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PERSPECTIVE
Relevance of Connexin Deafness (DFNB1) to Human Evolution

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The connexins are the subunits of a family of proteins that form gap junctions, allowing ions and small molecules to move between adjacent cells. At least four connexins are expressed in the ear, and, although there are known mutations at >100 loci that can cause deafness, those involving DFNB1, in the interval 13q11–q12 containing the *GJB2* and *GJB6* genes coding for connexins 26 and 30, are the most frequent cause of recessive deafness in many populations. We have suggested that the combined effects of relaxed selection and linguistic homogamy can explain the high frequency of connexin deafness and may have doubled its incidence in this country during the past 200 years. In this report, we show by computer simulation that assortative mating, in fact, can accelerate dramatically the genetic response to relaxed selection. Along with the effects of gene drift and consanguinity, assortative mating also may have played a key role in the joint evolution and accelerated fixation of genes for speech after they first appeared in *Homo sapiens* 100,000–150,000 years ago.

Profound deafness has an incidence of ~0.8 per 1,000 births and is genetically determined in at least half of all cases (Morton 1991; Marazita et al. 1993). Most inherited forms of deafness are monogenic, although examples of digenic interactions involving specific loci are being identified with growing frequency (Morell et al. 1977; Balciuniene et al. 1998; del Castillo et al. 2002). There is extensive allelic and locus heterogeneity, and >100 genes for deafness have already been mapped or cloned (see Hereditary Hearing Loss Web site). Recessive transmission is the most common pattern of inheritance but, despite the high level of genetic heterogeneity, mutations involving a single gene complex, DFNB1, account for most genetic deafness in many, but not all, populations (Denoyelle et al. 1999; Pandya et al. 2003). DFNB1 maps to the 13q11–q12 region and contains the *GJB2* and *GJB6* genes, which code for connexin 26 (CX26 [*GJB2*; MIM 121011]) and connexin 30 (CX30 [*GJB6*; MIM 604418]), respectively. Both genes are expressed in the cochlea (Forge et al. 2003), and pairs of recessive mutations involving either or both loci can cause deafness (del Castillo et al. 2002). Although >50 *GJB2* mutations have been identified, three alleles—35delG, 167delT and 235delC—account for up to 70% of the pathologic alleles in whites, Ashkenazi Jews, and Asians, respectively (Pandya et al. 2003). In the United States, carrier frequencies as high as 3.5% have been reported in the hearing population, making it one of the most common recognized single-gene defects (Green et al. 1999). Despite the fact that the vast majority of connexin 26 mutations show recessive transmission, 11% of deaf probands in this country are apparent heterozygotes with a single pathologic connexin-26 allele. Of these, 7%–16% are now known to carry a 342-kb deletion involving the connexin-30 locus (del Castillo et al. 2003). The proteins coded by *GJB2* and *GJB6* are known to form heteromeric gap-junctions that allow the passage of ions and small molecules between cells, and they are thought to play a critical role in the recycling of potassium ions back into the cochlear endolymph (Souter and Forge 1998). Several possibilities have been considered to explain the maintenance of the connexin deafness polymorphism, but, apart from the documentation of linkage disequilibrium with respect to common mutations in several populations, there is little evidence to support the idea that heterosis, drift, or a mutation hot spot cause the high prevalence of the phenotype in so many large populations (Van Lear et al. 2001). We proposed an alternative hypothesis on the basis of an analysis of the proportion of noncomplementary marriages among the deaf during the nineteenth century, which suggests that the frequency of DFNB1 may have doubled in the United States during the past 200 years (Nance et al. 2000). These marriages between individuals with the same type of recessive deafness are inca-

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pable of producing hearing offspring, and the square root of their frequency among deaf marriages provides an upper limit for the prevalence of the most common form of recessive deafness at that time. To explain the increase, we suggested that the combination of intense assortative mating and relaxed selection increased both the gene and phenotype frequencies for DFNB1. Our proposed model assumes that in previous millennia the genetic fitness of individuals with profound congenital deafness was very low and that genes for deafness were then in a mutational equilibrium. The introduction of sign language in Europe 300–400 years ago (Bender 1970) was a key event that dramatically improved the social and economic circumstances of the deaf, along with their genetic fitness. In many countries, schools for the deaf were established, contributing to the onset of intense linguistic homogamy or mate selection based on the ability to communicate in sign language. We also speculated that the combination of relaxed selection and assortative mating should affect preferentially the most common form of recessive deafness in a population (Nance et al. 2000) and may also be relevant to the acceleration in human evolution that accompanied the acquisition of speech (Nance 2003). In their classic papers on assortative mating, Wright (1921) and Fisher (1918) showed that phenotypic assortative mating increases the genetic variance, thus enhancing the potential for evolutionary change in response to selection. Crow and Felsenstein (1982) showed that assortative mating, in the absence of selection, only changes the genotype frequencies and not the underlying gene frequencies. With respect to deafness, they concluded that if the phenotype resulted from genes of equal frequency at 35 loci (as was believed at that time), then even intense assortative mating, in the absence of selection, would result in only a 2%–3% increase in the incidence of deafness. However, experimental studies in *Drosophila* have shown that when assortative mating is combined with phenotypic selection, accelerated progress that can lead to the apparent fixation of major genes is observed (McBride and Robertson 1963). To our knowledge, however, this mechanism has not been proposed elsewhere as a natural cause for the recent acceleration in human evolution.

Several human populations are known in which specific forms of genetic deafness have reached remarkably high frequencies. DFNB3, a form of recessive deafness caused by a *MYO15* mutation, has a prevalence of 2% among the 2,385 inhabitants of the village of Benkala on the island of Bali (Friedman et al. 1995), with a carrier frequency of 17% in the hearing population. The incidence of DFNB3 in Benkala is >20 times that of all forms of genetic deafness combined in most regions of the world. Remarkably, the inhabitants of Benkala, generations ago, developed an indigenous sign language, which is now learned by all villagers. Because of their integration into the community, the fitness of the deaf is unimpaired. Deaf-by-deaf marriages are common, and virtually all of them are noncomplementary, as is expected because there is only one form of genetic deafness in the community. Although gene drift and endogamy undoubtedly played essential roles in the survival and initial phenotypic expression of the *MYO15* mutation, it is hard to escape the conclusion that relaxed selection and assortative mating must have also contributed to the subsequent increase in the frequency of both the gene and the phenotype, as well as the strong evidence for a founder effect. The Bedouins of North Africa and the Middle East are another population with a high frequency of deafness, in which an indigenous sign language has had an impact on the fitness of the deaf. Historically, the Bedouins have been a nomadic, tribal people, and, although they have begun to undergo gradual settlement at fixed localities in recent decades, they have retained a traditional mating structure that includes polygamy and rates of consanguinity as high as 30%–40%, with a preference for patrilateral parallel first-cousin marriages (Jaber and Halpern 2000; Kenan and Burck 2002). As might be expected, >35 recessive syndromes have been identified among the Bedouins in recent years, including at least four different forms of genetic deafness (OMIM). In some tribes, the incidence of deafness is as high as 2.6% (Scott et al. 1995), and though deaf-by-deaf marriages are avoided, the frequency of the deafness still has increased because of pseudodominant transmission resulting from the patrilateral pattern of cousin marriages preferred by the community. These examples illustrate the importance of stochastic effects and nonrandom mating on the initial survival and expression of new recessive mutations. Consanguinity leads to an increase in identity by decent for all loci, indiscriminately. In contrast, once recessive genes are expressed phenotypically, assortative mating creates "gametic phase disequilibrium" (Denniston 2000), or the nonrandom association and gametic transmission of potentially very rare alleles at unlinked loci (genocopies) that have similar effects on the phenotype. As a consequence, in human pedigrees involving several generations of marriages among the deaf, it is not uncommon to observe two or more distinct genetic forms of deafness in a single nuclear family, or to observe individuals who carry a single recessive connexin mutation and are deaf because of mutations at some other locus. In the presence of positive selection, rather than merely the relaxation of "purifying selection," the resulting cosegregation of rare non-allelic mutations with similar and potentially synergistic effects on the same phenotype would lead to their coordinate evolution and accelerated fixation.

We now have conducted computer simulation studies

showing that, in the case of deafness, linguistic homogamy can accelerate the genetic response to relaxed selection. We also showed that the effect is confined substantially to the most frequent form of recessive deafness.

Rather than attempting to simulate simultaneously the effects of relaxed selection and of assortative mating on the >100 known loci for deafness, we addressed a more tractable, but equally informative, question about the effects of these variables on one to three recessive loci. To simulate the period preceding the modern era, hearing individuals in the computer model mate at random with respect to hearing genes, but the deaf are assumed not to reproduce. So, the mutant alleles reach frequencies based on mutation-selection balance, and, if drift is ignored, differences in the initial phenotype frequencies would reflect differences in the underlying mutation rates, which remain constant during the 150 generations of simulation. The proportions of deaf individuals who reproduce, as well as their probability of choosing partners who are deaf, partners who are sibs or offspring of deaf people, or partners who are hearing individuals, can be varied over time to explore the effects of changing customs. Mating types are created by randomly sampling pairs of individuals, with replacement, until the constraints of assortative mating are met. Then, offspring are generated randomly according to the parental genotypes and, depending on the phenotypic fitness of the mother, retained in the succeeding generation. The population size, fitness, and degree of assortative mating can be specified, and the effects of these variables on forms of deafness with different frequencies can be observed. A plausible value of the total initial phenotypic frequency of all forms of deafness is assumed, along with the mutation rates required to maintain the desired frequencies of the genotypes being simulated. All other deaf individuals are assumed to arise each generation from nontransmitted environmental causes that do not interact with the simulated deafness genes. The program also assumes nonoverlapping generations.

The results of the simulation studies are given in figure 1. Figure 1*a* shows the change in the frequency of deafness, following the onset of relaxed selection, with and without assortative mating. The initial fitness is assumed to be zero, rising to 1.0 in five generations, while assortative mating increased from 0% to 90% during the same period. The increase in the phenotype frequency is greatly accelerated in the presence of assortative mating, and could account readily for a doubling of the prevalence of DFNB1 in 200 years. As shown in figure 1*b*, where three loci are considered simultaneously, the effects of assortative mating are virtually confined to the form of recessive deafness that was most frequent at the onset.

This is because all of the offspring of noncomplementary marriages between individuals with the same form of recessive deafness are deaf and make a disproportionate contribution to the pool of deaf individuals in the next generation, who benefit from the relaxed selection. Since these marriages are proportional to the fourth power of the gene frequency, the most common form of recessive deafness in a population is affected preferentially. An important feature of these results is that the proposed mechanism for accelerating the response to selection is not locus specific. The frequency of mutations for deafness at any locus could be increased preferentially, if those mutations determine the most common form of recessive deafness in the specified population.

The effect of assortative mating and relaxed selection in our simulation studies support the idea that this mechanism has contributed to the high frequency of DFNB1 in many developed countries. In other large populations, connexin-26 deafness has been observed, but at a much lower frequency. In Mongolia, for example, where there is only one residential school for the deaf, sign language was not introduced until 1995. Moreover, the fitness of the deaf is still much lower than that of their hearing siblings, assortative mating is much less frequent than in the United States, and connexin mutations account for only 1.3% of all deafness (Pandya et al. 2001). To explain why connexin deafness has been amplified in so many large populations, we must assume it was the most frequent form in those populations at the time that relaxed selection and assortative mating began, possibly because of a somewhat higher intrinsic mutation rate. In small populations, such as the village of Benkala and the Bedouin community, gene drift and consanguinity led to the initial expression of other recessive genes for deafness, whose frequencies were then increased by the combined effects of relaxed selection and the nonrandom characteristics of the mating structure of the two populations. In regions where national or statewide schools for the deaf have been established and marriages among the students have occurred, the effects of endogamy have been reduced, leading to amplification of the most common form of recessive deafness in the overall population.

Since this genetic mechanism is not locus specific, other implications of this hypothesis have not escaped our notice, such as its potential involvement in the evolution of speech. Many evolutionary biologists believe the development of complex syntactic language, beginning with the acquisition of speech, is the trait that most clearly distinguished early *Homo sapiens* from other possible ancestors of modern man (Lewin 1993). Bipedal hominids are known to have inhabited areas of Africa $\geqslant$6–7 million years ago (Brunet et al. 2002) and were present in regions of Europe and Asia 1–2 million years ago. They almost certainly developed some primitive forms of communication during their long period of evo-

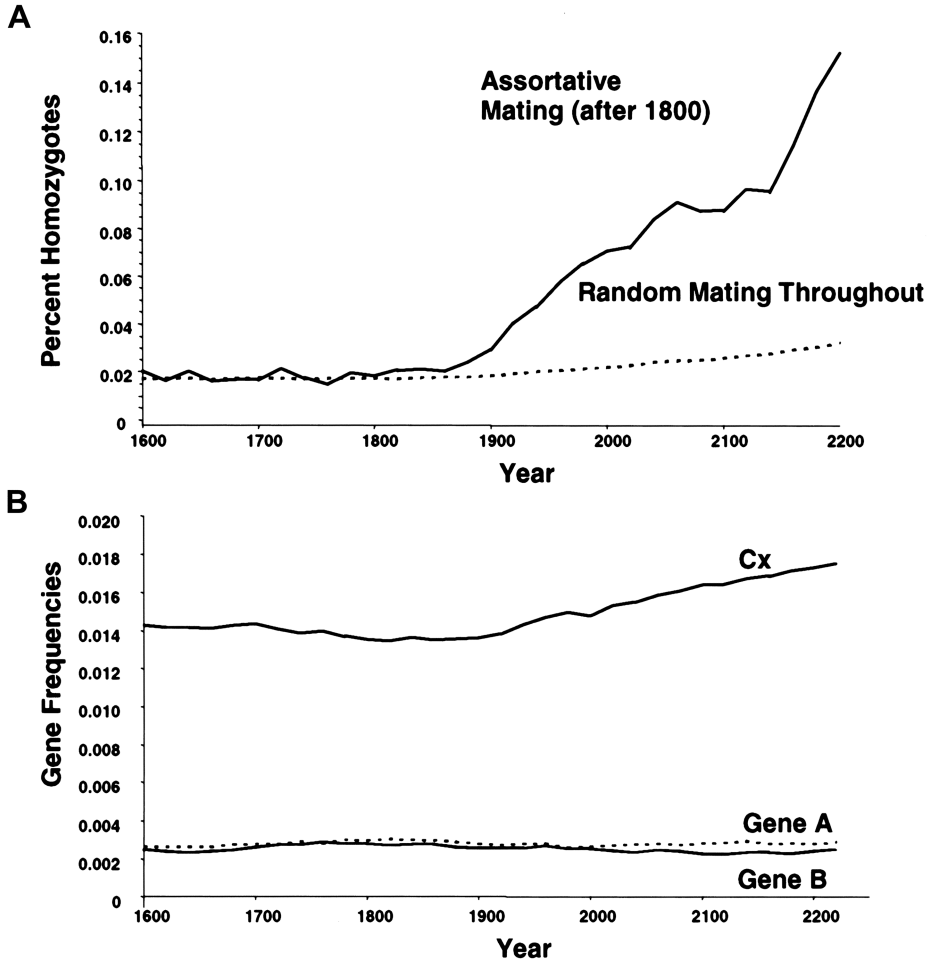

Figure 1 Computer simulation showing the effects of relaxed selection and assortative mating on the Cx gene, beginning in 1800 with a generation time of 20 years. *A*, Frequency of Cx homozygotes in the presence (*solid line*) and absence (*dotted line*) of assortative mating; *B*, Frequency of a common recessive deafness gene (Cx) and two rare genes, either linked at 1 cM (Gene A) or unlinked (Gene B) to the Cx locus. A fixed population size of 200,000 and an equal sex ratio were assumed. In *B*, a mutation-selection balance initially was assumed with frequencies for Cx, A, and B of .01304, .002881, and .002881, respectively. In *A* and *B*, the reproductive fitness of the deaf rose from 0 to 1.0 in five generations, whereas assortative mating rose from 0 (random mating) to .9 and remained constant thereafter. To incorporate linguistic homogamy, deaf subjects choosing hearing partners were assumed to select "native signers" who were the offspring of deaf parents, with a probability of .3 by the fifth generation. Such spouses frequently carry multiple nonallelic recessive genes for deafness.

lutionary ascendancy, but it was not until 154,000–160,000 years ago that the *H. sapiens* with features resembling those of modern humans first appeared (White et al. 2003) and rapidly spread out of Africa to displace all other hominids. Although *H. neanderthalensis* dates back ⩾400,000 years, they are not thought to have been the progenitors of modern man (Cavalli-Sforza 1998), and it is interesting to conjecture that they may have lacked the facility with language that *H. sapiens* developed. Two schools of thought exist as to the process by which language evolved. Some scholars point to the gradual increase in the size of the primate brain and view human evolution as merely an extension of this slow process (Halloway 1983). Others believe that the acquisition of language triggered an explosive acceleration in the evolution of the human brain (Klein 1992). This view is supported by fossil records, which show that several potential ancestors of modern man were displaced by the advent and rapid radiation of *H. sapiens*. Cultural artifacts, such as much more sophisticated weapons, tools, ornaments, artistic creations, and ritualistic burial sites, soon accompanied the first indications of a distinct human species. These relics adumbrate a level of cultural complexity that is hard to imagine as being without some form of language. The American paleoanthropologist Stephen Gould popularized the concept of "punctuated equilibrium," the idea that the pace of evolutionary change in an organism can sud-

denly accelerate during specific periods (Gould and Eldridge 1993). Gould's proposals remained controversial because they were largely descriptive and provided no specific mechanism, apart from selection, by which the fixation of a favorable mutation could be accelerated. However, it seems plausible to assume that once the first mutations for improved oral-communication arose and survived to be expressed phenotypically, intense linguistic homogamy would have ensued, just as it did after the introduction of sign language among the deaf. Viewed in this light, the subsequent acceleration of human evolution had both a genetic basis and an essential cultural component that profoundly altered the mating structure of the population. There are important ways in which the relaxation of "purifying" selection against a genetic lethal clearly differs from positive selection for a favorable new mutation. Although assortative mating accelerates both forms of selection, only the later is likely to progress to gene fixation. As noted elsewhere, a unique feature of assortative mating is its potential for creating gametic phase disequilibrium by bringing together rare combinations of genes with similar and potentially synergistic effects on the phenotype (Crow and Kimura 1970). Once the first mutation(s) for speech began to approach fixation, they would have provided the altered genetic background required to promote the selection and potential fixation of additional genes influencing a wide range of other traits that depend on speech or on changes in lifestyle that resulted from the acquisition of language. In this way, linguistic homogamy may have led to an accelerated fixation of many of the mutations and traits that distinguish humans from other primates.

The recent identification of dominant mutations in genes that impair speech, including mutations at FOXP2, a winged-helix/forkhead-class transcription factor, suggests that the mutation and subsequent fixation of a relatively small number of their recessive allelomorphs may have been sufficient to initiate this process (Lai et al. 2001). Bioinformatic studies have shown that, since the divergence between man and the chimpanzee, the *FOXP2* gene has evolved more rapidly than any other comparable gene whose sequence in the chimpanzee is currently known (Enard et al. 2002; Zhang et al. 2002). Although its amino-acid sequence is generally well conserved across species, the human FOXP2 protein differed from all other species, and differed from seven primate species by two amino-acid substitutions in exon 7. The substitution rate for this gene in the human lineage increased by a factor of 60 after the divergence between *H. sapiens* and the chimpanzee, and it also was associated with a high proportion of nonsynonymous substitutions but a lower than expected frequency of neutral base-pair substitutions in the adjacent introns, suggesting that the observed evolutionary acceleration reflected strong positive selection within the past 100,000 years (Zhang et al. 2002). More recently, gene sequence comparisons have suggested that as many as 1,547 human genes show evidence for positive selection, with representatives from a wide range of biological and functional groups, including 21 genes known to be involved in hearing (Clark et al. 2003). The authors speculate that fine-tuning of the human cochlea may have been required for the discrimination of spoken language. No one who is familiar with how digital hearing aids can transform muffled sounds into intelligible speech will have difficulty believing that mutational changes in genes expressed in the cochlea could have similar effects. Since the analysis was done on DNA from a single chimpanzee, however, it is not clear how many of the reported differences reflect complete substitutions between the two species. However, the large number of genes that appear to be involved in each functional group suggests the action of an evolutionary mechanism that can lead to the aggregation and joint selection of rare, nonallelic mutations that exert synergistic effects on the same phenotype. Many evolutionary hypotheses are difficult to prove, other than by strong inference. With respect to the evolution of speech, completion of the chimpanzee genome sequence should confirm the number and identity of mutations, in addition to FOXP2, that have become fixed in the human species. The use of transgenic technology could lead ultimately to the identification of those genes that have been of greatest importance in the acquisition of the language, whereas bioinformatics studies conceivably could provide insight as to the order in which the relevant genes were fixed. Although the question of whether it is technically feasible to amplify nuclear DNA from skeletal remains of recent Neanderthal specimens remains controversial, studies of more recent specimens of early *H. sapiens* could shed light on the sequence and timing of the two FOXP2 substitutions, as well as mutations at other loci. Whether the acquisition of syntactic language turns out to have resulted from the effects of a small or a large number of genes, the combination of improved fitness and assortative mating is a plausible mechanism by which the accelerated fixation of the mutations that distinguish humans from other primates may have occurred.

Conclusions

Assortative mating can accelerate the genetic response to relaxed selection and may have doubled the frequency of connexin deafness in this country during the past two centuries. In combination with positive selection, linguistic homogamy may also have accounted for the rapid fixation of the mutations required for the acquisition of speech when they first arose in *H. sapiens* 100,000–150,000 years ago.

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Hereditary Hearing Loss, http://www.uia.ac.be/dnalab/hhh/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM=Limits

References

Balciuniene J, Dahl N, Borg E, Samuelsson E, Koisti MJ, Pettersson U, Jazin EE (1998) Evidence for digenic inheritance of nonsyndromic hereditary hearing loss in a Swedish family. Am J Hum Genet 63:786–793

Bender RF (1970) The conquest of deafness. Case Western Reserve, Cleveland, pp 1–243

Brunet M, Guy F, Pilbeam D, Mackaye HT, Likius A, Ahounta D, Beauvilain A, et al (2002) A new homonid from the Upper Miocene of Chad, Central Africa. Nature 418:145–151

Cavalli-Sforza, LL (1998) The DNA revolution in population genetics. Trends Genet 14:60–65

Clark AG, Glanowski S, Neilsen R, Thomas PD, Kejarwal A, Todd MA, Tannenbaum DM, Civello D, Lu F, Murphy B, Ferriera S, Wang G, Zheng X, White TJ, Sninsky JJ, Adams MD, Cargill M (2003) Inferring nonneutral evolution from human-chimp-mouse orthologous gene trios. Science 302: 1960–1963

Crow JF, Felsenstein F (1982) The effect of assortative mating on the composition of a population. Soc Biol 29:22–35

Crow JF, Kimura M (1970) An introduction to population genetics theory. Harper & Row, New York

del Castillo I, Moreno-Pelayo MA, del Castillo FJ, Brownstein Z, Marlin S, Adina Q, Cockburn DJ, et al (2003) Prevalence and evolutionary origins of the del (GJB6D13S1830) mutation in DFNB1 locus in hearing-impaired subjects: a multicenter study. Am J Hum Genet 73:1452–1458

del Castillo I, Villamar M, Moreno-Pelayo MA, del Castillo FJ, Alvarez A, Telleria D, Menendez I, Moreno F (2002) A deletion involving the connexin 30 gene in nonsyndromic hearing impairment. N Engl J Med 346:243–249

Denniston C (2000) Equivalence by descent: pedigree analysis with inbreeding and gametic phase disequilibrium. Ann Hum Genet 64:61–82

Denoyelle F, Marlin S, Weil D, Moatti L, Chauvin P, Garabedian EN, Petit C (1999) Clinical features of the prevalent form of childhood deafness, DFNB1, due to a connexin-26 gene defect: implications for genetic counseling. Lancet 353: 1298–1303

Enard W, Przeworski M, Fisher SE, Lai CS, Wiebe V, Kitano, T, Monaco AP, Paabo S (2002) Molecular evolution of FOXP2, a gene involved in speech and language. Nature 418:869–872

Fisher RA (1918) The correlation between relatives on the supposition of Mendelian inheritance. Trans Roy Soc Edinb 52:399–433

Forge A, Becker D, Casalotti S, Edwards J, Marziano N, Nevill G (2003) Gap junctions in the inner ear: comparison of distribution patterns in different vertebrates and assessment of connexin composition in mammals. J Comp Neurol 467: 207–231

Friedman TB, Liang Y, Weber, JL, Hinnant JT, Barber TD, Winata S, Arhya IN, Asher JH (1995) A gene for congenital, recessive deafness DFNB3 maps to the pericentromeric region of chromosome 17. Nat Genet 9:86–91

Gould SJ, Eldredge N (1993) Punctuated equilibrium comes of age. Nature 366:223–227

Green GE, Scott DA, McDonald JM, Woodworth GG, Sheffield VC, Smith RJ (1999) Carrier rates in the Midwestern United States for GJB2 mutations causing inherited deafness. JAMA 281:2211–2216

Halloway RL (1983) Human brain evolution. Can J Anthropol 3:215–230

Jaber L, Halpern GJ (2000) Trends in the frequencies of consanguineous marriages in the Israeli Arab community. Clin Genet 58:106–110

Kenan G, Burck L (2002) Trends in patrilineal parallel first cousin marriages among Israeli Arabs: 1949–1995. Ann Hum Biol 29:398–413

Klein R (1992) The archeology of modern humans. Evol Anthropol 1:5–14

Lai CS, Fisher SE, Hurst JA, Vargha-Khadem F, Monaco AP (2001) A forkhead-domain gene is mutated in a severe speech and language disorder. Nature 413:519–523

Lewin R (1993) The origins of modern man. W.H. Freeman, New York, pp 1–204

Marazita ML, Ploughman LM, Rawlings B, Remingto E, Arnos KS, Nance WE (1993) Genetic and epidemiological studies of early onset deafness in a school-age population. Am J Med Genet 46:486–491

McBride G, Robertson A (1963) Selection using assortative mating in Drosophila melanogaster. Genet Res 4:356–369

Morell R, Spritz R, Ho L, Pierpont J, Guo W, Friedman, TB, Asher JH Jr (1977) Apparent digenic inheritance of Waardenburg syndrome type 2 (WS2) and autosomal recessive ocular albinism (AROA). Hum Mol Genet 6:659–664

Morton NE (1991) Genetic epidemiology of hearing impairment. Ann NY Acad Sci 630:16–31

Nance WE, Liu XZ, Pandya A (2000) Relation between choice of partner and high frequency of connexin 26 deafness. Lancet 356:500–501

Nance WE (2003) The genetics of deafness. Ment Retard Dev Disabil Res Rev 9:109–19

Pandya A, Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB, Sanchez GG, Liu XZ, Morell R, Nance WE (2003) Frequency and distribution of GJB2 (connexin 26) and GJB6 (connexin 30) mutations in a large North American repository of deaf probands. Genet Med 5:295–303

Pandya A, Xia XJ, Erdenetungalag R, Tekin M, White TW, Radnaabazar J, Dangaasuren B, Nance WE (2001) Low fre-

quency and unique spectrum of connexin 26 (Cx26) mutations in Mongolia: role of relaxed selection and assortative mating. Am J Hum Genet Suppl 69:590

Scott DA, Carmi R, Elbedour K, Duyk GM, Stone EM, Sheffield VC (1995) Nonsyndromic autosomal recessive deafness is linked to the DFNB1 locus in a large inbred Bedouin family from Israel. Am J Hum Genet 57:965–968

Souter M, Forge A (1998) Intercellular junctional maturation in the stria vascularis: possible onset and rise of endocochlear potential. Hear Res 119:81–95

Van Lear L, Couke P, Mueller RF, Caethoven G, Flothman K, Prasad SD, Chamberlin, GP, Houseman M, Taylor GR, Van de Heyning CM, Fransen E, Rowland J, Cucci RA, Smith RJ, Van Camp G (2001) A common founder for the 36delG GJB2 gene mutation in connexin 26 hearing impairment. J Med Genet 38:515–518

White TD, Asfaw B, DeGusta D, Gilbert H, Richards GD, Suwa, G, Howell FC (2003) Pleistocene Homo sapien from Middle Awash Ethiopia. Nature 423:742–747

Wright S (1921) Systems of mating. III. Assortative mating based on somatic resemblance. Genetics 6:144–161

Zhang J, Webb DM, Podlaha O (2002) Accelerated protein evolution and origins of human-specific features: Foxp2 as an example. Genetics 162:1825–1835