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Genetics and epidemiology of adult-type hypolactasia with emphasis on the situation in Europe

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ABSTRACT

The decline in gastrointestinal lactase activity, adult-type hypolactasia, is genetically determined by a recessive single gene. A genetic selection associated with the consumption of milk or milk products for hundreds or thousands of years explains the differences in the prevalence of hypolactasia seen nowadays. The lowest European prevalence has been reported in Denmark (4%) and the highest prevalence in the Mari population in Russia (81%).

Key words: Hypolactasia, lactase, lactose intolerance

Genetics of adult-type hypolactsia

It is well known that the prevalence of adult-type hypolactasia varies from less than 5% to almost 100% between different races and populations (1,2). The main reason for the wide range of variation lies in the fact that the decline in the production of the lactase enzyme is genetically determined.

In 1973, Sahi et al. (3) and, in 1974, Sahi (4) published the results of a major Finnish family study with probands and 327 family members (all study subjects were over 20 years of age) and showed that the segregation of adult-type hypolactasia fitted very well to the inheritance of an autosomal, recessive single gene. Later the results of other studies (5,6) have supported these findings.

In addition to formal family studies and pedigree analysis, other studies gave strong support to the assumption of monogenic determination of adult lactase activity. In Hungary, Metneki et al. (7) studied 102 adult twin pairs. There was complete concordance in 52 pairs of monozygous twins as regards lactase phenotype, which was determined on the basis of breath hydrogen or ethanol lactose tolerance test. In dizygous pairs, the phenotype distribution was in accordance with the hypolactasia prevalence in the whole Hungarian population.

In some population studies small-intestinal biopsies were taken and disaccharidase activities determined. Ho and his coworkers (8) reported in their autopsy study a trimodal distribution in the sucrase/lactase ratio, and the proportions of the three groups were compatible with the Hardy-Weinberg equilibrium calculated using the prevalence of hypolactasia in the respective population.

All together, the evidence from formal family studies, a twin study, and the distributions in disaccharidase activity ratios give strong support to the theory of dimorphism in adult lactase activity and the recessive inheritance of adult-type hypolactasia.

So far, no studies have revealed any DNA-variations which would correlate with lactase persistence/non-persistence, but that trait/hypolactasia is likely to be controlled by *cis*-acting elements residing adjacent to the lactase gene (9). It has been suggested that both transcriptional and posttranscriptional control of the expression of the lactase gene may be involved in the ætiology of adult-type hypolactasia (10). Research is being actively pursued by many research groups.

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Hypotheses to explain the differences in the prevalence of hypolactasia

Since the decline in lactase activity is genetically determined, and since the prevalence of hypolactasia varies very widely, there must have been strong factors which have led to these differences over perhaps thousands of years. The factors must have been correlated with the consumption of milk or milk products (1,2). The culture-historical hypothesis, originally presented by Simoons (11), is based on genetic selection in people who have consumed milk for hundreds or even thousands of years: People in whom lactase activity persisted through their life were better able to use all the nutrients of milk without diarrhoea and therefore more likely to survive. Possibly they had more children than subjects with hypolactasia and so the proportion of people with lactase persistence increased in a population.

Flatz and Rotthauwe (12) presented another hypothesis to explain the low prevalence of hypolactasia in Northern Europe. They thought that pelvic deformity, rickets and osteomalacia were common in Northern Europe because of low solar irradiation. Nutritional supply of vitamin D was also low. Because subjects with lactase persistence absorbed calcium better than people with hypolactasia, they had also less rickets and pelvic deformity and more children. The result was genetic selection in favour of the lactase persistence gene.

Prevalence of adult-type hypolactasia in Europe

In Europe, the lowest reliable prevalence has been reported in Denmark, (4%) (13). In all, the lowest prevalence, with some rare exceptions, occurs in north-western Europe around the North Sea and around the south-western parts of the Baltic Sea (2). This matches well with the original core area of the Germanic populations where the prevalence of hypolactasia was low possibly rather early, perhaps in the 4th century. The highest European prevalence has been found in southern Europe and in eastern parts of Russia (2), Figure 1.

A question has been raised whether the selective advantage of lactase persistence has been so significant that it can explain the differences in the prevalence of hypolactasia that are seen now. The answer is yes. Flatz (1) estimated that the selection power of 3-5% would be able to explain the present low prevalence of hypolactasia in Northern Europe. A smaller selection power would be sufficient to explain the prevalence in other parts of Europe.

The average prevalence of hypolactasia in Italy is now about 50%. Assuming that dairy farming started there 6000–7000 years (250 generations) ago, it can be estimated that the selective advantage of lactase persistence has been about 1% per generation (1). In southern Scandinavia, however, the selective advant-

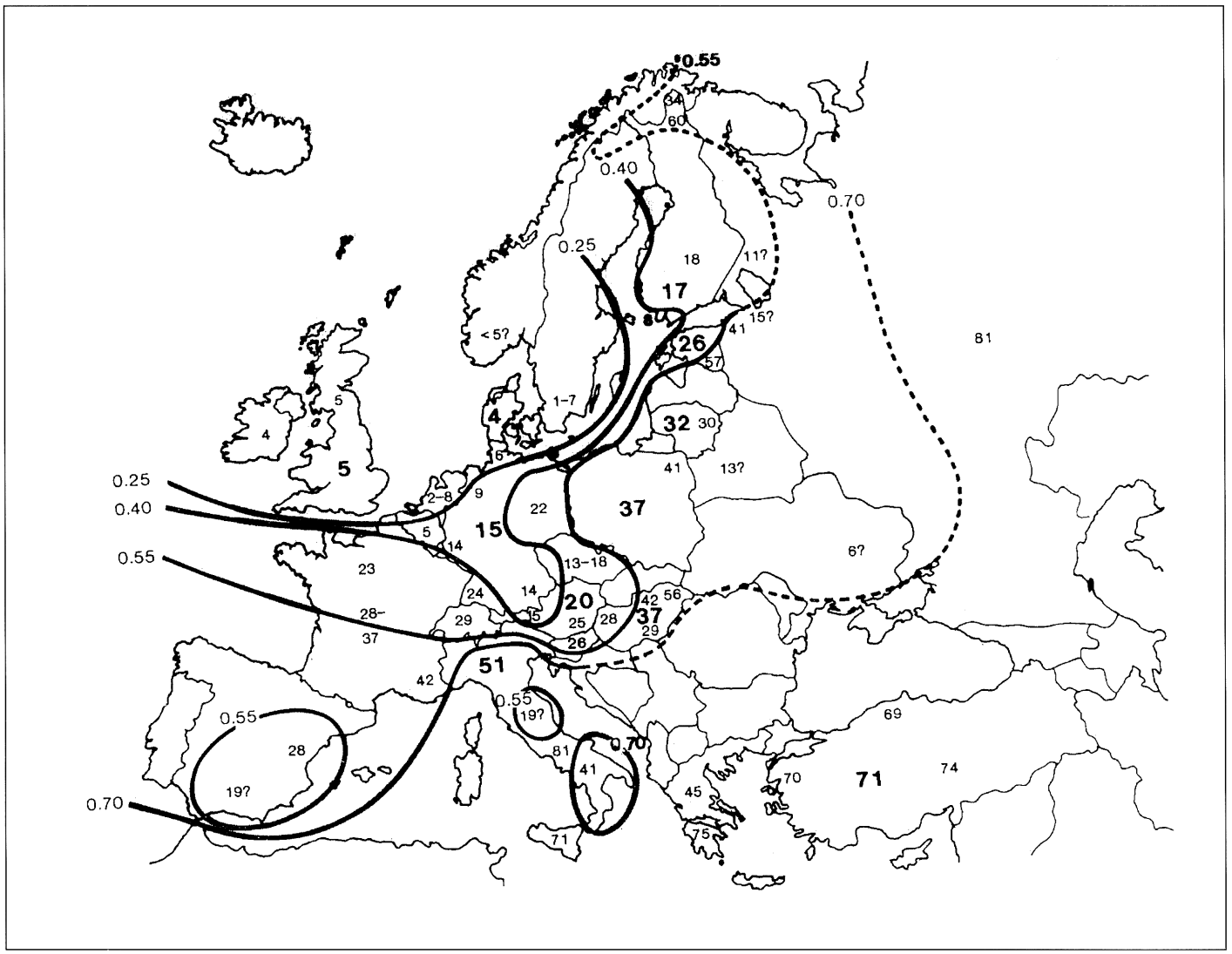

Figure 1. Prevalence (%) of adult-type hypolactasia in different European countries and populations (small number = prevalence of a specific population, large number = average prevalence of the country) and hypothetical isograms for the frequencies of the hypolactasia gene. From Sahi T: Genetics and epidemiology of adult-type hypolactasia. Scand J Gastroenterol 1994;29 Suppl 202:7-20.

age of lactase persistence has been much greater. If dairy farming started about 5500 years (220 generations) ago and the prevalence of hypolactasia has decreased since then from almost 100% to 5%, the selection power has been about 5%, five times higher than in Italy. This is credible, because dairy farming has been more common and milk a more important component of food in north-western Europe than in Italy. It is also possible that in Northern Europe lactase persistence has had some other advantage than this nutritional one, e.g. the enhancing of calcium absorption and the prevention of rickets.

REFERENCES

1. Flatz G: Genetics of lactose digestion in humans. Adv Hum Genet 1987;16:1-77.
2. Sahi T: Genetics and epidemiology of adult-type hypolactasia. Scand J Gastroenterol 1994;29 Suppl 202:7-20.
3. Sahi T, Isokoski M, Jussila J, Launiala K, Pyörälä K: Recessive inheritance of selective adult type lactose malabsorption. Lancet 1973;2:823-6.
4. Sahi T: The inheritance of selective adult-type lactose malabsorption. Scand J Gastroenterol 1974;9 Suppl 30:1-73.
5. Lisker R, Gonzales B, Daltabuit M: Recessive inheritance of the adult type intestinal lactase deficiency. Am J Hum Genet 1975;227:662-4.
6. Ransome-Kuti O, Kretchmer N, Johnson JD, Gribble JT: A genetic study of lactose digestion in Nigerian families. Gastroenterology 1975;68:431-6.
7. Metneki J, Czeizel A, Flatz SD, Flatz G: A study of lactose absorption capacity in twins. Hum Genet 1984;67:296-300.
8. Ho MW, Povey S, Swallow D: Lactase popymorphism in adult British natives: estimating allele frequencies by enzyme assays in autopsy samples. Am J Hum Genet 1982;34:650-7.
9. Wang Y, Harvey CB, Pratt WS et al: The lactase persistence/non-persistence polymorphism is controlled by a *cis*-acting element. Hum Mol Genet 1995;4:657-62.
10. Rossi M, Maiuri L, Fusco MI et al: Lactase persistence versus decline in human adults: multifactorial events are involved in down-regulation after weaning. Gastroenterology 1997;112:1506-14.
11. Simoons FJ: Primary adult lactose intolerance and the milking habit: a problem in biological and cultural interrelations. II. A culture historical hypothesis. Am J Dig Dis 1970;15:695-710.
12. Flats G, Rotthauwe HW: Lactose nutrition and natural selection. Lancet 1973;276-7.
13. Busk HE, Dahlerup B, Lytzen T, Juul-Jørgensen B, Gudmand-Høyer E. Hyppigheden af laktosemalabsorption blandt danske studenter. Ugeskr Læger 1975;137:2062-4. □