An unexpectedly high frequency of heterozygosity for \(\alpha\)-thalassemia in Ashkenazi Jews

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Abstract

\(\alpha\)-Thalassemia is among the world’s most common single gene disorders, which is most prevalent in the malaria belt. This geographic distribution has been attributed to a selective advantage of heterozygotes against this disease. Unexpectedly, we have found a high frequency of heterozygosity for deletional \(\alpha\)-thalassemia \((-\alpha^{3.7})\) in Ashkenazi Jews (carrier frequency of 7.9%, allele frequency of 0.04). This population has resided in temperate climates for many centuries and was therefore not subjected to malarial selection pressure. In comparison, heterozygosity for \(\beta\)-thalassemia, which is highly subject to malarial selection pressure, is very low (estimated <0.1%) in this group. It is possible that founder effect and genetic drift have contributed to the high frequency of deletional \(\alpha\)-thalassemia in Ashkenazim, as may occur in closed populations. Alternatively, we hypothesize that positive selection pressure for an as yet unknown linked allele on chromosome 16 may be a significant factor leading to this high frequency.

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Introduction

\(\alpha\)-Thalassemia is among the world’s most common single gene disorders [1] generally caused by gene deletions due to unequal crossing over in the \(\alpha\)-globin gene cluster [1,2]. Deletions are found at very high frequencies in the “malaria belt,” where falciparum malaria was (or still is) prevalent [3]. Much epidemiological evidence [3,4] supports Haldane’s hypothesis that heterozygosity for \(\alpha\)-thalassemia, like other globin disorders, confers a selective advantage against malaria. The mechanism of this protection is not clear but may relate to the hematological phenotype of \(\alpha\)-thalassemia trait.

Ashkenazi Jews resided for many centuries in a region in which falciparum malaria was not prevalent. Therefore, they would not be expected to have a significant frequency of \(\alpha\)-thalassemia or other globin gene disorders. Indeed, \(\beta\)-thalassemia is very rare in Ashkenazim (estimated <0.1% [5]) as well as in other northern European populations [6,7]. Surprisingly, our previous work on \(\alpha\)-thalassemia in an Israeli referral population suggested a high frequency: nearly 17% over 300 nonrelated chromosomes, which carried an \(\alpha\)-globin gene abnormality, were of Ashkenazi Jewish decent [8]. Of these Ashkenazi chromosomes, 87% carried a single gene deletion, \(-\alpha^{3.7}\). We therefore undertook the present study to assess the frequency of the \(-\alpha^{3.7}\) allele in an unselected sample of Ashkenazim. In comparison, we studied a smaller sample of individuals of northern European (Polish) extraction.

Materials and methods

DNA was isolated from peripheral blood leukocytes according to standard procedures [9]. PCR was performed for the \(-\alpha^{3.7}\) allele and the \(\alpha\alpha^{\text{anti}3.7}\) as described [8]. One hundred and fifty-one anonymous DNA samples of Ashkenazim were received from three sources: maternity...
patients who were the control group of a study on the frequency of BRCA mutations; the DNA Bank of normal individuals at the National Laboratory for Genetics of Israeli Populations of the Sackler School of Medicine of Tel Aviv University; and patients referred for DNA-based diagnosis of hematological diseases other than anemia, such as hereditary coagulation disorders or malignancies. In addition, DNA was isolated from 50 blood or bone marrow samples of Polish patients being treated for various hematological malignancies.

Results

Of the 151 Ashkenazi samples screened, 12 were found to be heterozygotes for the $-\alpha^3.7$ allele (carrier frequency of 7.9%, allele frequency of 0.04). On the basis of our previous results that 87% of all Ashkenazi $\alpha$-thalassemia chromosomes carried the $-\alpha^3.7$ allele [8], we extrapolate the total allele frequency of $\alpha$-thalassemia to be 0.045. This frequency is even higher than that of typical “Ashkenazi” recessive diseases, such as cystic fibrosis (0.02) [10], Tay-Sachs (0.02) [11], and Gaucher’s disease (0.03) [12,13], and is comparable to that of factor XI deficiency (0.045) [14]. In contrast, only 1/151 samples was found to carry the reciprocal allele (aa,aa,aa,aaa), which results from the recombination event leading to the $-\alpha^3.7$ allele. The difference in the frequencies for the $-\alpha^3.7$ allele and aa,aa,aa,aaa were highly statistically significant ($P < 0.003$) (using two-sided Fisher’s exact test). Interestingly, of 50 DNA samples of Polish nationals, none were found to be heterozygous for deletional alpha thalassemia.

Discussion

We have found that $\alpha$-thalassemia is frequent among Ashkenazi Jews. In contrast, heterozygosity for $\beta$-thalassemia is exceedingly low [5] and other hemoglobinopathies, such as sickle cell anemia, are virtually unknown in this group. This finding was surprising as the genetic epidemiology of thalassemia is usually associated with malarial selection. The frequency of $\alpha$-thalassemia heterozygosity in Ashkenazim is far from that seen in regions where malaria is highly endemic, such as Nepal (0.8) [15] or Nigeria (0.27) [16]. However, it is similar to or exceeds that found in a number of Mediterranean and Middle Eastern countries such as Egypt (0.08) [17], Jordan (0.031) [18], Sicily (0.041) [19], and the Greek Cypriot population (0.07) [20] where malarial selection was also presumed to be operating.

Ashkenazim are known to be carriers of a number of autosomal recessive diseases, possibly due to founder effects and genetic drift [21]. Many Ashkenazi diseases have one predominant mutation, supporting the founder hypothesis. Indeed, an apparently similar pattern was found here for $\alpha$-thalassemia (87% of the alleles were $-\alpha^3.7$). This remains to be further clarified since the $-\alpha^3.7$ allele has several subtypes, each of which is believed to have occurred independently.

We considered whether $\alpha$-thalassemia could provide genetic protection against Plasmodium vivax, which was endemic in northern Europe until the 20th century and could cause fatal infections, particularly in anemic or malnourished children [22]. However, the absence of $\alpha$-thalassemia in our small sample of Polish nationals does not support this hypothesis.

Recurrent unequal crossing over events were excluded by the virtual absence of the reciprocal recombination product in the Ashkenazi population tested here.

A more attractive explanation for the high frequency is nonmalarial selection. Indeed, protection against other non-malarial infectious diseases has been hypothesized to be associated with $\alpha$-thalassemia trait [23]. Alternatively, selective advantage could have been conferred by a linked genetic element in one of the many developmentally important genes, which are linked to the $\alpha$-globin cluster.

Modern techniques have greatly simplified the molecular diagnosis of $\alpha$-thalassemia [8]. These should enable large scale population studies based on northern European populations, which may clarify some of these questions.

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