalence of different mutations in the β-globin gene (*HBB*) that cause thalassaemia is likely to be explained by selection for resistance to malaria in heterozygotes among Kurdish Jews[42]. Resistance to cholera or typhoid fever might have a role in heterozygote advantage for cystic fibrosis carriers[43,44].

The effects of selection might be strong and manifested over relatively short time frames. The 32-bp deletion mutation (del32) in the *CCR5* (chemokine receptor 5) gene, is not associated with disease, but rather with resistance to infection with HIV1 (human immunodeficiency virus 1). This mutation is found at high frequencies across European groups, including Ashkenazi Jews, and the coalescence time has been calculated to be 28 generations, indicating that enhanced reproductive fitness occurs for carriers of this mutation across population groups[45].

Genetic testing in Jewish populations

Identification of Tay–Sachs disease heterozygotes was among the first population-based genetic screening programmes in the world and its impact has been substantial[46]. Between 1970 and 1992, more than 1.4 million people were screened. The incidence of new Jewish births affected by Tay–Sachs disease plummeted from 40–50 per year worldwide to 4–5 per year (the remaining cases usually a result of physician or lab error). Tay–Sachs carrier testing became a model for heterozygote screening: the disorder was fatal at an early age with no effective treatment. Testing was accurate and inexpensive, and offered reproductive options to carriers. The emerging fields of genetic counselling and prenatal diagnosis through amniocentesis (and later chorionic villus sampling) provided carrier couples with

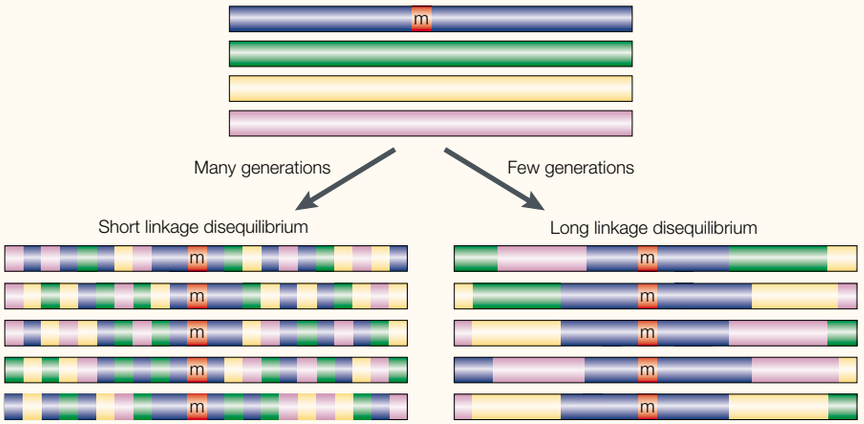


Figure 1 | **Patterns of linkage disequilibrium based on time of origin of a disease mutation.** The disease mutation (m) is shown in red and the adjacent chromosomal markers are shown in other colours, according to their chromosome of origin. These are shuffled by recombination during meiosis in egg or sperm cells. Mutations that occurred recently have had fewer recombinational events and therefore are associated with long intervals of linkage disequilibrium (LD) (right). Mutations that occurred a long time ago have had many recombinational events and so are associated with short intervals of LD (left).

the option of terminating affected pregnancies. Among ultra-Orthodox groups, carrier testing is followed by discouraging marriages between carriers with mutations in the same disease gene, and is the preferred way of avoiding affected offspring. As genetic testing became available for cystic fibrosis, Gaucher disease, Canavan disease and others, it was offered to Ashkenazi Jewish people and was generally embraced by professional societies, although sometimes with considerable debate[47–49]. The pace of discovery of human disease genes has been rapid. Genetic testing is available for at least 16 autosomal recessive conditions and is offered for eight conditions at several centres in North America and Israel. The likelihood that an Ashkenazi Jewish person will be a carrier for at least one of these eight conditions is 1 in 4 and the likelihood that he or she will have an affected child, without testing, is 1 in 368. Conditions that are associated with mild to moderate morbidity or disability or low PENETRANCE, such as factor XI deficiency or *GJB2* deafness, might not be candidates for screening; however, the emergence of multiplex low-cost genetic testing indicates that a new model could occur in countries where Jews are a minority population and that heterozygote screening might serve as a surrogate for newborn screening. Some of these conditions, including familial Mediterranean fever, non-classical congenital adrenal hyperplasia, *GJB2* deafness, Gaucher disease, cystic fibrosis and glycogen storage disease, could be candidates for newborn screening programmes in Israel.

Glossary

ADMIXTURE
Inter-population gene flow.

COALESCENCE
The joining of genetic lineages to common ancestors when they are traced backwards in time.

COMMON ERA
(C.E.). A neutral term for the period of time since the birth of Christ.

ENDOGAMY
Mating or marriage within a social or cultural unit.

GENETIC DRIFT
Random changes in allele frequency that result because the genes appearing in offspring are not a perfectly representative sample of the parental genes (for example, in small populations).

GENE FLOW
The movement of alleles between local populations owing to the migration of individuals.

HAPLOTYPE
A set of genetic markers present on one chromosome.

HUMAN LEUKOCYTE ANTIGEN
Protein present on the surface of white cells and most other cells in the body that allows the immune system to recognize self from non-self.

LINKAGE DISEQUILIBRIUM
(LD). The condition in which the frequency of a particular haplotype for two loci is significantly greater than that expected from the product of the observed allelic frequencies at each locus.

MICROSATELLITE
A class of repetitive DNA that is made up of repeats that are 2–8 nucleotides in length. They can be highly polymorphic and are frequently used as molecular markers in population genetics studies.

PENETRANCE
The proportion of genotypically mutant organisms that show the mutant phenotype. If all genotypically mutant individuals show the mutant phenotype, then the genotype is said to be completely penetrant.

PHRENOLOGY
The study of the conformation of the skull on the basis of the belief that it is indicative of mental faculties and character.

Linkage disequilibrium

LINKAGE DISEQUILIBRIUM (LD) has been observed for many of the disease-associated mutations and neighbouring microsatellite and single nucleotide polymorphism (SNP) markers in Jewish populations. As a consequence of the limited number of meioses that have occurred since the founder mutation in such populations, larger (1–20 cM) chromosomal regions flanking the disease locus are preserved identical by descent as compared with non-homogeneous populations (<<1 cM)[50]. This has led to LD between the disease alleles at one locus and the marker alleles at adjacent loci (FIG. 1). The length of the LD intervals, as well as the preservation of the microsatellite alleles, tends to correlate inversely with the time since the mutation arose in the population. Analysis of LD has been useful for narrowing crucial regions, identified originally by linkage, for the subsequent identification of genes associated with Bloom syndrome, familial dysautonomia, mucolipidosis IV and familial Mediterranean fever[26,51,52]. The existence of LD between disease mutations and surrounding markers has been proposed as a method for discovering mutations for common diseases, using a case–control design[53]. In this strategy, marker alleles that are in LD with the disease-causing locus will be found in a higher proportion of cases compared with controls; so narrowing down the location of a linked disease-associated allele. This theory has led to the creation of at least one biotechnology company, ID Gene (see link), whose avowed corporate mission is to identify mutations for common diseases using LD mapping approaches among Ashkenazi Jews in Israel.

Caveats have surrounded the LD approach to mapping disease loci in Jewish groups because limited scans of SNP markers in Ashkenazi Jews showed heterozygous frequencies comparable with other endogamous groups and to non-endogamous groups[54,55]. Assuming that these observations of short (5–10 kb) intervals of LD for random SNP markers are correct, then genome-wide screens at high densities that involve 300,000 or more markers would be required

to identify a significant association between markers[56]. However, studies of LD in endogamous populations have used small numbers of people and few loci. The loci studied have not necessarily involved common diseases, and the individuals studied were not selected for having these diseases. So, some of the assumptions about the use of LD approaches in isolated populations, such as Jews, might still be valid[57]. Moreover, the power of LD methods might be augmented by strategies that use, among others, highly polymorphic, and therefore more informative, microsatellite markers and population-specific SNPs. The distinction between disease-conferring and normal chromosomes could be augmented further by creating haplotypes involving several markers. The haplotypes can be constructed either by using family studies, that show which alleles are inherited together on a chromosome, or using somatic-cell genetic techniques, in which one of the chromosomes of a pair is isolated in human–rodent hybrid cells in culture. Haplotypes might then be identified that are present on a high proportion of disease-conferring chromosomes and on a low proportion of normal chromosomes.

The identification of disease genes using LD methods is therefore an issue that is very much in flux. Mapping the disease gene is easier when the interval of LD is relatively long; however, within these longer intervals, there might be many genes and so further refinement of the map might require studying other, unrelated populations in which the interval is shorter. Such comparisons might be ideal among the many Jewish groups that have had divergent histories of varying length.

Implications for other populations

Molecular genetic testing has shown that, despite migration and physical separation, Jews have retained not only their religious identity, but also their genetic identity over thousands of years. Similar conservation of group genetic identity has been observed for the Roma, another migratory people[58]. The findings of many prevalent founder mutations is not unique to Jewish people, but can be found in other groups. Among these groups are the Finns, Icelandics, Afrikaaners, Dutch and Flemish, Swedes and French Canadians[59–64]. A common feature among these groups is geographical, linguistic or religious isolation from their neighbours. Even for β-thalassaemia, distinctive alleles are observed among groups residing in different geographical locales[65]. These mutations are part of a mosaic that includes mutations that are common across population groups.

Conclusion

None of the studies so far has shown that genetic differences within Jewish groups are smaller than differences between groups or between Jews and non-Jews. Jewishness is not determined by genetics. Nonetheless, genetic threads run through Jewish populations that provides them with a group identity. This genetic identity has been retained and modified, much as the religious and cultural identity of Jews has been retained and modified over more than two millennia.

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Online links

DATABASES

The following terms in this article are linked online to:

LocusLink: http://www.ncbi.nlm.nih.gov/LocusLink/
BRCA1 | *BRCA2* | *CCR5* | *CFTR* | *DYT1* | factor XI | *GJB2* | glucocerebrosidase locus | *HBB* | LDL receptor | *LMAN1* | *MEFV* | *OCMD* | *PRNP*

OMIM: http://www.ncbi.nlm.nih.gov/Omim/
11-hydroxylase deficiency | 21-hydroxylase deficiency | β-thalassaemia | autosomal-recessive non-syndromic hearing loss | Bloom syndrome | Canavan disease | combined factors V and VIII deficiency | corticosterone methyl oxidase II deficiency | Creutzfeldt–Jakob disease | cystic fibrosis | factor VII deficiency | factor XI deficiency | familial dysautonomia | familial Mediterranean fever | Fanconi anaemia | Gaucher disease | glycogen storage disease type I | glycogen storage disease type III | idiopathic torsion dystonia | Laron dwarfism | mucolipidosis IV | Niemann–Pick disease | non-classical congenital adrenal hyperplasia | oculopharyngeal muscular dystrophy | Tay–Sachs disease

FURTHER INFORMATION

Chicago Center for Jewish Genetic Disorders:
http://www.juf.org/news_public_affairs/article.asp?key=2244
Genetic testing at NYU School of Medicine:
http://www.med.nyu.edu/genetics/ashkenazi.html
ID Gene: http://www.idgene.com
JewishGen: The Home of Jewish Genealogy:
http://www.jewishgen.org/
Mazor Guide to Jewish Genetic Diseases:
http://www.mazornet.com/genetics/
National Foundation for Jewish Genetic Diseases:
http://www.nfjgd.org/
Study of Jewish origins at NYU School of Medicine:
http://www.med.nyu.edu/genetics/jewishorigins.html
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TIMELINE

The origins of maize genetics

Edward H. Coe Jr

Early geneticists, and generations since, have been drawn to maize to study basic questions, its curious phenomena and its practical applications. Part of the allure of this unique crop plant lies in the collegiality of the Maize Genetics Cooperation, extending all the way from the 'roaring twenties' of genetics to today.

The prominence of an organism for research can depend on a particular purpose, a particular moment in time, or particular existing knowledge about that organism. The prominence of maize, *Zea mays* L. ssp. *mays*, as one of the well-springs of genetic advance today derives in fact from a wide range of experimental purposes both now and in the