Sequence analysis reveals a β-thalassaemia mutation in the DNA of skeletal remains from the archaeological site of Akhziv, Israel

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β-Thalassaemia is manifested by severe anaemia and extensive bone pathology. Similar pathology may also result from other forms of anaemia. To clarify the precise cause, we performed DNA analyses on archaeological remains of a child with severe bone pathology. We found homozygosity for frameshift in codon 8 of β-globin, causing a β-null phenotype. Paradoxically, the child died when eight years old, whereas such patients are transfusion dependent from early infancy. An infrequent polymorphic marker in the child's DNA, and information from present-day patients, indicated that amelioration of the clinical condition was due to elevated fetal haemoglobin production. Thus this analysis provided not only precise diagnosis of a genetic disease but also allowed clarification of the molecular mechanism underlying the clinical presentation.

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β-Thalassaemia major is a severe hereditary anaemia caused by any of approximately 150 mutations in the β-globin gene. Without frequent blood transfusions the disease is lethal in early childhood. The high prevalence of this autosomal recessive disease in malaria-infested regions led Haldane[1] to propose that heterozygous carriers have a selective advantage in a malarial environment. Angel[2] suggested that the disease is ancient, providing genetic protection in the heterozygous state against the increased prevalence of malaria that followed the establishment of permanent settlements near standing water in the Neolithic period. Until now the evolution of the disease has been studied from two perspectives. The first is extrapolation from the distribution of present day mutations in different modern populations[3–5]. The second is through attempts to identify the disease in skeletal remains on the basis of bone pathology.

The severe anaemia and increased spatial demands for the hyperplastic erythropoietic marrow cause extensive skeletal pathology, which is most pronounced in the skull and characterized by diploic thickening and "hair on end" appearance[6]. Such pathology in archaeological specimens has been attributed to thalassaemia[2]. It has also been suggested that anaemia from other causes as well as malnutrition may cause similar effects[7]. The differential diagnosis is important both for tracing the evolution and spread of this disease and for understanding environmental pressures experienced by past populations. Recent developments in DNA technology provide the opportunity for probing this question. Using this approach we identified a β-thalassaemia mutation in skeletal remains of a child, excavated from an archaeological site at Akhziv, on the Northern coast of Israel.

The archaeological site

Tel Akhziv, located 15 km north of Acre, has been inhabited with only slight interruptions for at least 4,000 years. The region was infested by malaria until the beginning of this century. Four distinct cemetery complexes have been identified in the vicinity of the Tel. At least two of those have been dated to the Phoenician period, 11th to 7th centuries B.C.E.[8]. While excavating the Northern Phoenician cemetery, a number of unmarked graves were found. They had been dug into the Phoenican cemetery and themselves disturbed by later burials. The skeletal remains were identified as Moslem by their position. They were lying on their backs in an east-west orientation with the head facing south towards Mecca. Coins found in some of the graves indicated that they dated to the Ottoman period, sometime between the 16th and 19th centuries. The skull of the child studied here was recovered from one of the disturbed Ottoman graves, containing the remains of four individuals. The disturbed graves probably belong to the earlier part of the period. Since ^{14}C variations in the atmosphere within that time period do not allow more precise calendrical determination (R. Hedges, personal communication), carbon dating was not performed.

Bone pathology

The skull showed severe bone pathology known as porotic hyperostosis (Fig. 1). Pathological features include extensive pitting of the posterior portion of the skull (parietal and occipital bones, Fig. 1*b*), mild pitting of the frontal bone and pitting of the orbital roof (cribra orbitalia, Fig. 1*c*). The cranial bones are thick with a maximum of 10 mm in the parietal region (Fig. 1*d*), compared with an average thickness of 4.5 mm for individuals of the same