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The Genetic Clock and the Age of the Founder Effect in Growing Populations: A Lesson from French Canadians and Ashkenazim

To the Editor:

Use of the genetic clock with molecular data allows analysis of the occurrence of genetic events in the context of population histories. These analyses suggest that the majority of disease mutations present at variable frequencies among human populations have been spread by neutral mechanisms related to migration and demographic expansion. In human genetics, "founder effect" refers to the presence of genetic disorders that are either endemic to an isolated population or very rare elsewhere (Diamond and Rotter 1987); it is observed in small human isolates such as Tristan da Cunha (Roberts 1968) and in populations as large as that of Europe (Kerem et al. 1989). New reports rekindle interest in the origin of founder effects: Do they involve neutral mechanisms (migration and drift)? Are they due to a selection in response to the environmental challenge or to other causes? Molecular approaches provide new insights into the underlying mechanisms. Here we discuss the use of linkage-disequilibrium data to estimate the age of founder effects in Ashkenazi Jews from eastern Europe (Motulsky 1995) and in French Canadians from the Charlevoix-Saguenay region (De Braekeleer 1991), populations in which a number of rare genetic disorders are found at particularly elevated frequencies. When their time of appearance is known, founder effects can be better understood in the context of the social and demographic history of the populations (Roberts 1968; Motulsky 1995; Risch et al. 1995*a*, 1995*b*; Zoosman-Diskin 1995; Labuda et al. 1996).

A founder chromosome carrying a new disease allele is introduced into a population by migration or by a de novo mutation. The mutation is then in extreme linkage disequilibrium with the adjacent polymorphisms. A set of alleles at these polymorphic sites represents the founder haplotype, a "genetic signature" of the founder chromosome. Because of recombinations, a fraction of the carrier chromosomes with the founder haplotype decrease over the time (Jennings 1917; Robbins 1917). If polymorphic loci in the haplotype recombine at a rate of θ/generation, then a proportion $(1 - \theta)$ will cosegregate; after g generations the expected proportion of the nonrecombined carrier chromosomes is $P = (1 - \theta)^g$. At a small θ, $(1 - \theta)^g \approx e^{-\theta g}$, and

$$\ln P = -\theta g . \quad (1)$$

In this equation, relating time, recombination rate, and the divergence ($\ln P$) of haplotypes, we recognize the *genetic clock*, by analogy to the molecular clock (Zuckerkandl and Pauling 1965) that relates time, mutation rate, and the divergence of genes.

In a recent study of idiopathic torsion dystonia (ITD), an autosomal dominant disease, equation (1) was applied to estimate the age of the founder effect in Ashkenazi Jews from eastern Europe (Risch et al. 1995*b*). Strong linkage disequilibrium over a considerable genetic distance around the ITD locus indicated a founder effect whose origin was estimated by the authors as being at the middle of the 17th century (time range 1400–1750). At that time however, the Jewish population of eastern Europe was already reaching hundreds of thousands, and numbered $\geq$10,000 individuals in 1400 (Barnavi 1992; Beinart 1992; Motulsky 1995; Risch et al. 1995*a*, 1995*b*; Zoosman-Diskin 1995). This would put the initial ITD mutation frequency at 10^{-4}–10^{-5}, too low to explain, on the ground of demographic growth alone, its current frequency of $2–6 \times 10^{-3}$. To resolve the discrepancy between the demographic and the genetic data in the case of ITD, social selection was proposed, whereby the present-day Ashkenazim descended from a smaller, wealthier fraction of the original population, a fraction with the higher survival rate (Motulsky 1995; Risch et al. 1995*b*).

Social selection could have influenced the genetic profile of the present-day Ashkenazi population and seems to provide a good collective explanation for an elevated frequency of a number of unrelated recessive disorders

(Motulsky 1995). However, it is difficult to imagine that the impact of social selection was sufficiently dramatic to account for a 1,000-fold frequency increase (i.e., from 10^{-5}–10^{-4} to 10^{-2}–10^{-1}) of a mutated allele at a dozen or so disease loci scattered all over the genome. At least nine autosomal recessive diseases with carrier frequencies as high as 1/100–1/20 are known among Askenazim (Motulsky 1995). Recently described mutations in the breast cancer–susceptibility genes (BRCA) have to be included in these considerations as well (e.g., 6174delT in BRCA2 and 185delAG in BRCA1, present in this population at the 1.4% and 1% level, respectively [reviewed in Tonin et al. 1996]). Given these frequencies, the founder effect would be more plausible if it had started earlier, in the period when the Jewish population of central and eastern Europe was much less numerous (Barnavi 1992; Beinart 1992). Indeed, it is possible that the age estimated from equation (1) is an underestimate: attention has been drawn to the fact that, when applied to growing populations, the genetic clock ticks more slowly than expected (Luria and Delbrück 1943; Hästbacka et al. 1992; Kaplan et al. 1995; Labuda et al. 1996); in other words, equation (1) is likely to lead to an underestimation of either θ or g, from P. This effect has been originally described for mutations in growing bacterial cultures and can be corrected for as proposed in the original study by Luria and Delbrück (1943). In the context of human genetics, this correction was first applied to estimates of the distances θ in the linkage-disequilibrium mapping study of diastrophic dysplasia in Finland (Hästbacka et al. 1992). In turn, when genetic distances are known and we ask about the age of the founder effect, its likely value corresponds to $g + g_0$, where g is the number of generations estimated from equation (1), and the correction

$$g_0 = -1/d \ln(\theta f_d) , \qquad (2)$$

where $f_d = e^d/(e^d - 1)$ in a population growing at a rate d (note that, for small d values, $f_d \approx 1/d$) (for details, see Labuda et al. 1996). This approach was used in a linkage-disequilibrium study of pseudo–vitamin D–deficiency rickets (PDDR), to estimate the age of the founder effect in French Canadians from Charlevoix-Saguenay in northeastern Québec (Labuda et al. 1996). Approximately a dozen rare genetic conditions with carrier rates $\leq 1/21$ are common in this population, resembling the pattern seen in Ashkenazim (De Braekeleer 1991; Motulsky 1995; Labuda et al. 1996). The analysis of PDDR haplotypes by use of equation (1) indicates a founder effect starting around 1800, when the population of Charlevoix already numbered a few thousand (Bouchard and De Braekeleer 1991; Labuda et al. 1996). The discrepancy disappears, however, when the corrected $g + g_0$ age is used: the genetic clock with the correction is congruent with demographic data pointing to the origin of the founder effect at the beginning of the Charlevoix colonization.

Use of the Luria-Delbrück correction in the case of ITD shifts the dating of the underlying founder event back by almost 2 centuries ($g_0 = 7$ for $\theta = .023$ or .018 of the haplotypes considered, under the assumption that $d = .4$ [Risch et al. 1995*a*] and that there are 25 years/generation). Thus, contrary to the original estimation, the founder effect could have started as early as 1200. Taking the reported values in a study of familial dysautonomia in Ashkenazim (Blumenfeld et al. 1993) ($P = .54$, $\theta = .03$), we estimated the corrected age at 27 generations ($g_0 = 6$, under the assumption that $d = .4$). This suggests that the origin of the founder effect occurred in the midst of the 13th century, consistent with the corrected ITD data above. Such dating coincides with the time of early migrations of Jews from Ashkenaz (medieval Germany) to central Europe. The work of Neuhausen et al. (1996), on BRCA1 mutations, corroborates well with these conclusions: these authors estimate that "the most likely date for the origin of the 185 del AG mutation found in the Ashkenazi Jewish population is ~1235 a.d." (Neuhausen et al. 1996, p. 275); however, they admit that their result depends on a number of assumptions, such as a uniform relationship between recombination rate and physical distance or equal mutation rates among microsatellite markers of the same class. Therefore, we can neither consider it as a strong support for our findings nor critically compare both approaches.

The lesson from the analysis of the colonization of Charlevoix (Labuda et al. 1996) shows that, although the early migrations provide opportunities for sampling of rare mutations, it is the demographic expansion that follows which establishes the founder effect. Within a few generations the contribution of the first migrants to the genetic pool becomes sufficiently large to withstand influx of later migrations and to allow some of the initially sampled rare alleles to be maintained at high frequencies. Such a demographic outcome is illustrated in figure 1. The model uses the simple assumption that migrants arriving at different time periods have the same probability to reproduce. In this example, new settlers arrive in three migration waves of 100 individuals each every 50 years (i.e., at $g = 0$, 2, and 4). The population is growing at the rate $d = .6$ (note that $d = .4$ was used above [Risch et al. 1995*a*], whereas $d = .8$ was characteristic of the early population of Charlevoix [Labuda et al. 1996]). The third wave of settlers contributes only 6.5% to the population, which, on its arrival, numbers 1,544 individuals; its genetic composition is dominated by descendants of the first and second waves of settlers, at the level of 71.8% and 21.6%, respectively. Thus, if unique copies of rare disease mutations were present among the first group of settlers, their initial population frequency of 1% would only go down to 0.7%. With

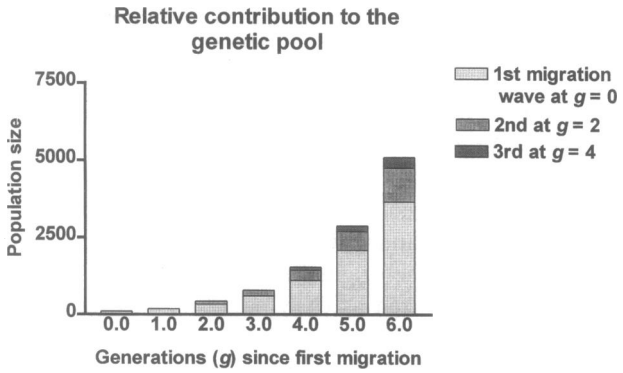

Figure 1 Relative contribution of subsequent waves of migrations to the genetic pool of an expanding population ($d = .6$).

further growth of the population (fig. 1), any new immigration would have to be extremely massive to radically change its genetic content. Therefore, the rare variants sampled among first settlers are expected to last and to be maintained at levels close to the starting frequencies. A simplifying assumption above—that everybody has the same reproductive chances—is conservative. In reality, the smaller the number of first settlers, the more likely it is that only a fraction of their genetic pool will be represented in future generations. In other words, because of genetic drift the initial frequency of sampled rare variants is expected to be higher than what the model in figure 1 suggests; some of the rare disease alleles are also lost in the process. This reinforces the effect of migration and subsequent demographic expansion illustrated in figure 1. The impact of genetic drift is reduced with the rising number of rare variant copies; the population growth stabilizes the founder effect.

A material illustration of the model presented in figure 1 is provided by demographic events from the well-documented history of Charlevoix (Gauvreau et al 1991). Between 1675 and 1850 this region was colonized by 599 settlers, 15 of which arrived before the turn of the 17th century. By the middle of the 19th century the population grew to 18,000 and started to expand toward the shores of the Saguenay River. At that time, the contribution of the first 15 settlers to the genetic pool, estimated by application of the same rules as are used in figure 1, was 22.5% (the contribution of the first 67 settlers was 58%). The opportunity for sampling rare mutations is evident: the initial carrier rate of 1/15 (6.7%) becomes 1.5% in 1850.

Our dating points to the origin of the founder effect in Ashkenazim at the time of their early migrations from western Europe eastward. Taken with caution, the familial dysautonomia data indicate a time period between the 11th and 15th century; ITD, between the 13th and 16th century. The difference may be fortuitous, but we actually expect ITD, which is less frequent, to be introduced later than diseases with carrier frequency $\geq 1\%$. Furthermore, as suggested by likelihood studies (Kaplan et al. 1995), the Luria-Delbrück correction may be conservative (i.e., $g + g_0$ is an underestimate); the founder effect thus would be older rather than younger. In any case, the genetic data are consistent with the historically plausible scenario in which a founder effect originates in a small group of successful migrants. The presence of Jews in medieval Poland at the end of 12th century is documented by coins with Hebrew inscriptions minted under the reign of Mieszko III the Old. These early migrations could have been encouraged by new opportunities in central and eastern Europe, related to the rise of towns in the developing new states (Davies 1984). In contrast, in the West the conditions were not conducive: persecutions of Jews increased at the time of the Crusades and intensified during the outburst of bubonic plague during the middle of the 14th century, resulting in the decimation of Jewish communities. On Polish soil, privileges granted in 1264 (Kalisz) and 1334 (Cracow) indicate the growing importance of Jews; their expansion eastward is marked by privileges obtained in 1364 (Lesser Poland and Red Russia) and 1388 (Lithuania). The favorable circumstances continued in the Jagiellonian commonwealth, uniting the Polish Crown, Lithuania, and Ukraine, leading to the great demographic expansion of the Ashkenazim in this part of Europe (Davies 1984; Barnavi 1992; Beinart 1992). They largely outnumbered their fellows in the West, eventually reaching several millions in the early 20th century. Thus, although other factors, such as social or other forms of selection, could have played a role there, the migration and demographic expansion requires no other assumptions to explain the founder effect in Ashkenazim.

Implementing the Luria-Delbrück correction in the application of the genetic clock appears to provide more realistic estimates of the age of founder effects, making these genetic events more understandable in the context of population histories. This is an easy, pocket-calculator approach to correct the genetic clock for the effect of a growing population, which is consistent with coalescence (Thompson and Neel 1997) and likelihood (Kaplan et al. 1995) data. Most present-day human populations underwent demographic expansion since the Neolithic; recurrent migrations provided opportunities for sampling of rare disease mutations and their frequency increase (Diamond and Rotter 1987). Analysis and understanding of the mechanisms underlying founder effects is an important aspect of genetic epidemiology dealing with the growing number of known mutations responsible for simple and complex traits and diseases.

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Approximate Variance of the Standardized Measure of Gametic Disequilibrium *D'*

To the Editor:

The detection of nonrandom association of alleles at different loci (i.e., gametic disequilibrium) is one of the first steps in the study of the multilocus systems, as well as a powerful tool for analysis of marker order and location of human disease genes. The magnitude of gametic disequilibrium can be estimated from a sample of haplotypes from the population, by means of a variety of disequilibrium coefficients (Hedrick et al. 1978; Hedrick 1987). Although no measure of disequilibrium is completely independent of allele frequency (Lewontin 1988), the standardized disequilibrium coefficient D', proposed by Lewontin (1964), is very useful for comparison of disequilibrium between loci with different allelic frequencies, because its range is frequency independent (Hedrick 1987, 1988; Lewontin 1988; Zapata and Alvarez 1992, 1993, 1997*a;* Zapata and Visedo 1995). It is surprising that, despite the extensive usage of D' since 1964, its variance has not been investigated, although Hedrick and Thomson (1986) and Hedrick (1987) examined the distribution of D', for sam-