Observing the founder effect in human evolution

Article *in* Nature · September 1987

DOI: 10.1038/329105a0 · Source: PubMed

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Population genetics

Observing the founder effect in human evolution

Jared M. Diamond and Jerome I. Rotter

In evolutionary biology the concept of the founder effect refers to "the establishment of a new population by a few original founders (in an extreme case, by a single fertilized female) which carry only a small fraction of the total genetic variation of the parental population"[1]. The resulting new population thereby instantly becomes genetically different from the parental population. Although the founder effect is often thought to be important in speciation, it has rarely been observed directly in nature, for the obvious reason that pedigrees of all individuals in an expanding population are generally unknown. In this respect, no other species can match the advantages of *Homo sapiens*: each individual of our species is named, our purported genetic relationships are known and our pedigrees can often be traced for many generations. Recent studies of human genetic disorders document the evolutionary significance of the founder effect in a way that would be impossible for other species[2-10].

Consider the Afrikaner population of South Africa[3], which was founded by a shipload of immigrants in 1652 and subsequently augmented by more immigrants. As documented by church registers, the early immigrants produced large families (often 10 or more children), underwent a population explosion and contributed disproportionately to the modern Afrikaner population, which now numbers about 2,500,000. Some original settlers left tens of thousands of descendants alive today, and nearly 1,000,000 living Afrikaners have the names of 20 original settlers.

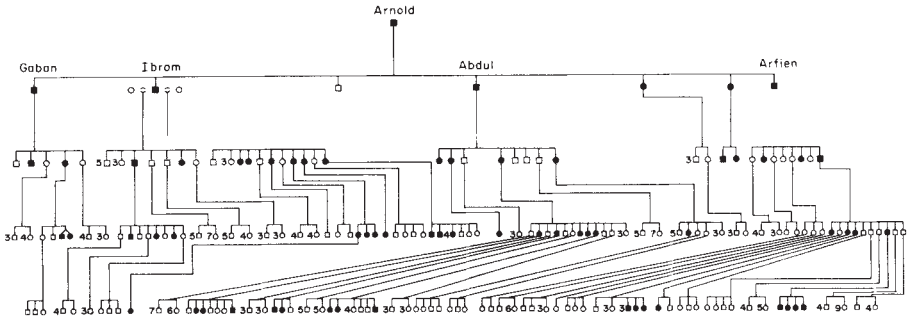
Among the founding immigrants in 1652 were one carrier of the gene for Huntington's chorea and two carriers of lipoid proteinosis, while carriers of porphyria variegata and familial colonic polyposis arrived a few decades later[3,4]. In porphyria variegata, an autosomal dominant defect in the enzyme protoporphyrinogen oxidase, carriers develop a severe and sometimes lethal reaction to barbiturate anaesthetics, but the condition was relatively benign until the advent of modern medicine. All traceable Afrikaner carriers are descendants of one couple, Gerrit Jansz and Ariaantje Jacobs, who emigrated from Holland in 1685 and 1688, respectively[4]. Now, about 30,000 of their South African descendants carry the gene that they brought — a far higher incidence than in Holland — due to this sampling accident. Similarly, all South African cases of lipoid proteinosis, an autosomal recessive disorder that is more frequent there than anywhere else in the world, are traceable to a brother and sister who arrived in 1652[3]. One of the brother's five children and five of the sister's thirteen children carried the gene, as did eight of the seventeen offspring of the sister's eldest son, thereby propelling the gene towards its modern frequency.

Although the founder effect is particularly easy to document among Afrikaners because of their church registers, there are many other examples in South Africa and in other parts of the world[5-12]. In South Africa's Cape Coloured population, an autosomal dominant bone disease (osteodental dysplasia), causing complete loss of teeth by age 20, stems from a polygamous Chinese immigrant called Arnold who, aided by 7 wives, transmitted the syndrome to at least 70 of his 356 traceable descendants (ref. 5; see figure). As for Huntington's chorea, a lethal autosomal dominant disease, most Afrikaner cases derive from a Dutch man who arrived in 1652 and his German wife who arrived in 1668[3]; 432 cases in Australia are descended from the British immigrant Miss Cundick and her 13 children[10]; and all known cases on the island of Mauritius are descendants of a French nobleman's grandson, Pierre Dagnet d'Assigne de Bourbon[9]. All 82 cases of autosomal recessive six-fingered dwarfism in the Pennsylvania Amish community stem from Samuel King and his wife[11]. Every human population has its own 'private' genetic disorders confined to or commonest in that population, and for which the founder effect must be considered as one possible explanation[8,11,12].

Naturally, deleterious genes eventually tend to be eliminated by natural selection, and the founder effect alone cannot explain their long persistence in a human population. It is therefore interesting to examine what sort of geographically localized genetic disorders are still traceable to founder effects among Finns and Afrikaners after several centuries of natural selection. Some of the disorders are too benign to interfere seriously with reproduction. Those that kill their carriers are either autosomal recessive diseases (so that homozygotes die but the far more numerous heterozygotes remain unaffected) or autosomal dominants that affect adults only after they have already reproduced. For instance, the sixteenth-century population explosion in central Finland bequeathed to modern Finns a characteristic legacy of 19 genetic disorders[13]. Four are autosomal dominants or sex-linked recessives that are thus expressed in all or many carriers but mainly lead just to visual impairment in adulthood and thus do not prevent reproduction. Although the other 15 Finnish disorders do include lethal diseases of childhood, they are autosomal recessive conditions, so that heterozygotes are protected from effects of natural selection. Similarly, among the common genetic disorders of Afrikaners, those that are lethal before adulthood or interfere with reproduction are autosomal recessives (sclerosteosis, spondylo-epimetaphyseal dysplasia) whereas the autosomal dominants are either benign (porphyria variegata before the advent of barbiturates) or lethal only in post-reproductive adults (Huntington's disease, familial colonic polyposis)[3].

The founder effect can thus be shown to endow populations temporarily for a few centuries with high frequencies of benign traits or of deleterious genes that are relatively protected from the effects of natural selection. What do these esoteric diseases tell us about the evolution of our persistent 'racial' characteristics that are selectively neutral or advantageous, such as skin colour, blood groups and disease resistance?

Throughout most of human evolution our population structure made us prime material to be moulded by founder effects[2]. Breeding populations of hunter–gatherers were small, of the order of 500 or less, and polygyny allowed a few



The founder effect in operation: how polygamy and fertility enabled one carrier of the gene for osteodental dysplasia to pass the gene to at least 70 descendants in the next four generations. Squares, males; circles, females; filled and open symbols, affected and unaffected individuals, respectively. (From ref. 5.)

successful males to skew the distribution of the next generation's gene pool. Tiny founder groups underwent massive population explosions in several large and formerly uninhabited areas of the globe, such as when the ancestors of American Indians, native (aboriginal) Australians and Polynesians reached their eventual homelands. Other founder groups underwent massive expansions at the expense of earlier inhabitants, such as when Indo–Europeans spread from the Ukraine over much of Eurasia; Austronesians spread from Taiwan over the Indo–Malayan archipelago; or Bantu speakers overran much of sub-Saharan Africa. These populations had to adapt to their new environments, but the genes that were initially available to them for adapting depended on the founder effect. This could help to explain why malaria resistance depends in different locations on many alternative genes, including mutant haemoglobins, thalassaemias and G6PD variants.

As an extreme case of the founder effect, the initial peopling of Australia from Indonesia 50,000 years ago probably resulted from the accidental arrival of a raft bearing a few people — perhaps no more than a pregnant woman expecting a son[14]. Which of the distinctive features of modern native Australians go back to the genes of that woman? □

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Jared M. Diamond is in the Department of Physiology and Jerome I. Rotter is in the Departments of Medicine and Pediatrics at the University of California Medical School, Los Angeles, California 90024, USA.

Alzheimer's disease

Tangled genes and proteins

Brian H. Anderton

DEVELOPMENTS in studying the molecular biology of Alzheimer's disease are coming thick and fast. It is only a few months since it was announced that the gene responsible for the rare autosomally dominant familial form of Alzheimer's disease (FAD) is located on chromosome 21. At the same time, the gene encoding the precursor amyloidogenic protein was also found in close proximity to the gene encoding FAD, the two perhaps being one and the same. This result seemed to offer a neat explanation, by a gene-dosage mechanism, for the development of Alzheimer's pathology in people more than 40 years old with Down's syndrome (see my recent News and Views article[1]). Results reported at a recent meeting*, and in two papers by J.A. Hardy and colleagues[2] and by J.F. Gusella and colleagues[3] on pages 153 and 156 of this issue, respectively, show that the situation is not so simple.

During the past decade, research has concentrated on three pathological changes in the brains of patients with Alzheimer's disease: intracellular neurofibrillary tangles, made of paired helical filaments; extracellular amyloid deposits at the centre of senile plaques, the areas of neuronal degeneration; and deficits of neurotransmitters, their synthetic enzymes and their receptors. Most cases of Alzheimer's disease are believed to be sporadic, although it is increasingly recognized that a familial tendency may be more common than was previously thought. In the few families in which FAD exists, however, the disease is usually more aggressive and has an earlier onset than the more common 'sporadic' or looser familially associated disease. Linkage analysis in four such FAD families where a large pedigree of inheritance is known is a new line of attack undertaken by Gusella's group in Boston, whose results were reported at the meeting by P. H. St George-Hyslop (Harvard Medical School).

The gene encoding FAD has now been more precisely mapped on chromosome 21 and lies close to the two markers *D21S16* and *D21S1/D21S11*. This region is outside the obligate Down's syndrome region, which is known because about 3 per cent of Down's cases do not have complete trisomy (three copies) of chromosome 21 but only of the part of the chromosome (the obligate region) at the distal end of the long arm. The gene encoding FAD is more proximal than this obligate segment. What is not known is if all Down's cases that have incomplete trisomy are demented and develop an Alzheimer's pathology, or if it is only those that have three copies of the FAD and/or amyloid-precursor gene.

Great excitement followed the finding reported a few months ago that the FAD and amyloid-precursor (AP) genes are on the same chromosome and not too far apart (see ref. 1). However, St George-Hyslop, J. Hardy (St Mary's Hospital Medical School, London) and C. Van Broeckhoven (University of Antwerp) all reported studies of families with Alzheimer's disease in which the disease failed to co-segregate exclusively with one particular allele of the AP gene. They concluded that it is very unlikely that the FAD gene is identical with the AP gene[2,3].

St George-Hyslop also reported a careful re-examination of the recent claim[4] that 'sporadic' cases of Alzheimer's disease result from a duplication of the distal portion of chromosome 21 that includes the AP gene. Both he and Hardy were unable to confirm this observation, and agreed that the AP gene is not responsible for Alzheimer's disease either in mutant form (FAD) or by the presence of an extra copy (sporadic Alzheimer's disease and Down's syndrome)[2,3].

These results imply that amyloid deposits are the consequence of other earlier events in the pathogenesis of the disease, the FAD gene perhaps encoding a protein that influences the processing of the amyloid precursor protein. The next step is therefore to study the biochemical changes that cause the M_r 4,000 amyloid A4 protein to be produced from its precursor. M. Salbaum (University of Heidelberg) reported that the precursor protein is a M_r 92,000 polypeptide of the particulate fraction from brain. The recombinant protein produced by *in vitro* transcription and translation of the complementary DNA is susceptible to proteolysis but can be protected from proteases by insertion into added microsomal membranes. The recombinant protein can also be glycosylated. All this suggests that it is a membrane glycoprotein as originally proposed by Salbaum and co-workers[1,5]. Hardy found by Northern blot analysis that the messenger RNA encoding this protein is more abundant than actin messenger RNA in brain, which suggests that the M_r 4,000 A4 amyloid protein is produced by proteolysis of one of the most abundant brain membrane proteins whose identity, for the moment, remains obscure.

The chemistry of the other main protein deposit, the paired helical filaments of the neurofibrillary tangles, is not so well advanced. C. Wischik (Laboratory of Molecular Biology, Cambridge) described the identification of a polypeptide of M_r 9,000–12,000, probably a fragment of a larger protein, that is present in the core of the paired helical filament and accessible only after treatment of isolated filaments with proteases. This polypeptide does not seem to cross-react with any cytoskeletal protein, the other constituents of neurofibrillary tangles. M. Landon (Nottingham University) and I can both confirm

*Meeting sponsored by the Brain Research Association and the Alzheimer's Disease Society of Great Britain, Southampton, 22–24 July 1987.