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NATURAL HISTORY OF ASHKENAZI INTELLIGENCE

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Summary. This paper elaborates the hypothesis that the unique demography and sociology of Ashkenazim in medieval Europe selected for intelligence. Ashkenazi literacy, economic specialization, and closure to inward gene flow led to a social environment in which there was high fitness payoff to intelligence, specifically verbal and mathematical intelligence but not spatial ability. As with any regime of strong directional selection on a quantitative trait, genetic variants that were otherwise fitness reducing rose in frequency. In particular we propose that the well-known clusters of Ashkenazi genetic diseases, the sphingolipid cluster and the DNA repair cluster in particular, increase intelligence in heterozygotes. Other Ashkenazi disorders are known to increase intelligence. Although these disorders have been attributed to a bottleneck in Ashkenazi history and consequent genetic drift, there is no evidence of any bottleneck. Gene frequencies at a large number of autosomal loci show that if there was a bottleneck then subsequent gene flow from Europeans must have been very large, obliterating the effects of any bottleneck. The clustering of the disorders in only a few pathways and the presence at elevated frequency of more than one deleterious allele at many of them could not have been produced by drift. Instead these are signatures of strong and recent natural selection.

Introduction

Albert Einstein is reputed to have said that 'Things should be described as simply as possible, but no simpler.' The same principle must be invoked in explaining Einstein himself. In this study, the hypothesis that the high intelligence test scores observed in the Ashkenazi Jewish population are a consequence of their occupation of a social niche over the last millennium that selected strongly for IQ is evaluated. The evidence of high intelligence test scores in this population, approximately one standard deviation higher than the north-western European average, is summarized, and then the relevant social history. We suggest that there was an increase in the frequency of particular genes that elevated IQ as a by-product of this selective regime, which led to an increased incidence of hereditary disorders.

There are several key observations that motivate our hypothesis. The first is that the Ashkenazi Jews have the highest average IQ of any ethnic group, combined with an unusual cognitive profile, while no similar elevation of intelligence was observed among Jews in classical times nor is one seen in Sephardic and Oriental Jews today. The second is that the Ashkenazim experienced very low inward gene flow, which created a very favourable situation for natural selection. The third is that they experienced unusual selective pressures that were likely to have favoured increased intelligence. For the most part they had jobs in which increased IQ strongly favoured economic success, in contrast with other populations, who were mostly peasant farmers. They lived in circumstances in which economic success led to increased reproductive success. The fourth is the existence of the Ashkenazi sphingolipid, DNA repair, and other disease clusters, groups of biochemically related mutations that could not plausibly have reached their present high frequencies by chance, that are not common in adjacent populations, and that have physiological effects that could increase intelligence.

Other selective factors have been suggested. 'Winnowing through persecution' suggests that only the smartest Jews survived persecution. Why this should be so is not clear. There was no similar outcome in other groups such as Gypsies, who have faced frequent persecution (Crowe & Kolsti, 1991). Another theory suggests that there was selective breeding for Talmudic scholarship. This seems unlikely to have been an important selective factor, since there weren't very many professional rabbis, certainly less than one per cent of the population. A selective force that only affects a tiny fraction of the population can never be strong enough to cause important evolutionary change in tens of generations. A plausible variant of the Talmudic scholarship model suggests that it was like a sexually selected marker and that rich families preferred to marry their daughters to males who excelled (Weyl & Possony, 1963; MacDonald, 1994) so that the payoff to intelligence was indirect rather than direct as we suggest. Without detailed historical demographic information it will be difficult to evaluate this hypothesis.

We proceed by summarizing IQ psychometrics and IQ as a quantitative genetic trait. We then describe relevant aspects of Ashkenazi social and demographic history with a focus on the centuries between AD 800 and 1600, after which we think many of the unique selective pressures were relaxed. We show that plausible mechanisms of social selection lead to large changes on a scale of centuries and that such selection also can lead to increases in the frequency of otherwise deleterious mutants, a phenomenon well known in agricultural genetics. Ashkenazi diseases have often been attributed to population size bottlenecks in their history: we review population genetic evidence of a bottleneck and find no support in the data for any bottleneck at all. If there were one or more bottlenecks with large effect then subsequent gene exchange with other groups has been large enough to erase the signature, and gene flow of this magnitude, greater than about one per cent per generation cumulative, would have overwhelmed genetic drift. We describe two main clusters of Ashkenazi inherited disease – the sphingolipid cluster and the DNA repair cluster – reviewing evidence that these modulate early central nervous system development. A sample of Gaucher disease patients show a startling occupational spectrum of high IQ jobs, and several other Ashkenazi disorders – idiopathic torsion dystonia and non-classical adrenal

hyperplasia – are known to elevate IQ. Finally we describe functional genomic associations between Ashkenazi mutations in order to formalize the argument that they are concentrated in a few biochemical pathways, more concentrated than could have occurred by chance alone.

The psychometric evidence about Ashkenazi IQ

Ashkenazi Jews have the highest average IQ of any ethnic group for which there are reliable data. They score 0·75 to 1·0 standard deviations above the general European average, corresponding to an IQ of 112–115. This has been seen in many studies (Levinson, 1959; Backman, 1972; Romanoff, 1976), although a recent review concludes that the advantage is slightly less – only half a standard deviation (Lynn, 2004). This fact has social significance because IQ (as measured by IQ tests) is the best predictor we have of success in academic subjects and most jobs. Ashkenazi Jews are just as successful as their tested IQ would predict, and they are hugely over-represented in occupations and fields with the highest cognitive demands. During the 20th century, they made up about 3% of the US population but won 27% of the US Nobel science prizes and 25% of the ACM Turing awards. They account for more than half of world chess champions.

While the mean IQ difference between Ashkenazim and other northern Europeans may not seem large, such a small difference maps to a large difference in the proportion of the population with very high IQs (Crow, 2002). For example, if the mean Ashkenazi IQ is 110 and the standard deviation is 15, then the number of northern Europeans with IQs greater than 140 should be 4 per thousand while 23 per thousand Ashkenazim should exceed the same threshold – a six-fold difference.

This high IQ and corresponding high academic ability have been long known. In 1900 in London Jews took a disproportionate number of academic prizes and scholarships in spite of their poverty (Russell & Lewis, 1900). In the 1920s a survey of IQ scores in three London schools (Hughes, 1928) with mixed Jewish and non-Jewish student bodies showed that Jewish students had higher IQs than their schoolmates in each of three schools – one prosperous, one poor, and one very poor. The differences between Jews and non-Jews were all slightly less than one standard deviation. The students at the poorest Jewish school in London had IQ scores equal to the overall city mean of non-Jewish children.

The Hughes study is important because it contradicts a widely cited misrepresentation by Kamin (Kamin, 1974) of a paper by Henry Goddard (Goddard, 1917). Goddard gave IQ tests to people suspected of being retarded, and he found that the tests identified retarded Jews as well as retarded people of other groups. Kamin reported, instead, that Jews had low IQs, and this erroneous report was picked up by many authors including Stephen Jay Gould, who used it as evidence of the unreliability of the tests (Seligman, 1992).

Ashkenazi Jews have an unusual ability profile as well as higher than average IQ. They have high verbal and mathematical scores, while their visuo-spatial abilities are typically somewhat lower, by about one half a standard deviation, than the European average (Levinson, 1977; Levinson & Block, 1977). Han Eysenck (Eysenck, 1995) noted 'The correlation between verbal and performance tests is about 0·77 in the

general population, but only 0·31 among Jewish children. Differences of 10–20 points have been found in samples of Jewish children; there is no other group that shows anything like this size difference.' The Ashkenazi pattern of success is what one would expect from this ability distribution: great success in mathematics and literature, and more typical results in representational painting, sculpture and architecture.

It is noteworthy that non-Ashkenazi Jews do not have high average IQ test scores (Ortar, 1967), nor are they over-represented in cognitively demanding fields. This is important in developing any causal explanation of Ashkenazi cognitive abilities: any such theory must explain high Ashkenazi IQ, the unusual structure of their cognitive abilities, and the lack of these traits among Sephardic and Oriental Jews (Patai, 1977; Burg & Belmont, 1990).

IQ as a quantitative trait

The study of human variation in intelligence appears controversial from the outside but there is little controversy in the field itself. IQ tests predict a host of characteristics of individuals including educational attainment, job performance, income, health and other non-obvious characteristics like susceptibility to Alzheimer's disease. In general the search for social and nutritional causes of IQ differences has not led to any convincing results and most workers now regard IQ as a biological rather than a social variable. It is highly heritable: correlations between identical twins reared apart are 0·7–0·8. Genetic manipulation can raise intelligence in mice (Routtenberg *et al.*, 2000), and it is our hypothesis that natural selection has hit upon several similar IQ-boosting chemical mechanisms in the history of the Ashkenazi population.

The basis of intelligence testing is that when people are given a battery of cognitive ability tests broadly defined – anything from general knowledge to vocabulary to digit memory to tasks requiring mental rotation of three-dimensional objects – those who do well on one of these tend to do well on all of them and people who do poorly do poorly on all of them. Different cognitive abilities are highly correlated with each other, and the underlying ability responsible for the correlations is called *g*. While the development of theory about general intelligence or *g* was entirely based on tests and correlations, it has recently become apparent that there is a neurobiological basis for variation in *g*, reflected for example in correlations between intelligence and brain volume, volumes of specific brain regions, current density tomography, reaction times, brain glucose utilization rate, and so on (Gray & Thompson, 2004).

There is variation in the way different subtests contribute to IQ. Males, for example, usually outperform females on spatial and quantitative tasks while females do better on tasks related to language. There are also group differences: Ashkenazim do not show any marked advantage on spatial tasks while they excel at linguistic and arithmetic tasks. North-east Asians have high spatial scores for a given overall IQ.

Whatever the reality or nature of *g*, for our purposes the important observation is that IQ test scores work in the sense that they are the best available predictor of academic success and job performance, especially for complex jobs (Herrnstein & Murray, 1994; Gottfredson, 1997, 2002). They are also one of the best predictors available of family stability, criminality, health and lifespan (Gottfredson, 2004).

IQ test scores are highly heritable, being almost always greater than 0·5 when adult scores are studied. Lower heritability estimates are found for children's IQ: the IQ of children does seem to reflect in part environmental influences like the social class of the home in which the child is reared, but these influences disappear as the child matures and are essentially gone in adulthood. In the same way enrichment programmes like Head Start cause a transient elevation in IQ scores of children but these effects disappear as the child matures. The phenomenon of heritability increasing with age is characteristic of many quantitative traits in mammals (Falconer, 1981).

The heritability of IQ is probably lower than 0·80 in most human populations, and it may be as low as 0·50, so there are apparently some environmental effects on IQ. Since siblings and twins raised apart are as similar as those raised together, it has become commonplace to speak of 'non-shared environment', which means that siblings are exposed to different environments even when raised together. It is important to realize that so-called environmental effects include non-additive gene interactions like dominance and epistasis as well as testing error. The correlation between one IQ test score and another taken later may be as low of 0·8 or so.

There is an apparent secular trend in many countries in IQ scores: people today score much higher on old IQ tests than people did at the time. The gain varies among countries but on average is about five points per decade. This 'Flynn effect' (Flynn, 1987) may include some real increases in IQ that reflect improvements in biological well-being: better nutrition, vaccination, antibiotics for childhood disease, etc. A perhaps more likely explanation is the increase in school attendance, leading to familiarity with the format of short-answer timed tests. Whatever its basis, the gain has occurred uniformly across ethnic groups and social classes so relative group differences have remained unchanged. It also seems to have stopped in recent decades (Jensen, 1998).

Some would suggest that, even though IQ scores are heritable, there are no biological differences in mean IQ between populations and that the well-known differences among ethnic groups in North America are the result of racism or deprivation or some other social cause. Similarly one might argue that high Ashkenazi scores are the result of home environments that encourage scholarship. There is scarcely any support in the literature for social effects like home environment on IQ (Rowe, 1993). A standard textbook on IQ, after reviewing environmental effects, concludes that '. . . it is all too easy to throw up one's hands in despair' (Mackintosh, 1998): despair presumably because there is a widespread desire to find environmental effects that can be manipulated. So far, after intensive searching, no one has found any, and the current consensus is that variation in IQ reflects variation in the underlying biology rather than in the social environment. This parallels the current consensus that mental illness is a biological phenomenon and that the folk beliefs of half a century ago about causes – harsh toilet training, aloof fathers, etc. – have no empirical basis (Haier, 2003).

Quantitative traits like height or IQ are influenced by many genes. The response of quantitative traits to selection is described by the fundamental relationship:

$$R=h^2S, \tag{1}$$

where R is the response to selection, S is the selection differential, the difference between the mean value in the population and the mean value in parents, and h^2 is the narrow sense heritability of the trait. This simple robust formulation is applicable to animal breeding, laboratory experiments and evolution in natural populations (Lande, 1976; Falconer, 1981). Estimates of the narrow-sense heritability of IQ vary, but generally range between 0·3 and 0·5 in children (Devlin *et al.*, 1997) up to 0·7 or higher when measured in adults (Jensen, 1998). Heritability must vary between populations since it is sensitive to demographic phenomena like assortative mating, the extent to which spouses are similar to each other with respect to IQ, and inbreeding. Assortative mating increases IQ heritability. Inbreeding lowers offspring IQ and so could contribute extra variance to the IQ distribution, lowering heritability.

With its high heritability, IQ should respond rapidly to directional selection according to equation 1. Assuming, for example, that the narrow-sense heritability of IQ is 0·8 and that the parents of the next generation have an average IQ one point above the population mean, the average IQ increases by 0·8 points per generation. In 20 human generations, about 500 years, it would increase by 16 points – slightly more than the difference between average Ashkenazi IQ scores and average European IQ scores. Change of this magnitude over historical time is not at all implausible.

Detailed demographic data about early medieval Ashkenazim are lacking, but we can infer plausible parameters from the scarce information that we do have. First, their jobs were cognitively demanding since they were essentially restricted to entrepreneurial and managerial roles as financiers, estate managers, tax farmers and merchants. These are jobs that people with an IQ below 100 essentially cannot do. Even low-level clerical jobs require something like an IQ of 90 (Gottfredson, 2003).

We also know that there were large fitness differentials between the rich and poor, the rich having large surviving families and the poor not. Such a strong positive correlation between fitness and wealth was characteristic of European societies before the demographic transition beginning in the eighteenth century and it is characteristic of low technology societies today where it has been studied.

Assume, for example, that the correlation between income and IQ is 0·4 (about the correlation in the United States today) and that individuals in the top 10% of income have twice the average fitness. The mean wealth of parents would be 0·16 standard deviations above the population average and the mean IQ of parents would be $0{\cdot}4 \times 0{\cdot}16$ or 0·064 IQ standard deviations, that is 1 IQ point above the population mean. This is the selective differential, and with a heritability of 0·8 IQ would increase by 0·8 points per generation. In 500 years – 20 generations – average IQ would increase by 16 points.

Another plausible scenario is that individuals with IQ lower than 80, i.e. individuals who could not join the United States army because of low IQ, could not find spouses: it is likely that such individuals could not participate in the early medieval Ashkenazi economy and simply drifted away from their natal ethnicity to become farmers or to find other work. In this scenario the mean IQ after one generation of selection changes from 100 to 101 if the selection applies only to males and the heritability is 0·7. A gain of 1 point per generation over five centuries – 20 generations – would lead to a population mean IQ of 120.

These model scenarios assume no gene flow from a population not subject to selection for IQ. Gene flow can substantially limit population response to selection. If S is the local selective differential, the change per generation is $R=h^2S$ with no gene flow. If the local population experiences a fraction m of inward gene flow per generation with a large outside population not subject to this selection, the change per generation is:

$$R=h^2\,(1-m)\,S+m\,(\textit{global average}-\textit{local average}).$$

The maximum possible difference between the local and global average is $Sh^2(1-m)/m$.

Assume that a population experienced selective pressures similar to those posited for the Ashkenazim, such that the parents of the next generation averaged one half an IQ point higher than the current average while also experiencing significant gene flow from the general population. For 10% gene flow and a narrow-sense heritability of 0·7, the maximum IQ increase over many generations would be 3·2 points. For 20% gene flow, the maximum increase would be 1·4 points. Clearly, any significant amount of gene flow greatly inhibits local adaptation. We know, however, that the Ashkenazim experienced very limited inward gene flow, of the order of 0·5% per generation (Hammer *et al.*, 2000).

Gene flow also limits the natural increase of locally favourable mutations. In a reproductively isolated population, a mutation that increases fitness in heterozygotes but is lethal to homozygotes will eventually (if not lost by chance shortly after its origin) reach an equilibrium frequency of $s/(s+1)$, when s is the heterozygote selective advantage. But if s is smaller than m (the fractional gene flow), the mutation will not reach this equilibrium: in fact, it will on average not increase in frequency at all. This means that in a reproductively isolated population ($m<1\%$) subject to strong selection for IQ like the Ashkenazim, mutations increasing IQ or other locally favoured traits could well have increased to polymorphic frequencies. Naturally, these would be mutations that increase IQ with costs attached: mutations that produced a 'free' increase in IQ, with no associated costs at all, would probably have already occurred and reached fixation in all human populations.

Since strong selection for IQ seems to be unusual in humans (few populations have had most members performing high-complexity jobs) and since near-total reproductive isolation is also unusual, the Ashkenazim may be the only extant human population with polymorphic frequencies of IQ-boosting disease mutations, although another place to look for a similar phenomenon is in India. In particular, the Parsi are an endogamous group with high levels of economic achievement, a history of long-distance trading, business and management, and who suffer high prevalences of Parkinson disease, breast cancer and tremor disorders, diseases not present in their neighbours (see the *UNESCO Parsi Zoroastrian Project*, http://www.unescoparzor.com).

Cost of selection

Falconer (1981, p. 303) describes what he calls an 'equilibrium population' as one that has reached a selection limit for fitness. He acknowledges that this is an abstraction

that would require an environment to have remained unchanged for a very long time, but 'most populations studied are probably near enough to equilibrium that we can infer from them what the genetic properties of an equilibrium population are.'

In such a population close to equilibrium, selection for a metric character that is not fitness itself must reduce mean fitness unless the character and genes controlling it are completely neutral. Falconer goes on to say that 'This expectation is amply born out by experience: experimental selection for metric characters almost always results in a reduction of one or more of the major components of fitness. To give just one example: the mean fitness of Drosophila was estimated as a competitive index after five generations of selection for abdominal bristle number (Latter & Robertson, 1962). There were two lines selected upwards and two downwards. The mean fitness, relative to an unselected control, was 79% in the upward selected lines and 65% in the downward selected lines.'

Rapid selection does not always yield efficient solutions. Overdominant mutations that increase heterozygote fitness and harm homozygotes are favoured in the short run, but over longer periods, modifier genes decrease the associated genetic load (Hammerstein, 1996). Sickle cell, the canonical example of overdominance in humans, is a response to a recent selective influence, since falciparum malaria in its present form is probably only a few thousand years old. Overdominant mutations are usually thought of as defences against infectious disease, and indeed many are, but rapid selection for metric traits other than disease resistance can also result in polymorphic frequencies of overdominant alleles. There are illustrative examples in domesticated animals, which have of course been subject to strong selection on metric characters.

Multiple ovulations are uncommon in most breeds of sheep. Presumably this was adaptive among the wild ancestors of sheep, since it is considerably harder to feed and protect twins. Singleton births were probably the optimal course until recent years, when some sheep farmers have created far more favourable environments than existed in the past. In such environments, twinning is favoured by selection, and mutations favouring twinning have reached polymorphic frequencies in some breeds of sheep. Inverdale sheep (Galloway *et al.*, 2000) carry a naturally occurring X-linked mutation of the BMP15 gene (bone morphological protein 15, a growth and differentiation factor expressed in ovaries) which causes increased ovulation rate and twin and triplet births in heterozygotes, but sterility due to primary ovarian failure in homozygotes. Hanna sheep carry a different mutation in BMP15 with similar effects. It is interesting that in these cases, the very function that is hypertrophied in heterozygotes and favoured by selection is completely destroyed in homozygotes. Booroola sheep (McNatty *et al.*, 2001) carry a mutation in the receptor of BMP-1B, another member of the bone morphological protein family. In this case ovulation is increased even further in homozygotes. Note the tendency of selection to affect genes that are closely biochemically related because they lead to similar outcomes.

In another example of overdominance resulting from quantitative trait selection, several breeds of cattle (such as Belgian Blue and South Devon) have polymorphic frequencies of a mutation of the myostatin gene that caused muscular hypertrophy (Wiener, 2002). This mutation has a frequency of 37% in the South Devon breed, where it significantly increases muscle mass but increases calving difficulty. The fact

that this mutation has not gone to fixation, even though selection favours heterozygotes, suggests that it is overdominant.

Selection for IQ among the Ashkenazim then would have had associated costs. First, genetic changes that aided fitness in an urban environment where most jobs had high IQ elasticity almost certainly reduced fitness in more typical environments, simply because any such gene frequency change is change away from the optimum mix for a traditional environment. The expectation is that Ashkenazim would most likely suffer competitive disadvantage as peasant farmers or hunter–gatherers, for example.

Mutations that increased heterozygote fitness in the unique environment experienced by the Ashkenazim (by increasing IQ, for example) while harming homozygotes could have become relatively common, just as sickle cell has. Our hypothesis is that many, perhaps most of the characteristic Ashkenazi genetic diseases fall into this category. Selection has imposed a heavy human cost: not crippling at the population level, cheaper than the malaria-defence mutations like sickle cell and G6PD deficiency, but tragic nonetheless.

Ashkenazi economic and social history

The ancient Jewish population suffered remarkable vicissitudes – the Babylonian exile, the Hellenistic conquest and Hasmonean state, the revolts against the Roman Empire – but most of that history is probably irrelevant to our thesis, except to the extent that it helped create necessary cultural preconditions. Irrelevant because in pre-Diaspora times, the Jews did not occupy an unusual ecological niche nor did they yet exhibit unusual cognitive traits. Most Jews then were farmers, just as in nearly all settled populations, and they must have experienced evolutionary pressures similar to those experienced by other peoples of the region. A fair amount of classical commentary on the Jews has been preserved, and there is no sign that anyone then had the impression that Jews were unusually intelligent. Certain aspects of Jewish culture were probably crucial in setting the stage for this unusual evolutionary phenomenon, but for the most part pre-Diaspora Jewish genetics seems not to have been remarkable in any way. The exact extent of Middle Eastern ancestry of the Ashkenazim is only important to our thesis insofar as it helps us estimate the extent of gene flow between the Ashkenazi and neighbouring populations. In much the same way, the details of the Ashkenazi settlement of and migrations in Europe interest us because of their potential for creating genetic bottlenecks.

The key cultural precondition among the Jews was a pattern of social organization that required literacy, strongly discouraged intermarriage, and that could propagate itself over long periods of time with little change. Literacy (which does not itself require high intelligence) was probably important in the shift from a nation to an urban occupational caste (Botticini & Eckstein, 2002), acting as an entree to many urban professions in which Jews, at first, had no special biological advantages.

After the Bar-Kochba revolt in AD 135, most Jews lived outside Israel. They were concentrated in the Parthian (later Sassanid) empire, and in the eastern half of the Roman Empire, but there was a substantial population of Roman Jews, along with

other poorly documented western settlements such as Cologne. After the Moslem conquests, the great majority of Jews lived under Islamic rule.

The Ashkenazim, the Jews living north of the Alps and Pyrenees, appear in the historical record in the eighth and ninth centuries. Their origins are misty. There are three different threads that may have led to the foundation of the Ashkenazi Jews, but their relative importance is unclear.

The first possibility is that the Ashkenazim – or some fraction of them – had already lived in France and the Rhineland for a long time, perhaps going back to Roman times. We know that there were Jews in Cologne around AD 300 (Williams, 2002), and that there were Jews living in France under the Merovingian monarchs (Gregory of Tours, 1982) in the fifth and sixth centuries. However, King Dagobert of the Franks ordered that the Jews convert, leave or face execution in his lands in 629. This conversion edict may have pushed them out of most of France. Certainly we hear little about French Jews for the next 150 years or so. The size, even the existence of this population is uncertain.

The second thread involves Jewish merchants originating from the lands of Islam, as far as Palestine and Iraq. The Carolingian kings encouraged and protected these merchants, who brought luxury items such as silks and spices from the East according to Agobard of Lyons (Ben-Sasson, 1976). A few such traders served as interpreters on diplomatic missions: one brought Charlemagne an elephant from Haroun Al-Rashid.

The third thread, generally thought to be the best supported, is that most of the founding Ashkenazi population migrated from southern Europe, especially Italy. There are accounts about particular individuals and families moving there from Italy; for example the Kalonymus family is said to have migrated to Mainz from Lucca in Italy in 917 (Weinryb, 1972; Ben-Sasson, 1976; Ankori, 1979; Barnavi, 1992).

When we first see them in the historical record, the Ashkenazim were long-distance merchants who traded with the Moslem world. This is the beginning of an occupation pattern that is very different from those of other Europeans and from those of other Jewish groups, as well. The majority of Jews had already given up agriculture (Botticini & Eckstein, 2002), but the Jews of Islam, although urban, mostly worked in various crafts. The Ashkenazim, from their beginnings and for a long time, seldom had such jobs. This pattern is detailed in Gross (1975, p. 147): 'Two entirely different patterns in the practice of crafts and their place in Jewish life and society are discernible throughout the Middle Ages. One characterizes the communities in countries around the Mediterranean, including in the south those in the continents of Asia and Africa, and in the north extending more or less to an imaginary demarcation line from the Pyrenees to the northern end of the Balkans. The other, in the Christian countries of Europe, was more or less north of the Pyrenees–Balkans line,' and (p. 151) 'North of the Pyrenees and in the Balkans crafts played a very small role as a Jewish occupation, from the inception of Jewish settlement there.'

The Ashkenazi population, established in northern France by the early 900s, prospered and expanded. They settled the Rhineland and England after the Norman Conquest. At first they were international merchants who acted as intermediaries with the Moslem world. As Moslems and Christians, especially Italians, increasingly found

it possible to do business directly, Ashkenazi merchants moved more and more into local trade. When persecution began to be a serious problem and the security required for long-distance travel no longer existed, the Ashkenazim specialized more and more in one occupation, finance, left particularly open to them because of the Christian prohibition of usury. The majority of the Ashkenazim seem to have been money-lenders by AD 1100 (Arkin, 1975; Ben-Sasson, 1976), and this continued for several centuries. Such occupations (sales, trade, finance) had high IQ demands, and we know of no other population that had such a large fraction of cognitively demanding jobs for an extended period.

In some cases, we have fairly detailed records of this activity. For example (Arkin, 1975, p. 58), concerning the Jews of Roussilon circa 1270: 'The evidence is overwhelming that this rather substantial group of Jews supported itself by money lending, to the virtual exclusion of all other economic activities. Of the 228 adult male Jews mentioned in the registers, almost 80% appear as lenders to their Christian neighbors. Nor were loans by Jewish women (mostly widows) uncommon, and the capital of minors was often invested in a similar manner. Moreover, the Jews most active as moneylenders appear to have been the most respected members of the community.'

The Jews in this period were prosperous. Ben-Sasson points out (p. 401) that '. . . Western Europe suffered virtual famine for many years in the tenth and eleventh centuries, there is no hint or echo of this in the Jewish sources of the region in this period. The city dweller lived at an aristocratic level, as befitted international merchants and honored local financiers.' Their standard of living was that of the lower nobility (Roth, 2002).

Although prosperous, they were not safe. The first major crisis was the First Crusade, resulting in the death of something like a quarter of the Jews in the Rhineland. Religious hostility, probably exacerbated by commercial rivalries, increased, manifesting itself in the form of massacres and expulsions culminating in the expulsion of the Jews from most of Western Europe. They were expelled from England in 1290, from France in 1394, and from various regions of Germany in the 15th century. The expulsions had greater effect in the long run than massacres and persecutions. Jewish population growth rates were high due to prosperity and distaste for family limitation; so numbers tended to recover from attacks after a generation or two. But the potential for such population recovery decreased as Jews were excluded from more and more of Western Europe.

Many of the Jews moved east, first to Austria, Bohemia and Moravia, then to the Polish–Lithuanian Commonwealth. The Polish rulers welcomed Jewish immigrants who could help modernize and reconstruct the country, which had been devastated by Mongol raids. Jews were welcome as urban investors and initiators of trade. Other skilled immigrants were also welcome, but some of those groups brought political risks, particularly the Germans through their connection with the Teutonic Knights. The Jews were politically neutral and therefore safe.

As they had in Western Europe, the Jews of Poland had a very unusual occupational profile. The very first to immigrate were mainly moneylenders, but that soon changed. They became tax-farmers, toll-farmers, estate managers, and they ran mills and taverns. According to Weinryb (1972), in the middle of the fourteenth

century 'about 15 per cent of the Jewish population were earners of wages, salaries and fees. The rest were independent owners of business enterprises.' They were the management class of the Polish–Lithuanian Commonwealth. Besides literacy, success in those specialized occupations depended upon skills similar to those of businessmen today, not least the ability to keep track of complex transactions and money flows.

Eventually, as the Ashkenazi population of the Polish–Lithuanian Commonwealth increased, more and more Jews became craftsmen – there are after all only so many managerial and financial slots. Still, for 800–900 years, from roughly AD 800 to AD 1650 or 1700, the great majority of the Ashkenazi Jews had managerial and financial jobs, jobs of high complexity, and were neither farmers nor craftsmen. In this they differed from all other settled peoples of which we have knowledge.

Jews who were particularly good at these jobs enjoyed increased reproductive success. Weinryb (1972, see also Hundert, 1992) comments: 'more children survived to adulthood in affluent families than in less affluent ones. A number of genealogies of business leaders, prominent rabbis, community leaders, and the like – generally belonging to the more affluent classes – show that such people often had four, six, sometimes even eight or nine children who reached adulthood. On the other hand, there are some indications that poorer families tended to be small ones. It should also be added that overcrowding, which favours epidemics, was more prevalent among the poorer classes. In short, the number of children surviving among Polish Jews seems to have varied considerably from one social level to another.' He goes on to suggest that wealthier Jews were less crowded as they lived in bigger houses, they could keep their houses warmer, they could afford wet-nurses, and they had better access to rural refugia from epidemics. As an example, in a census of the town of Brody in 1764 homeowner households had 1·2 children per adult member while tenant households had 0·6.

This differential fitness (high reproductive success associated with high income) decreased effective population size, increasing the effects of drift, as Risch and others (Risch *et al.*, 1995, 2003) have pointed out. However, plausible amounts of fitness variance have only a small effect on effective population size. For example, if the richest 20% of the population averages four children, while the remaining 80% averages two, effective population size is 79% as large as it would have been if everyone had two children. The effects of genetic drift are not much increased. On the other hand the same fitness variance has a big effect on selection. Increased fitness among the wealthy would have resulted in strong selection for cognitive and psychological traits that increased income in that social niche.

We know that individuals with high status and/or wealth typically had significantly higher than average fitness in Europe before the demographic transition beginning in the 18th century (Clark & Hamilton, 2003). This resulted in selective pressures favouring those traits that led to high status and wealth, selection easily strong enough to cause significant change over historical time. It is likely that the selective pressures affecting the medieval Ashkenazi were far stronger and somewhat different, because such a high percentage had cognitively demanding jobs, and because the Ashkenazi niche was so specifically demanding of accounting and management skills, while upper classes elsewhere experienced a more diverse set of paths to wealth.

Societies reward different behavioural traits. In some times and places successful warriors and soldiers have had high status, in others merchants, in still others bureaucrats as in ancient China. There were societies in pre-modern Europe in which merchants and businessmen ranked near the top, but this was atypical. To the extent that status and wealth were inherited rather than earned, the correlation between cognitive traits and reproductive success in elite groups may have been quite weak.

In almost every case elite groups experienced substantial gene flow with other, much larger groups that were not subject to the same selective pressures. This means that the selective pressures experienced by such groups were diluted, and spread out into the general population. Christian merchants in London or Rotterdam may have experienced selective pressures similar to those of the Ashkenazi Jews, but they intermarried: there was extensive gene flow with the general population, the majority of whom were farmers. The selection pressures experienced by farmers were probably quite different: most likely cognitive skills did not have as high a correlation with income among farmers that they did among individuals whose occupations required extensive symbol manipulation, such as moneylenders, tax-farmers and estate managers.

The Ashkenazi occupational pattern was different from that of the Jews living in the Islamic world. The Jews of Islam, although reproductively isolated, did not have the concentration of occupations with high IQ elasticity. Some had such jobs in some of the Arab world, in some periods, but it seems it was never the case that most did. In part this was because other minority groups competed successfully for these jobs: Greek Christians, Armenians, etc., in part because Moslems, at least some of the time, took many of those jobs themselves, valuing non-warrior occupations more highly than did medieval Christians. In fact, to a large extent, and especially during the last six or seven hundred years of relative Moslem decline, the Jews of Islam tended to have 'dirty' jobs (Lewis, 1984). These included such tasks as cleaning cesspools and drying the contents for use as fuel, a common Jewish occupation in Morocco, Yemen, Iraq, Iran and Central Asia. Jews were also found as tanners, butchers, hangmen and other disagreeable or despised occupations. Such jobs must have had low IQ elasticity; brilliant tanners and hangmen almost certainly did not become rich.

The suggested selective process explains the pattern of mental abilities in Ashkenazi Jews: high verbal and mathematical ability but relatively low spatio-visual ability. Verbal and mathematical talent helped medieval businessmen succeed, while spatio-visual abilities were irrelevant.

Genetic evidence about Ashkenazi history and the bottleneck hypothesis

Evidence from polymorphic gene frequencies

The prevalence of several inherited diseases among Ashkenazim is often attributed to one or more population size bottlenecks in the past. Since the only evidence for such a bottleneck is the mutations themselves, it is important to look at other genetic markers for signs of any bottleneck. Episodes of small effective size could have

Table 1. Genetic statistics of Ashkenazim and other populations, all multiplied by 1000

	EU	AS	DR	RU	SA	YJ
Europeans	150	14	44	10	120	58
Ashkenazim	26	148	33	27	101	41
Druze	57	47	146	62	122	52
Russians	27	44	80	149	146	80
Samaritans	138	120	142	169	129	137
Yemeni Jews	76	59	72	103	162	144

Unbiased genetic distances are above the diagonal, average population heterozygosities are on the diagonal, and biased distances, to compare with simulations, are below the diagonal. These statistics are based on frequencies at 251 loci from the ALFRED database.

allowed deleterious mutants to increase in frequency by chance. While the concentration of Ashkenazi mutations in a few pathways is a very strong argument against the bottleneck hypothesis, it is nevertheless important to evaluate the bottleneck hypothesis with available genetic data. The conclusion of this section is that Ashkenazi gene frequencies are so similar to those of Europeans that any bottleneck of fewer than five or ten thousand effective size is excluded by the data and that drift cannot account for the Ashkenazi diseases.

Patterns on the Y-chromosome and mitochondrial DNA suggest that the Ashkenazi founding population originated in the Middle East, in accord with tradition and the historical record. Gene flow from neighbouring non-Jewish populations has been low, averaging less than 0·5% per generation (Hammer *et al.*, 2000). Such a low per-generation rate of gene flow still means that a substantial proportion of the Ashkenazi genome has been replaced by European genes over the 80 or so generations since AD 0: at a rate 0·5% per generation only $0{\cdot}995^{80} \sim 67\%$ of the genome would still be Middle Eastern, while at 1% per generation the Middle Eastern proportion would be 45%.

If there was a significant bottleneck in Ashkenazi history there ought to be a trace of it in contemporary Ashkenazi gene frequencies. We obtained from the ALFRED website maintained at Yale University by Kenneth and Judy Kidd (http://alfred.med.yale.edu/alfred) frequencies of 652 markers at 251 loci for which data were available for mixed Europeans, Ashkenazim, Russians, Samaritans, Druze and Yemeni Jews. The mixed Europeans, Ashkenazim and Russians are from large groups while the Samaritans, Druze and Yemeni Jews are smaller ethnic groups. Table 1 shows statistics computed from these data.

On the diagonal of the matrix in Table 1 are average heterozygosities for each population. Since a bottleneck should reduce heterozygosity, we expect reduced Ashkenazi heterozygosity under the bottleneck hypothesis. Instead there is no suggestion of any bottleneck at all in the overall heterozygosity values: Ashkenazim (148) are close to mixed Europeans (150) and Russians (149) while the Samaritans (129) do indeed show the genetic trace of history of small population size.

The standard errors of all the values on the diagonal, estimated by bootstrapping, are slightly less than 4.

The off-diagonal entries in Table 1 are genetic distances, statistics describing how different the pairs of populations are from each other. The biased distances were computed as:

$$d_{ij} = \frac{\sum_{alleles}(p_i - p_j)^2}{\sum_{alleles} \bar{p}(1-\bar{p})}$$

where the p_i and p_j are allele frequencies in the two populations and $\bar{p}=(p_i+p_j)/2$ (Cavalli-Sforza *et al.*, 1994). These distances are biased because of the binomial variance associated with finite samples from the populations: two samples from the same population would yield a positive distance. The unbiased distances in the lower triangle of the table were computed by subtracting the average of $1/2N_i + 1/2N_j$, where the Ns are the sample sizes from each population. The unbiased distances should be used to compare these data with theory or with distances from other populations, but the biased distances are of more interest in this paper. They can be compared with the results of our simulations, since the simulations are of the same number of loci and the same sample sizes as the data. Bootstrapping shows that the standard errors of the biased distances in the table are about 2.

The important datum for evaluating the bottleneck hypothesis in Table 1 is the genetic distance between mixed Europeans and Ashkenazim: Ashkenazim are nearly as similar to mixed Europeans as Russians are, and the differences are easily within the range of sampling error. From the perspective of a large collection of largely neutral genetic variation Ashkenazim are essentially European, not Middle Eastern.

This small genetic distance from a large collection of markers is crucial evidence that denies the bottleneck hypothesis for the Ashkenazi disorders. Simulations (below) show that either there was low gene flow into the Ashkenazim and no bottleneck else, if there was a significant bottleneck, subsequent gene flow was so high that it erased the effects of the bottleneck. In either case drift could not have been strong enough to allow deleterious mutants to increase to high frequencies.

The small genetic distance between Ashkenazim and other Europeans also shows that patterns in neutral markers may not be informative about biologically meaningful differences among populations. The genetic distance between Ashkenazim and other Europeans computed from IQ is roughly one hundred times greater than the distance from polymorphic markers.

Evidence from rare genes

Even though gene frequencies in Ashkenazim are nearly indistinguishable from mixed Europeans overall, there are clear genetic signatures of the Middle Eastern ancestry of the population and of shared history with other Jewish groups.

Factor XI deficiency is a bleeding disorder. Usually mild, it can become serious after injury, surgery or childbirth. It is partially dominant: 20–50% of carriers (not just homozygotes) also experience excessive bleeding. It is rare in most populations but quite common among Ashkenazi Jews: the gene frequency is about 5%.

Two mutations of approximately equal frequency, E117X and F283L, account for almost all of the Ashkenazi Factor XI cases. The type III mutation, F283L, is found at elevated frequency only among the Ashkenazim, but the type II mutation, E117X, is roughly as frequent among Iraqi Jews and can be found at lower frequency among Sephardic Jews and Palestinian Arabs.

Female heterozygotes for BRCA1 mutations have a very risk high of breast cancer and ovarian cancer. This mutation is apparently lethal in homozygotes, since none has ever been observed, even though the Ashkenazi gene frequency is about 0·6%, surprisingly high for a deleterious dominant. About two-thirds of the Ashkenazi BRCA1 mutations are the 187delAG mutation, while the other third are the 5382insC mutation. The 5382insC mutation seems to be limited to the Ashkenazi, but the 187delAG mutation is found at comparable levels in Iraqi and Moroccan Jews.

Most mutations of APC, the gene causing adenomatous polyposis of the colon, cause huge numbers of polyps of the colon and rectum, leading almost inevitably to colon cancer in early adult life. The disorder is dominant. There is a common APC variant (I1307K) among the Ashkenazi that causes a much milder syndrome in which there are many fewer polyps, usually less than 100. The I1307K mutation increases the risk of colon cancer by a factor of 1·5–2. This variant is very common among the Ashkenazim: the gene frequency is about 4%. It is also found in other Jewish groups at lower levels: the average gene frequency among non-Ashkenazi Jews in Israel is 0·7% (Niell *et al.*, 2003).

There are other alleles at relatively high frequency in Ashkenazim that are even more widely shared with Middle Eastern populations. These are mostly old mutations, probably older than the origin of Jews as an ethnic group, and most are plausibly defences against infectious disease. This category includes alpha-thalassaemia (Rund *et al.*, 2004), familial Mediterranean fever (Aksentijevich *et al.*, 1999) and the 167delT mutation of connexin-26 causing non-syndromic deafness (Meyer *et al.*, 2002).

These mutations show that Ashkenazi Jews and other Jewish groups share common ancestry. The exact extent of shared ancestry is unclear since all these alleles are subject to selection. There is a hint of an odd pattern in which a given mutation first becomes surprisingly common in the ancestral Jewish population, then, much later, becomes even more common among the Ashkenazim, sometimes accompanied by other mutations of the same gene.

The Ashkenazi mutations

There are a number of genetic diseases that are unusually common among the Ashkenazim. We also know a fair amount about genetic disease among the Sephardic and Asian Jews. How can these diseases and the associated mutations be categorized?

Most fall into a few categories, as noted by Ostrer (2001): sphingolipid storage diseases, glycogen storage diseases, clotting disorders, disorders of adrenal steroid biosynthesis and disorders of DNA repair. It is interesting that although several

Jewish disorders fall into each of these categories, sometimes several in the same population, none of the Finnish genetic diseases, for example, fall into any of these categories (Norio, 2003), while only one of the genetic disorders common in Quebec does: Tay-Sachs (Scriver, 2001). But that is as expected: genetic diseases made common by drift would be very unlikely to cluster in only a few metabolic paths, as if on a few pages of a biochemistry text. The existence of these categories or disease clusters among the Jews suggests selective forces at work, just as the many different genetic disorders affecting haemoglobin and the red cell in the Old World tropics suggest selection, which we know is for malaria resistance.

The two most important genetic disease clusters among the Ashkenazim are the sphingolipid storage disorders (Tay-Sachs, Gaucher, Niemann-Pick and mucolipidosis type IV) and the disorders of DNA repair (BRCA1, BRCA2, Fanconi anaemia type C and Bloom syndrome) but there are several others that are at quite elevated frequency in Ashkenazim. Using published allele frequencies it can be calculated that the probability at conception of having at least one allele of the sphingolipid or DNA repair complex is 15%. If we add Canavan disease, familial dysautonomia, Factor XI deficiency (Peretz *et al.*, 1997) and the I1307K allele of the APC locus (Gryfe *et al.*, 1999) this figure grows to 32%, and if we further include non-classical congenital adrenal hyperplasia the probability of having at least one allele from these disorders is 59%.

The sphingolipid disorders

There are four common sphingolipid storage diseases: Tay-Sachs, Gaucher, Niemann-Pick and mucolipidosis type IV (MLIV). Each is an autosomal recessive lysosomal storage disorder. Tay-Sachs, Gaucher and Niemann-Pick are caused by defective sphingolipid catabolism, while MLIV involves abnormal lysosomal sorting and trafficking. In each case the main storage substances are sphingolipids.

Each of these diseases is surprisingly common among the Ashkenazi Jews, particularly surprising because Tay-Sachs, Niemann-Pick and MLIV homozygotes do not reproduce, while Gaucher homozygotes often have health problems. Table 2 shows the relevant gene frequencies and allele variants.

Each of these gene frequencies is much higher than in the general European population. Each disease involves elevated frequencies of several different mutations of the same gene, especially Niemann-Pick. All result in the accumulation of sphingolipids. What can explain this? This question is of course not new: people have been arguing about this for decades (Chase & McKusick, 1972; Chakravarti & Chakraborty, 1978; Cavalli-Sforza, 1979; Motulsky, 1979; Jorde, 1992; Diamond, 1994; Risch *et al.*, 2003; Zlotogora & Bach, 2003).

Some believe that the elevated disease frequencies reflect genetic drift (Risch *et al.*, 2003), but drift is an extremely implausible explanation for the pattern. First, there is strong statistical evidence that the sphingolipid storage mutations are products of selection. Conservative population-genetic calculations of the probability of a deleterious mutant achieving an appreciable frequency are negligible (see below). The probability that four such unlikely mutation distributions occurred by chance in genes

Table 2. The Ashkenazi sphingolipid disorders

Mutation	Homozygote fitness	Frequencies	Alleles
Gaucher	N370S has residual activity, fitness ~ 0·8, 84 GG lethal	$2{\cdot}8 \times 10^{-2}$ (Beutler & Grabowski, 2001)	N370S (74%), 84 GG (12%), L444P (3·9%), IVS2 (2·6%), V394 L (2·6%)
Tay-Sachs	Lethal	$2{\cdot}0 \times 10^{-2}$ (Bach *et al.*, 2001)	1278insTATC (85%), IVS12+1(10%), G269S (4%)
Niemann-Pick	Lethal	$5{\cdot}25 \times 10^{-3}$ (Schuchman & Miranda, 1997)	Type A: R496 L (43%), L302P (29%), fsP330 (25%), Type B: R608P(?)
Mucolipidosis IV	Lethal	$4{\cdot}45 \times 10^{-3}$ (Bargal *et al.*, 2001; Edelmann *et al.*, 2002)	VS3–2AG (72%), 411del6434 (23%)

that have closely related functions, that all have a similar biochemical result, is harder to estimate but must be extraordinarily small: some estimates of this probability are provided below.

Biology of the sphingolipid mutations

The sphingolipid storage mutations were probably favoured and became common because of natural selection, yet we don't see them in adjacent populations. We suggest that this is because the social niche favouring intelligence was key, rather than geographic location. It is unlikely that these mutations led to disease resistance in heterozygotes for two reasons. First, there is no real evidence for any disease resistance in heterozygotes (claims of TB resistance are unsupported) and most of the candidate serious diseases (smallpox, TB, bubonic plague, diarrhoeal diseases) affected the neighbouring populations, that is people living literally across the street, as well as the Ashkenazim. Second and most important, the sphingolipid mutations look like IQ boosters. The key datum is the effect of increased levels of the storage compounds. Glucosylceramide, the Gaucher storage compound, promotes axonal growth and branching (Schwartz *et al.*, 1995). *In vitro*, decreased glucosylceramide results in stunted neurones with short axons while an increase over normal levels (caused by chemically inhibiting glucocerebrosidase) increases axon length and branching. There is a similar effect in Tay-Sachs (Walkley *et al.*, 2000; Walkley, 2003): decreased levels of GM2 ganglioside inhibit dendrite growth, while an increase over normal levels causes a marked increase in dendritogenesis. This increased dendritogenesis also occurs in Niemann-Pick type A cells, and in animal models of Tay-Sachs and Niemann-Pick.

Figure 1, from Schwartz *et al.* (1995), shows the effect of glucosylceramide, the sphingolipid that accumulates in Gaucher disease. These camera lucida drawings of cultured rat hippocampal neurones show the effect of fumonisin, which inhibits glucosylceramide synthesis, and of conduritol B-epoxide (CBE), which inhibits lysosomal glycocerebrosidase and leads to the accumulation of glucosylceramide, thus mimicking Gaucher disease. Decreased levels of glucosylceramide stunt neural growth, while increased levels caused increased axonal growth and branching.

Dendritogenesis appears to be a necessary step in learning. Associative learning in mice significantly increases hippocampal dendritic spine density (Leuner *et al.*, 2003), while enriched environments are also known to increase dendrite density (Holloway, 1966). It is likely that a tendency to increased dendritogenesis (in Tay-Sachs and Niemann-Pick heterozygotes) or to increased axonal growth and branching (in Gaucher heterozygotes) facilitates learning.

Heterozygotes have half the normal amount of the lysosomal hydrolases and should show modest elevations of the sphingolipid storage compounds. A prediction is that Gaucher, Tay-Sachs and Niemann-Pick heterozygotes will have higher tested IQ than control groups, probably in the order of 5 points.

There is strong but indirect evidence that one of these, Gaucher disease, does indeed increase IQ. Drs Ari Zimran and Deborah Elstein, of the Gaucher Clinic at the Shaare Zedek Medical Centre in Jerusalem, provided a list of occupations of 302 Gaucher patients. Because of the Israeli medical care system, these are essentially all the Gaucher patients in the country. Of the 255 patients who are not retired and not students, 81 are in occupations that ordinarily average IQs greater than 120. There are thirteen academics, 23 engineers, fourteen scientists and 31 in other high-IQ occupations like accountants, physicians or lawyers. The government of Israel states that 1·35% of Israeli's working age population are engineers or scientists, while in the Gaucher patient sample 37/255 or 15% are engineers or scientists. Since Ashkenazim make up 60% of the workforce in Israel, a conservative base rate for engineers and scientists among Ashkenazim is 2·25% assuming that all engineers and scientists are Ashkenazim. With this rate, we expect six in our sample and we observe 37. The probability of 37 or more scientists and engineers in our sample, given a base rate of 2·25%, is approximately 4×10^{-19}. There are five physicists in the sample, while there is an equal number (five) of unskilled workers. In the United States the fraction of people with undergraduate or higher degrees in physics is about one in one thousand. If this fraction applies even approximately to Israel the expected number of physicists in our sample is 0·25 while we observe 5. Gaucher patients are clearly a very high IQ subsample of the general population.

Are there Ashkenazi mutations other than these sphingolipid storage disorders that probably became common because of strong selection for IQ? There are several candidates.

Ever since torsion dystonia among the Ashkenazim was first recognized, observers have commented on the unusual intelligence of patients. Flatau and Sterling (Eldridge, 1976) describe their first patient as showing 'an intellectual development far exceeding his age', and their second patient as showing 'extraordinary mental development for his age'. At least ten other reports in the literature have made similar comments. Eldridge (1970, 1976) studied fourteen Jewish torison dystonia patients:

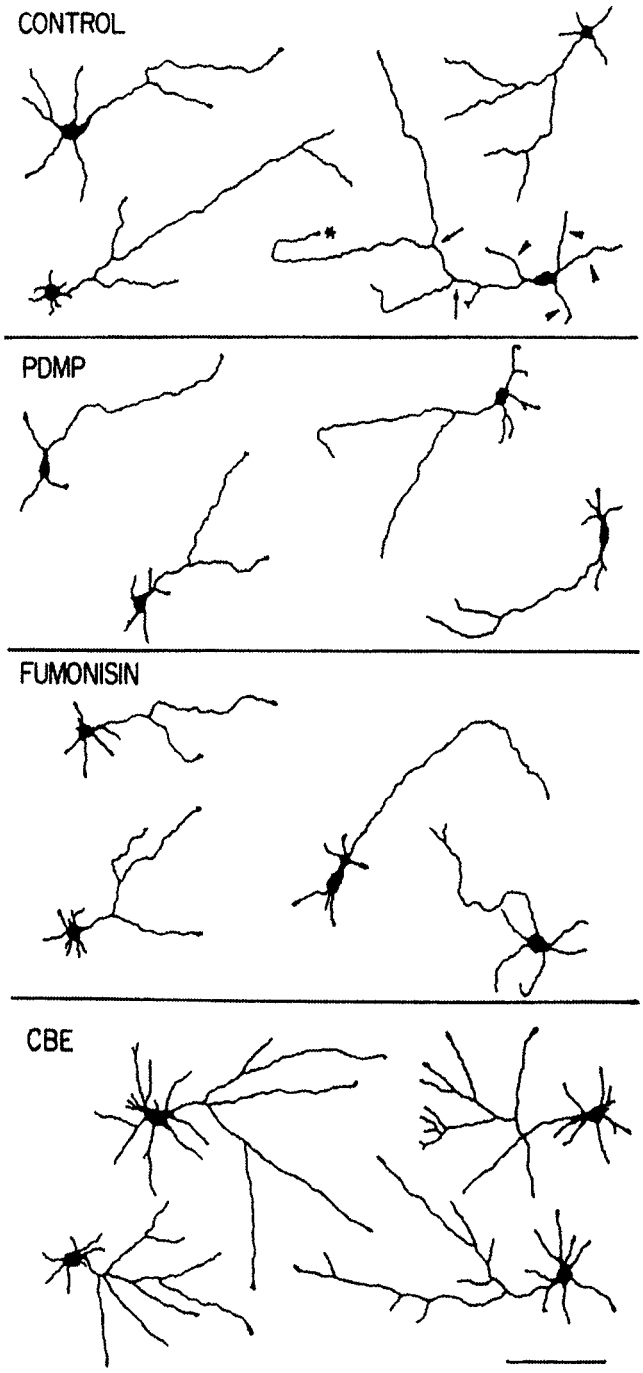

Fig. 1. Glucosylceramide increases axon growth. From Schwartz *et al*. (1995), reproduced by permission of the *Journal of Biological Chemistry*.

he found that their average IQ before the onset of symptoms was 121, compared with an averge score of 111 in a control group of fourteen unrelated Jewish children matched for age, sex and school district. Riklan and colleagues found that fifteen Jewish patients with no family history of dystonia (typical of DYT1 dystonia) had an average verbal IQ of 117 (Riklan *et al.*, 1976; Eldridge, 1979).

Torsion dystonia is unusual among the Ashkenazi mutations in that it is caused by a low-penetrance dominant rather than a recessive, so disease risk and any heterozygote advantage exist in the same individual. About 10% of heterozygotes have crippling muscular spasms (usually curable by modern neurosurgery), and such individuals seldom reproduced in the past. A net fitness advantage could have existed if healthy carriers had a greater than 10% fitness edge, presumably from increased intelligence. Risch (Risch *et al.*, 1995) found that linkage data indicate that the DYT1 mutation came into existence around 300 years ago. He suggests that a high reproductive variance may have decreased the effective Ashkenazi population size, resulting in drift, but as pointed out earlier, this proposed mechanism strengthens selection far more than drift. The high gene frequency and recent origin of the DYT1 are signs of positive selection, while the many observations of increased intelligence among people with ITD strongly suggest that increased fitness resulted from increased intelligence.

Non-classic congenital adrenal hyperplasia (CAH) is another mutation that is unusually common among the Ashkenazim and has been reported to increase IQ. At least seven studies show high IQ in CAH patients, parents and siblings, ranging from 107 to 113. Parents are obligate carriers and two-thirds of siblings are carriers. There is also socioeconomic status elevation in patient families (Nass & Baker, 1991). This mainly applies to the milder forms of CAH; there is no apparent IQ advantage in seriously ill patients like salt-wasters. The Ashkenazi gene frequency is almost 20% (New & Wilson, 1999).

The DNA repair cluster

The second major cluster of Ashkenazi mutations is the DNA repair cluster, involving BRCA1, BRCA2, Fanconi anaemia and Bloom syndrome. These diseases all affect a group of functionally related proteins involved in DNA repair. This is mainly an Ashkenazi cluster, but the common Ashkenazi BRCA1 mutation 187delAG is also common in Sephardic populations, while the Tyr978X BRCA1 mutation exists in 1–2% of Iraqi and Iranian Jews. There are two Ashkenazi BRCA1 mutations: 187delAG has an Ashkenazi carrier frequency of 0·96–1·14% and 5382insC has a carrier frequency of 0·15–0·28%. Table 3 lists the relevant gene frequencies and allele variants (from Dong *et al.*, 2002).

All of these DNA repair mutations participate in homologous recombination repair (HRR), a process that is important in repairing double-strand breaks, a common byproduct of DNA replication. BRCA1 and BRCA2 participate in the processes that implement cell cycle checkpoints in response to double-strand breaks, help coordinate the repair of those breaks, facilitate transcription coupled repair of oxidative base damage and also act as transcription modifiers.

Table 3. The Ashkenazi DNA repair cluster disorders

Mutation	Homozygote fitness	Frequency of mutants	Alleles
BRCA1	Breast and ovarian cancer risk in heterozygotes, lethal in homozygotes	$5{\cdot}8 \times 10^{-3}$ (Hartge *et al.*, 1999)	187delAG (66%), 5832insC (33%)
BRCA2	Breast cancer risk in heterozygotes, lethal in homozygotes	$5{\cdot}55 \times 10^{-3}$ (Hartge *et al.*, 1999)	6174delT (100%)
Fanconi anaemia	Homozygote fitness close to zero	$5{\cdot}6 \times 10^{-3}$ (Auerbach, 1997)	IVS4+4A (100%)
Bloom syndrome	Homozygote fitness close to zero	$4{\cdot}7 \times 10^{-3}$ (Li *et al.*, 1998)	2281delta6ins (100%)

Fanconi anaemia (FA) is a genetically complex autosomal recessive disorder characterized by chromosomal instability and defective crosslink repair. It is caused by mutations in any of eight genes. The genes A, C, E, F and G form the FA nuclear complex: mutations in the C protein cause the Ashkenazi form of Fanconi anaemia. The FA complex is required for the activation of a portion of FANCD2 protein, which is then localized to nuclear foci that contain the breast cancer susceptibility protein BRCA1. Most recently, the B and D1 complementation groups were surprisingly identified as having homozygous mutations in BRCA2, suggesting that FANCB and FANCD1 are synonymous with BRCA2 (Howlett *et al.*, 2002). Mutations that completely destroy BRCA2 function apparently cause embryonic death in homozygotes, while milder mutations with residual function cause Fanconi anaemia. Thus there are really two kinds of Fanconi anaemia among the Ashkenazim: Fanconi C and BRCA2.

Bloom syndrome is an autosomal recessive disorder, characterized at the cellular level by a greatly increased frequency of sister-chromatid exchange. An increase in exchanges between homologous chromosomes is also seen. Cultured BS cells also show a greatly increased number of chromatid breaks, gaps and rearranged chromosomes.

The BLM protein is a DNA helicase, and considerable evidence suggests that the BLM protein plays a role in HRR, although its exact role is unclear, and is involved in repairing damage at stalled replication forks. *In vitro*, a complex containing BLM, termed BRAFT, also contains five of the Fanconi anaemia complementation group proteins (Meetei *et al.*, 2003). BRAFT displays a DNA-unwinding activity, which requires the presence of BLM because complexes isolated from BLM-deficient cells lack such an activity. The complex also contains topoisomerase III and replication protein A, proteins that are known to interact with BLM and could facilitate unwinding of DNA. This suggests a connection between the BLM and FA pathways of genomic maintenance.

Again we see a set of improbably common mutations among the Ashkenazim that have a close biochemical relationship, a strong suggestion that natural selection has acted on the biochemical pathways involved. As it turns out there are other signs. Looking at linkage disequilibrium and allele frequency, Slatkin & Rannala (2000) conclude that both BRCA1 and BRCA2 have been under recent strong selection in many populations. In fact, BRCA1 appears to have been under positive selection in the hominid lineage over the past few million years as well (Huttley *et al.*, 2000).

What could the selective advantage be? It seems unlikely that any degree of disruption of a basic housekeeping process such as DNA repair could ever be favoured by selection. In fact BRCA1 and BRCA2 heterozygotes face cancer risks. Still, those risks come fairly late in the reproductive schedule and have only a slight effect on fertility, so heterozygote advantage is not impossible. Our original speculative notion of how these DNA repair mutations might in some cases give heterozygote advantage was inspired by the fact that BRCA1 is expressed by embryonic and adult neural stem cells and is involved in cell proliferation (Korhonen *et al.*, 2003). It apparently limits growth, and BRCA1 is known to down-regulate cellular proliferation. It seemed possible that a defective BRCA1 gene might, in heterozygotes, slightly unleash neural growth in a way that might favour cognition. Assuming that there is anything to this notion, the other Ashkenazi HRR-path DNA repair mutations may have similar effects.

Recent work (Evans *et al.*, 2004) supports this hypothesis. Evans *et al.* show that microcephalin, a gene controlling brain size, has evolved rapidly throughout the primate lineage leading to humans, and that this evolutionary process exhibits strong signs of positive selection (see also Wang & Bing, 2004). Microcephalin and BRCA1 both show signs of positive selection during primate evolution, share BRCT domains and have critical functions in regulating the development of neural stem cells. Evans *et al.* suggest that the observed positive selection on BRCA1 has been driven by its effect on brain development rather than tumour suppression. It may be, then, that the Ashkenazi DNA repair mutations in genes such as BRCA1 may be the most recent manifestation of an evolutionary trend that goes back many millions of years, from lemurs to human subpopulations.

The age of the Ashkenazi mutations may help clarify this story. In general, we expect that the IQ-increasing mutations with the highest frequency today should have originated shortly after conditions began favouring high IQ among the Ashkenazim, shortly after they began to occupy their niche as financiers. Mutations that came into existence earlier, when IQ did not have an unusually high reproductive payoff, would very likely have disappeared by chance. It might be that a mutation would have side-effects that would, in the absence of high payoffs to IQ, actually reduce carrier fitness. This must be the case for torsion dystonia. IQ-increasing mutations could certainly have originated later, but would not have had as many generations in which to increase. This implies that almost all of this class of mutations should have originated after the Ashkenazim began to occupy their niche in finance, perhaps 1200 to 1300 years ago, with the most common mutations originating early in this period.

Seven of the most common Ashkenazi mutations (GD(1226), GD(84 GG), TSS(1278insTATC), MLIV(IVS3), DYS(IVS20), BLM(2281) and BRCA1*

(187delAG)) seem to have originated around that time (Risch *et al.*, 2003; Frisch *et al.*, 2004). This might also be consistent with a genetic bottleneck in the founding of the Ashkenazim, but as we have shown above, genetic evidence at many loci denies the existence of any bottleneck.

Population genetic test of the bottleneck hypothesis

The clearest statement of the bottleneck hypothesis has been provided by Slatkin (2004). He studied a model in which there were two potential bottleneck events: one during after the Diaspora from the Middle East and another during the late Middle Ages in Europe. He takes the Jewish population in AD 50 to be one million. The population size was reduced, in his model, to N_0 during the first bottleneck at AD 70 and N_1 during the second around AD 1350, with N_0 and N_1 taking values of 150–3000 and 600–6000 respectively. Intermediate values, from historical sources, are 150,000 in AD 1096, 200,000 in 1648, 750,000 in 1765, 6,000,000 in 1900 and 10,500,000 today. Given values of his two parameters the population size of Ashkenazim from year 0 to the present is given by interpolation in his Table 1. These numbers are census sizes, and effective sizes are taken to be one-third of these values.

Slatkin then examines the bottleneck hypothesis in the following way: assuming that a mutation was present in the bottleneck population, he asks whether there is today so much linkage disequilibrium with neighbouring sites on the chromosomes that selection must be invoked; selection would cause gene frequency to rise rapidly and recently so little recombination would have occurred in the mutant's history. He proceeds by taking the current frequency of the mutation and the population history as parameters, then averaging over the allele age and the distribution of the number of ancestral lineages at the time of the hypothesized bottleneck. Notice that he is not concerned with the probability that a new mutant actually could have reached observed proportions; he is only concerned with the evidence of linkage disequilibrium about the need to invoke selection. Perhaps not surprisingly he is able to reject very few hypotheses about these genes and their history, but he does conclude from consideration of allele age that an earlier bottleneck, around AD 70, rather than a late medieval bottleneck, is the more plausible.

We have simulated Ashkenazi population history using a coalescent algorithm and the population size scenarios used by Slatkin back to AD 70. Before AD 70 we set the number of migrants between Ashkenazi and European ancestors to six in order to generate an initial genetic distance of about 50, on the scale of Table 1, to mimic current genetic distances between European and Middle Eastern Populations. After AD 70 we set the number of migrants exchanged between Ashkenazi and European ancestors each generation to the current Ashkenazi population size multiplied by a migration rate, conventionally 0·005 following Hammer *et al.* (2000).

Our simulations show that a bottleneck about AD 70 of 150 or even 300 is incompatible with the small genetic distance between Europeans and Ashkenazim. With a migration rate of 0·005 the genetic distance is always greater than 30 and there is a 5% heterozygosity loss in the Ashkenazi population. In order to have such a small

Table 4. Probabilities estimated from one million simulations each of the probability of a Tay-Sachs mutation introduced during a bottleneck at AD 70 reaching a frequency of 2% or greater in Ashkenazim

		$N_0=150$	$N_0=600$	$N_0=3000$
	$N_1=600$	0·01	0·002	0·0001
$m=0·005$	$N_1=3000$	0·002	0·0001	0
	$N_1=6000$	0·001	0·00004	0
	$N_1=600$	0·003	0·0004	0·00002
$m=0·01$	$N_1=3000$	0·0001	0·000002	0
	$N_1=6000$	0·00004	0·000002	0

distance the migration rate needs to be set to 0·01, and with a 1% rate of gene flow per generation the Ashkenazi population becomes essentially $1–0·99^{80}\sim0·55$ or over half European. Such a high rate of gene flow is incompatible, as we show below with simulation, with Tay-Sachs and other inherited disorders reaching their observed frequencies through drift. Even a bottleneck of 600 is only marginally possible with $m=0·005$.

Slatkin's model assumes that the heterozygous carriers of Tay-Sachs suffer no fitness impairment and that the gene frequency is low enough that selection against homozygotes can be ignored, i.e. that neutral theory can be applied. We have examined this by doing forward simulations of his postulated population histories that incorporate selection. Specifically we assume that complete reproductive compensation occurs so that every death due to Tay-Sachs is replaced with a carrier, with probability 2/3, or a non-carrier, with probability 1/3, since the parents must have been both carriers. The estimated probabilities of Tay-Sachs reaching the observed gene frequency of 2% from a single mutant introduced during the bottleneck are shown in Table 4. Each of these is based on one million simulations of the postulated history. Our assumption of full reproductive compensation is unreasonable and it favours the bottleneck drift hypothesis. The probabilities in Table 4 are cut approximately by one-half if we do not assume reproductive compensation.

The results shown in Table 4 show that neutral theory (e.g. Frisch *et al.*, 2004) gives wildly incorrect answers in the case of these recessive lethals. For example, the chance that a Tay-Sachs mutation introduced at AD 70 exceeds 2% under the extreme Slatkin model of two severe bottlenecks and a low migration rate of 0·005 is 1% with full reproductive compensation. With no gene flow and no selection, i.e. the neutral model, the corresponding probability is 15%: the answer given by the neutral model is wrong by a factor of 15.

Table 4 refers to mutations introduced during the hypothesized early bottleneck at AD 70. Simulations of a mutation introduced during the later hypothesized bottleneck, after the plague and the Crusades in AD 1350, never reach a frequency of 2% in our simulations. This is in agreement with Slatkin's conclusion that if a bottleneck were responsible for the high frequency of Tay-Sachs it must be the early and not the late one.

These simulations show that the scenario of a severe early bottleneck coupled with a low migration rate is the only one in which there is a reasonable chance of recessive lethal mutant reaching a frequency of 2% by drift alone. The low genetic distance between Ashkenazi and European populations denies this scenario, however, and we are left with the conclusion that the bottleneck hypothesis is wrong.

Functional genomics of the Ashkenazi mutation clusters

The bottleneck hypothesis has also been advanced by Risch *et al.* (2003). They compare the frequency of Ashkenazi sphingolipid mutations (lysosome storage diseases, LSD) with some other characteristic Ashkenazi mutations (non-LSD): Bloom syndrome, Canavan disease, cystic fibrosis and Fanconi anaemia. They find that no differences exist between LSD and this set of non-LSD mutations with respect to (1) number and frequency of disease mutations, (2) coalescence times, and (3) geographic distribution of mutation frequencies. They conclude that there is no reason to believe that some special selective force has operated on the LSDs compared with the other genetic diseases found in the Ashkenazi population. They then argue that this must mean that all are the result of drift since it would be unparsimonious to suppose that most of the Ashkenazi Jewish mutations were the result of a selective process.

Our hypothesis in this paper is precisely that most of these are the result of the same selective force, on IQ. (Cystic fibrosis and connexin-26 are probably involved in disease resistance.) Their findings are in fact in good agreement with our model. Just as the LSD disorders are all biochemically related, Bloom Syndrome and Fanconi anaemia fall on the same page of the biochemistry textbook as BRCA1 and BRCA2. These probably affect early neurological development (Evans *et al.*, 2004), while Canavan disease looks like a neurological booster that modifies myelin.

A different force probably favoured the cystic fibrosis mutations – typhoid resistance, just as in neighbouring populations. The time scale and strength of selection on cystic fibrosis is different, and the del508 mutation is much older than the Ashkenazi mutations.

Risch *et al.* dismiss the argument that the clustering of mutations into a few pathways is statistically strong evidence of selection. In order to evaluate the significance of the clustering we have done a direct test.

It is possible to quantify just how probable it is that the functional clustering of Ashkenazi mutant genes would happen by chance. To do this, we used the Gene Ontology database (GO-EBI & EMBL-EBI, 2003), an established tool used to assess the statistical significance of human gene clusters obtained by high-throughput methods such as microarrays. Gene Ontology's framework is advantageous because it moves beyond simple text-string annotations and instead roots function in a hierarchical network of meaning. For example, the term 'sphingolipid metabolism' is a child of 'membrane lipid metabolism', which is in turn a child of 'lipid metabolism', and so on. Genes are assigned places in the network by a consortium of human curators along with evidence codes that indicate the level and type of experimental or computational confirmation for the placement (or placements, as genes can be involved in multiple processes).

The Gene Ontology database is relevant for our analysis because it contains the best estimate to date of the number of genes involved in various functional categories, such as sphingolipid metabolism or lytic vacuole assembly. As such it can be used to estimate the statistical significance of an observed functional clustering. For example, if there are K known lipid metabolism genes in a genome with N genes, and we observe k lipid metabolism genes in a putative functional cluster of n genes, we can compute the likelihood that this concentration of lipid metabolism genes would happen at random. Specifically, we can regard this as a problem of picking n balls at random out of a jar of N balls, K of which are red. The hypergeometric distribution provides the likelihood of obtaining k or more red balls in a sample of size n in this case.

In practice these raw p values must be corrected. The inference algorithm is more complicated both because of multiple testing issues and because of the dependency structure of the network. First, testing several hypotheses at a time (such as whether a cluster is involved in lipid metabolism, vacuole assembly or DNA repair) can result in false positives if the hypothesis test threshold is not calibrated to account for multiple tests. Second, many of the hypotheses tested in a GO analysis are dependent. For example, an assessment of whether a given cluster is involved in lipid metabolism is not statistically independent from an assessment of whether it is involved in membrane lipid metabolism. These dependencies and multiple testing issues have been accounted for by exhaustive statistical simulation of the network, and the convention is that corrected p values less than about 0·01 represent biologically significant groups (Boyle *et al.*, 2004).

The GO-TermFinder software can be used on 21 genes with frequent mutant alleles in Ashkenazi Jews (Table 5) to find functional clusters and assess their statistical significance. These 21 genes were searched against the UniProt Gene Ontology annotation maintained by the European Bioinformatics Institute (Camon *et al.*, 2004).

The results are summarized in Table 6. We note that the software picked up most of the clusters we had independently discovered, and several of them (lytic vacuole assembly, sphingolipid metabolism, glycosyl hydrolase activity) have statistical significance far beyond the 0·01 heuristic for corrected p values. Furthermore, the DNA repair cluster we identified is right on the edge of this heuristic with a p value of 0·015. In sum, it is highly unlikely that several such tightly functionally linked groups would be present in a random collection of 21 genes. This is extremely strong evidence against the hypothesis that these mutations became frequent through drift rather than natural selection.

Conclusion

Our general hypothesis is that high IQ test scores of Ashkenazim, along with their unusual pattern of abilities, are a product of natural selection, stemming from their occupation of an unusual social niche. All the required preconditions – low inward gene flow and unusually high reproductive reward for certain cognitive skills, over a long-enough period – did exist. These preconditions are both necessary and sufficient, so such a selective process would almost inevitably have this kind of result.

Table 5. Ashkenazi mutations examined for occurrence in clusters

Disease	Uniprot ID	GO common name	NCBI name
Tay-Sachs	P06865	HEXA_HUMAN	HEXA
Niemann-Pick Type A	P17405	ASM_HUMAN	SMPD1
Gaucher disease	P04062	GLCM_HUMAN	GBA
MLIV – mucolipin-1	Q9 GZU1	MLN1_HUMAN	MCOLN1
BRCA1	P38398	BRC1_HUMAN	BRCA1
BRCA2	P51587	BRC2_HUMAN	BRCA2
BLM	P54132	BLM_HUMAN	BLM
Fanconi anaemia	Q00597	FACC_HUMAN	FANCC
APC	P25054	APC_HUMAN	APC
Canavan	P45381	ACY2_HUMAN	ASPA
Familial dysautonomia	Q8N516	—	IKBKAP
Congenital adrenal hyperplasia	Q16874	—	CYP21A2
Torsion dystonia	O14656	TO1A_HUMAN	DYT1
Cystic fibrosis	P13569	CFTR_HUMAN	CFTR
Familial Mediterranean fever	O15553	MEFV_HUMAN	MEFV
Connexin-26	P29033	CXB2_HUMAN	CXB2
Factor XI	P03951	FA11_HUMAN	F11
Familial hyperinsulinism	Q09428	ACC8_HUMAN	ABCC8
Familial hypercholesterolaemia	P01130	LDLR_HUMAN	LDLR
Glycogen storage disease type VII	P08237	K6PF_HUMAN	PFKM
Cystinuria	Q07837	SC31_HUMAN	SLC3A1

The pattern of high achievement among Ashkenazi Jews and the observed psychometric results are certainly consistent with this hypothesis.

Our more specific prediction is that some or most of the characteristic Ashkenazi genetic diseases are byproducts of this strong selection for IQ. In particular we think that this is the most likely explanation of the sphingolipid mutations. The improbably high frequency and observed effects of the storage compounds of axonal and dendritic growth are very suggestive of selection for some neurological trait. We predict that heterozygotes for the sphingolipid storage mutations should have higher scores on psychometric tests of verbal and mathematical abilities than their non-carrier sibs. In the case of Gaucher disease, homozygotes for mild mutations such as N370S may also have elevated scores, and the occupational profile of the sample of Gaucher patients supports the hypothesis. Considering the reports of elevated IQ in torsion dystonia and CAH heterozygotes, we think that carriers of other common Ashkenazi mutations should also be studied, including the DNA repair mutations but also carriers of mutations with neurological effects such as familial dysautonomia and Canavan disease.

It should not be difficult to compare full sibs who are and are not carriers of specified mutations. It will also be worthwhile to look at other indicators like income and occupation. While we think that IQ is the most relevant outcome measure it may be that the historical process we have discussed selected for other traits that led to

Table 6. Clustering of mutations into pathways

NCBI name	GO ID	Term	*p*	Ashkenazi	Total
MCOLN1, SMPD1, HEXA, GBA	GO:0000323	Lytic vacuole	0	4	108
MCOLN1, SMPD1, HEXA, GBA	GO:0005764	Lysosome	0	4	108
MCOLN1, SMPD1, HEXA, GBA	GO:0005773	Vacuole	0·0001	4	114
ABCC8, SLC3A1, SMPD1, HEXA, PFKM, GBA	GO:0005975	Carbohydrate metabolism	0·002	6	612
SMPD1, HEXA, GBA	GO:0006665	Sphingolipid metabolism	0·002	3	50
SLC3A1, SMPD1, HEXA, GBA	GO:0016798	Hydrolase activity, glycosyl bonds	0·003	4	193
SLC3A1, F11, BLM, CFTR, ASPA, DYT1, ABCC8, SMPD1, HEXA, GBA	GO:0016787	Hydrolase activity	0·009	10	2951
FANCC, BLM, BRCA2, BRCA1	GO:0006281	DNA repair	0·015	4	266
FANCC, BLM, BRCA2, BRCA1	GO:0006974	Response to DNA damage stimulus	0·025	4	303
SLC3A1, F11, BLM, IKBKAP, CFTR, ASPA, PFKM, BRCA1, ABCC8, DYT1, FANCC, SMPD1, CYP21A2, HEXA, GBA	GO:0003824	Catalytic activity	0·026	15	7623
FANCC, BLM, BRCA2, BRCA1	GO:0009719	Response to endogenous stimulus	0·032	4	321
DYT1, FANCC, BLM, MEFV, BRCA2, BRCA1	GO:0006950	Response to stress	0·032	6	995
APC, BRCA1	GO:0015631	Tubulin binding	0·035	2	29
SMPD1, HEXA, GBA	GO:0006643	Membrane lipid metabolism	0·040	3	131

The last two columns are the number out of 21 Ashkenazi genes in the cluster and the number out of 24,021 human genes in the cluster.

success and fitness in medieval times, so a broad spectrum of outcomes should be examined.

Our hypothesis is consistent with the neo-Darwinian synthesis, the historical record and the genetic and psychometric data. If it is confirmed, we believe that in

the future researchers will have to consider the role of selective change in the historical process. In addition, neuroscience may benefit from this natural experiment.

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