

The past within us

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The recognition of new Y-chromosome markers represents a major leap in the investigation of human genetic diversity (in male lineages, complementing the information from female lineages derived from mitochondrial DNA). The resulting phylogeny supports the out-of-Africa origins of our species and opens the way to further insights into prehistoric demography and world prehistory.

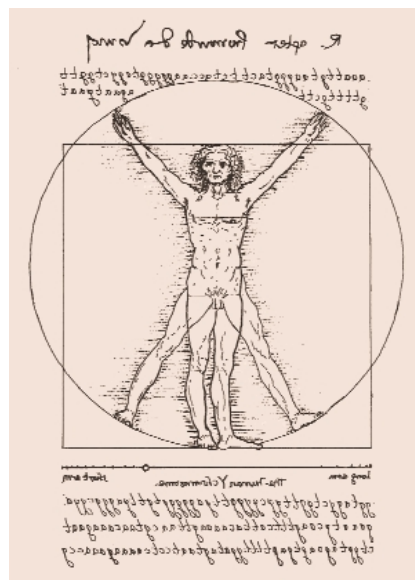
Young man, Are you listening to me I said, young man, what do you want to be I said, young man, you can
make real your dreams, but you've got to know this one thing Just go to the Y
The Village People

With their report published on page 358 of this issue, Peter Underhill and colleagues¹ begin a new chapter in the study of world population history. For the past dozen years or so, mitochondrial DNA (mtDNA) has gloried in the limelight of genetic forays to elucidate human history. The study of female lineages has provided a uniquely authoritative glimpse of the African origin and subsequent dispersal of our species². Now, the Y chromosome³ has come into its own. The acquisition of no fewer than 87 informative new markers, and their combination with others⁴ to produce the most comprehensive phylogenetic tree of the Y-chromosome, takes historical population genetics, or 'archaeogenetics'⁵, a quantum leap forward.

To the archaeologist, it seems altogether remarkable that the history of our species is most effectively obtained by characterizing the DNA of living populations, supplemented by just a few samples of ancient DNA (refs 6–8). The most comprehensive overview of human population diversity, *The History and Geography of Human Genes*⁹, relies upon classical genetic markers (for example, those that specify blood groups and enzymes) and was published as recently as 1994. The pioneering analysis² that demonstrated the usefulness of mtDNA (in archaeogenetics) was published in 1987; it also indicated an African origin of *Homo sapiens* and a number of population expansions into Europe from Anatolia in the Upper Palaeolithic period¹⁰ (also known as the later old stone age and beginning about 40,000 years ago). The study by Underhill and colleagues demonstrates that Y-chromosome analysis is equally potent.

The phylogeny relating all haplotypes defined by 167 markers in a single, parsimonious tree¹ contrasts with the array of 'rival' trees arising from mtDNA analysis. The successive mutations at the key nodes of the tree, considered alongside the specific geographical distributions of the indi-

vidual haplogroups, mark the story of the initial expansion out of Africa and of subsequent population expansions. The hierarchical structure of successive mutations, in addition to indicating chronology, will permit efficient haplotyping—that is, the simultaneous typing of multiple loci.



This tree, based on the analysis of just 1,062 individuals worldwide, supports the 'out-of-Africa' scenario. The most deep-rooting clade, haplogroup I, is restricted to Africa: three mutations present in all the other haplogroups preceded the first expansion from Africa to Asia. The estimated age of this expansion—about 44,000 years—is similar to earlier estimates, including the recent estimate of 47,000 years (89,000 to 35,000 years with a 95% confidence interval¹¹). It does not contradict the age (about 60,000 years) of a 'modern' human burial site in Australia associated with the use of red ochre¹², but it might imply that the archaic *sapiens* hominids believed to live in the Near East¹³ as early as 100,000 BC may have become extinct before or perhaps

as a consequence of this dispersal¹⁴.

The remarkable power of the method is reflected in the large amount of information contained in the phylogeny of haplotypes and dendrogram of populations that are illustrated. The most parsimonious phylogeny permits the outlining of a whole demographic narrative; for example, the distribution of haplogroup VIII (identified as the source of haplogroup IX) confirms the early peopling of New Guinea and Australia. The population of Europe and Central Asia seems to have followed. Japan has a special place in this story as the main location for haplogroup IV. It is one of the few localized regions to be so highlighted at this level of analysis, with a population strikingly different from surrounding populations.

The suggestion that the populations represented by haplogroups III to X—which represent all populations outside of Africa—"remained small throughout the last glaciation" (that is, until some time after 16,000 years ago), "before they underwent roughly simultaneous expansions in size" will stimulate additional research into the subsequent histories of each of these haplogroups. To enable facile interpretation and comparison between publications, it is imperative that a standard phylogenetic nomenclature be established.

The greater geographical variability of the Y chromosome (with respect to mtDNA; ref. 15) promises a vision of world population history at a finer resolution than is currently available, a history that extends back into the Upper Palaeolithic period in a manner quite unthinkable only a decade ago. This is quite a feat, considering that the non-recombining portion of the Y chromosome is but a single locus. Dates need to be tested and refined, and it remains to be determined how chronologies established from mtDNA and the Y chromosome will synchronize—although they should, given the equal parts that women and men have had in the human story. The extent to which population events

indicated by these analyses were closely determined by climatic factors remains to be established. Indeed, there are many “whys” and “wherefores” that have yet to be addressed: the current study provides a solid platform upon which to do so. □

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Of giant axons and curly hair

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Giant axonal neuropathy (GAN) is a recessive motor and sensory neuropathy of the central and peripheral nervous system. People with GAN show a distortion of nerve fibres due to axonal swellings caused by the accumulation of neurofilaments. A new study reports the cloning of the gene underlying GAN, whose protein product, gigaxonin, is a novel protein of the cytoskeleton and a member of the kelch-repeat superfamily.

The key function of peripheral nerves is to transmit information between fixed points in the organism. These trajectories, up to one metre in the lower limbs, are bridged by axons, which are single continuous nerve-cell extensions. Normal peripheral nerves contain axons in which the variation in the diameter of the axonal calibre is impressive; thin unmyelinated axons are nearly 10,000 times smaller than large myelinated fibres. The linear relationship between the velocity of conduction and nerve-fibre diameter in myelinated fibres indicates a relationship between function and form, which in turn focuses attention on the cytoskeleton. This is made up of microfilaments, microtubules and neurofilaments, the latter of which are composed of three proteins: the neurofilament light (NEFL), mid-sized (NEFM) and heavy (NEFH) chains¹. The assembly of the intermediate filament network, to which the neurofilaments belong, requires a complex set of cell-specific proteins, such as integral membrane, cross-linking and motor proteins². A study presented by Pascale Bomont and colleagues³ on page 370 of this issue presents a gene whose product resembles a cross-linking, cytoskeletal protein, and whose mutation results in GAN—a cardinal feature of which is an accumulation of neurofilaments.

In fact, accumulation of cytoskeletal proteins is also the hallmark of a few other rare inherited neurodegenerative disorders, including some variants of Charcot-Marie-Tooth disease type 2 (CMT2), amyotrophic lateral sclerosis (ALS)

and spinal muscular atrophy (SMA). Evidence from spontaneous mutant and knockout animal models indicates that at least some of the inherited disorders in humans may be caused by mutations in genes encoding cytoskeletal components⁴. The first hint that this hypothesis is indeed correct came from the observation⁵ of *NEFH* alterations in a small number of people with ALS. But the majority of sporadic and familial ALS patients do not have *NEFH* alterations. More substantive support for the hypothesis was provided by the recent identification of the genetic defect, a mutation in *NEFL* in CMT2, a common axonal form of hereditary motor and sensory neuropathies⁶ (HMSN).

Jumping the GAN

First described in 1972, GAN is a rare recessive neurodegenerative disorder of the peripheral nerves that presents in early childhood as HMSN and leads to death, usually by late adolescence^{7–9}. Patients often have curly hair and some have involvement

of the central nervous system, including cerebellar ataxia and signs of damage of the pyramidal tract. Magnetic resonance imaging shows abnormalities within the cerebellum and cerebral white matter. The diagnosis is made by a peripheral nerve biopsy, which demonstrates distorted nerve fibres due to giant axonal swellings (Fig. 1). These swellings start at the node of Ranvier and are caused by spheroids of densely packed bundles of neurofilaments (Fig. 2). The density of myelinated nerve fibres is reduced, indicating a progressive axonal loss.

In 1997 the disease locus, GAN-1, was assigned to chromosome 16q24.1 by homozygosity mapping in three unrelated Tunisian families¹⁰. The absence of curly hair and a different course of the disease in some individuals indicated genetic heterogeneity, but subsequent linkage studies in these atypical families and in families from different geographic origins confirmed that GAN is a homogeneous disease with a single locus^{11,12}. Bomont *et al.* used standard physical mapping and cloning techniques to identify a novel gene (*GAN*) encoding a protein they called gigaxonin. They screened *GAN* in 15 families and identified 14 distinct mutations (9 missense, 4 nonsense and 1 frameshift). Three other families show homozygosity at the *GAN* locus but no mutations could be detected, indicating the possible involvement of other gene alterations such as inversions, partial duplications, activation of cryptic splice sites, or mutations in the promoter.

Some German Shepherd dogs have a phenotype mimicking GAN, including a

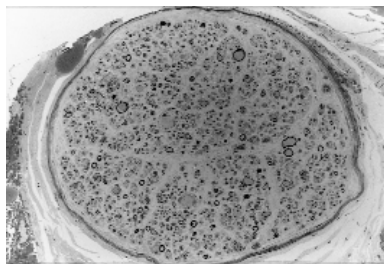


Fig. 1 Light microscopic examination of a transverse section of a fascicle of the sural nerve shows thinly myelinated and unmyelinated giant axons. Myelinated fibres are reduced in number.