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# Consanguineous marriages: do genetic benefits outweigh its costs in populations with $\alpha^+$-thalassemia, hemoglobin S, and malaria?

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**Abstract**

Consanguinity is widespread in populations with endemic malaria. This practice, leading to an increase of homozygosis, could be either detrimental for lethal alleles (like hemoglobin S) or be potentially advantageous for beneficial alleles (like $\alpha^+$-thalassemia). The objective of this study was to analyze the effects of inbreeding on the fitness of a population with both, $\alpha^+$-thalassemia and hemoglobin S mutations. We calculated the relative fitness of an inbred population with $\alpha^+$-thalassemia and sickle cell anemia using a standard formula, and then compared it to that of an outbred population. An increase in the frequency of $\alpha^+$-thalassemia allele (0–1) results in a gain of relative fitness that is proportional to the coefficient of inbreeding; it is maximal at an allele frequency in the vicinity of 0.5. For hemoglobin S, an increase of frequency (0 to equilibrium point) produces a progressive loss of relative fitness that is also proportional to the coefficient of inbreeding; it is lowest at the equilibrium frequency that is always lower than 0.5. In a consanguineous population with both $\alpha^+$-thalassemia and hemoglobin S under selection pressure of malaria, the sum of contrary effects of inbreeding on the relative fitness of population depends on the frequencies of the two alleles and the coefficient of inbreeding.


*Keywords:* Consanguineous marriages; Inbreeding; Malaria; Thalassemia; Hemoglobin S; Relative fitness; Simulation model

## 1. Introduction

Globally, there is a high rate of consanguineous marriages in populations where malaria is endemic. In such populations, the rate of such marriages with biologic relatives correlates with the intensity of malaria infestation (Denic & Nicholls, 2007). The same populations have an increased frequency of many different alleles protective against malaria (Weatherall et al., 2002). The precise effect of inbreeding on the fitness and selection of those alleles is unclear.

Consanguineous marriages, which are practiced by an estimated 10% of the world population, are traditionally attributed to their multiple socioeconomic benefits, e.g., better preservation of family wealth, increased social security, or better treatment of wife (Alwan & Modell, 1997; Bittles, 2001; Khlat, 1997). Recently, we have shown that inbreeding could enhance selection of $\alpha^+$-thalassemia and increase relative fitness in populations (Denic, Frampton, Nagelkerke, & Nicholls, 2007).

Malaria emerged in the early human settlements approximately 4000 to 10000 years ago. The Agrarian Revolution, which increased the efficiency of food production, resulted in a population explosion. There was also an increased practice of domesticating animals during this time. This overcrowding and the proximity of people to animals resulted in poor hygiene. This potentially allowed the transmission of *Plasmodium* from animals to humans and, subsequently, between humans, via the mosquito. Other epidemic infections (e.g., tuberculosis, plague), until then unknown to humans, emerged as well (Diamond, 1997; Smith, 1995). A high case fatality rate of malaria in

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susceptible populations (up to 50%) exerted a strong selection pressure (Carter & Mendis, 2002). Subsequently, various mutations protective against malaria were introduced and positively selected in rapidly growing populations. What were possible effects of higher growth rates and bigger population sizes on adaptation against malaria was not previously considered.

$\alpha^+$-Thalassemia is one of the many such mutations that protects against malaria and is characterized by a deletion of one of the two alleles on the chromosome coding for the hemoglobin α-chain (Weatherall & Clegg, 2001). The heterozygotes (−α/αα) and homozygotes (−α/−α) are less likely to develop fatal forms of malaria (odds 0.66 and 0.40, respectively) than the wild type homozygotes (αα/αα), a codominantly inherited trait protecting against malaria (Allen, O'Donnell, &, Alexander, 1997). As $\alpha^+$-thalassemia causes no harm to carriers, it has become the most common monogenic condition of men, found in all populations in which *Plasmodium falciparum* is widespread. In some populations, its frequency has reached near fixation levels (Weatherall & Clegg, 2001).

Inbreeding increases the number of homozygotes while decreasing the frequency of heterozygotes. In populations with $\alpha^+$-thalassemia and malaria, inbreeding could theoretically increase the number of homozygotes (who are less likely to die from malaria) and, thus, their relative fitness. However, this would happen only if its positive effects (through increased homozygotes) exceeds the negative effect (by decreased heterozygotes) on the population fitness. Earlier, we have shown in a stochastic model that inbreeding could increase the speed of $\alpha^+$-thalassemia selection (Denic et al., 2007). However, this has left unanswered a question of the effect of inbreeding on some other monogenic conditions also protective against malaria and simultaneously present in the population.

Indeed, heterozygotes for hemoglobin S and E, β-thalassemia, and Malaysian ovalocytosis are protected against *P. falciparum*, but homozygotes often die prematurely (Weatherall et al., 2002). This causes balancing selection of these alleles with frequencies that increase up to their equilibrium point. In populations with hemoglobin S and E, β-thalassemia, and Malaysian ovalocytosis, inbreeding decreases the frequency of heterozygotes while increasing the fraction of homozygotes whose premature death also removes protective allele from the gene pool. Consequently, by reducing the overall frequency of these lethal antimalaria alleles, inbreeding reduces the relative fitness of these populations.

In this study, we examined the sum effect of inbreeding on a population under a strong selection pressure from malaria and with an increased frequency of two types of protective alleles—non-lethal ($\alpha^+$-thalassemia) and lethal (hemoglobin S). This effect of inbreeding is important to study because it potentially concerns 500–1000 millions of people of consanguineous parentage, located mostly in regions with endemic malaria (Bittles, 2001; Denic & Nicholls, 2007). We calculated and compared the relative fitness of an inbred and outbred human population with both $\alpha^+$-thalassemia and hemoglobin S mutations.

## 2. Methods

The relative fitness of a hypothetical population was calculated separately for $\alpha^+$-thalassemia and hemoglobin S genes. Relative fitness of a population ($w$) in a two-allele system depends on the frequency of alleles, relative survival value of genotypes, and the coefficient of inbreeding ($F$) and was calculated using the formulas for relative fitness and allele frequency change ($\Delta_s p$) (Gillespie, 1998).

$$w = 1 - (1 - F)\left(2pqsh + q^2 s\right) - Fqs$$

$$\Delta_s p = (1 - F)\frac{pqs[ph + q(1 - h)]}{w} + F\frac{pqs}{w}$$

The frequency of mutation is $p$ and that of its wild type allele is $q$ ($q$=1−$p$). Parameters $h$ (heterozygosity effect) and $s$ (selection coefficient) have been previously determined for hemoglobin S, and their values are −0.176 and 1, respectively (Gillespie, 1998). For $\alpha^+$-thalassemia, we have determined these two parameters using reciprocal values of published odds of development of severe form of malaria in children with three genotypes as probability of their survival (Allen et al., 1997). Then, we adjusted those survivals to approximate historical rates of growth of the world population over the last several thousands of years when most of the selection of the genes occurred (Haub, 1995). If, historically, the average family had six offspring, probability of survival of "normal" αα/αα genotype of 0.34 assures a slow positive growth of population. Higher survivals of $\alpha^+$-thalassemia silent-carrier (−α/αα genotype) and $\alpha^+$-thalassemia trait (−α/−α genotype) were obtained by multiplying the survival of αα/αα genotype with the reciprocals of the odds of severe forms of malaria for the two $\alpha^+$-thalassemia carriers, 1.5 and 2.5 times, respectively (Allen et al., 1997). Using those genotype survivals and standard formulas for $h$ and $s$, they were determined to be 0.666 and 0.4, respectively (Gillespie, 1998).

In most inbred human populations reported within the last half century, $F$ does not exceed 0.045 (Bayoumi, Taha, & Saha, 1995; Bittles & Neel, 1994). We used $F$ that varied between 0 and 0.09 in order to cover a broader range of possible historic scenarios.

Starting with $p$=.01, we calculated the relative fitness of population and then determined the frequency of allele in the second generation. We than proceeded to calculate the relative fitness of the population in the second generation followed with determination of the frequency of allele in the third generation, and so on, for 50 generations. As the main goal of the study was to examine the change of relative fitness caused by inbreeding, we expressed this change as the ratio of the relative fitness of inbred ($F$>0)

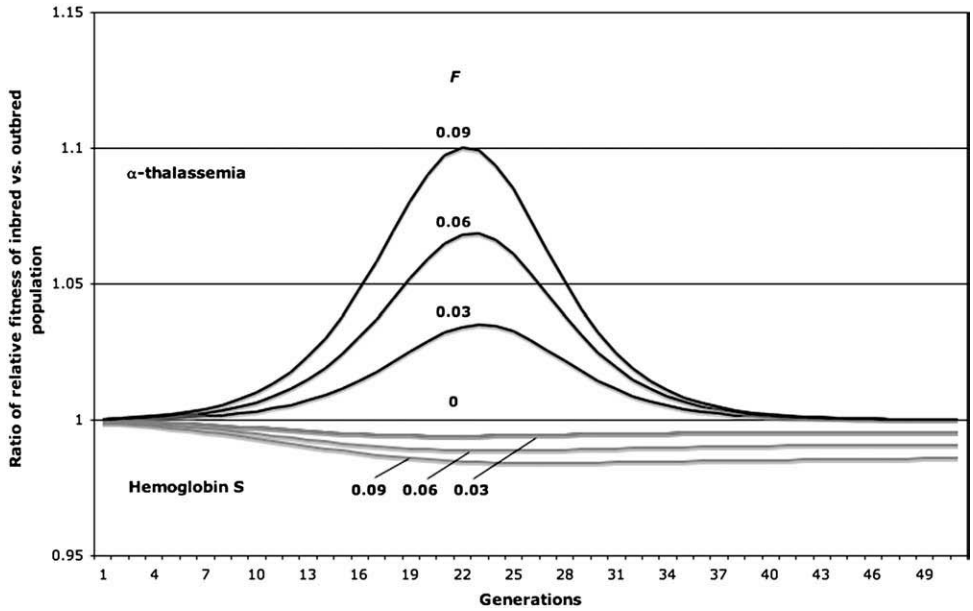


Fig. 1. Ratio of relative fitness of inbred ($F$=0.03, 0.06, and 0.09) vs. outbred ($F$=0) population over 50 generations. At the beginning of simulation, the frequency of mutations was 0.01.

vs. non-inbred ($F$=0) population (Fig. 1). After separate calculation of the relative fitness for $\alpha^+$-thalassemia and hemoglobin S, we superimposed them in the same graph in order to compare the opposing effects of inbreeding on population fitness (Fig. 1).

## 3. Results

Results of simulation are shown in Fig. 1. For $\alpha^+$-thalassemia, as its frequency increases due to positive selection, inbreeding increases the relative fitness of a population. Earlier, we have shown that the relative gain in fitness depends on allele frequency (Denic et al., 2007). When the frequency of $\alpha^+$-thalassemia is around 0.5, the positive contribution of inbreeding to the relative fitness of population is maximal (Fig. 2). As its frequency further increases to reach the fixation level, the positive contribution of inbreeding starts to decrease and then becomes nil. In addition, inbreeding-aided fitness for $\alpha^+$-thalassemia is directly related to $F$ (Fig. 1).

For hemoglobin S, as expected, inbreeding decreases relative fitness of a population being directly proportional to $F$ (Fig. 1). However, the decrease is relatively small because the frequency of hemoglobin S gene, due to balanced polymorphism, never increases as high as the frequency of $\alpha^+$-thalassemia (Fig. 1). The negative impact of inbreeding on population fitness is maximal at the equilibrium frequency of hemoglobin S.

On the assumption that $\alpha^+$-thalassemia and hemoglobin S mutation were simultaneously introduced into a population, the net effect of inbreeding on relative population fitness early into their selection history (when their frequencies are relatively low) is neutral (Fig. 1). Later, when the frequency of $\alpha^+$-thalassemia allele is around 0.5 and that of hemoglobin S is at its equilibrium point, the summed fitness is increased by inbreeding. As the frequency of $\alpha^+$-thalassemia further increases and approaches the fixation level, this summed fitness becomes neutral again and then negative (Fig. 1).

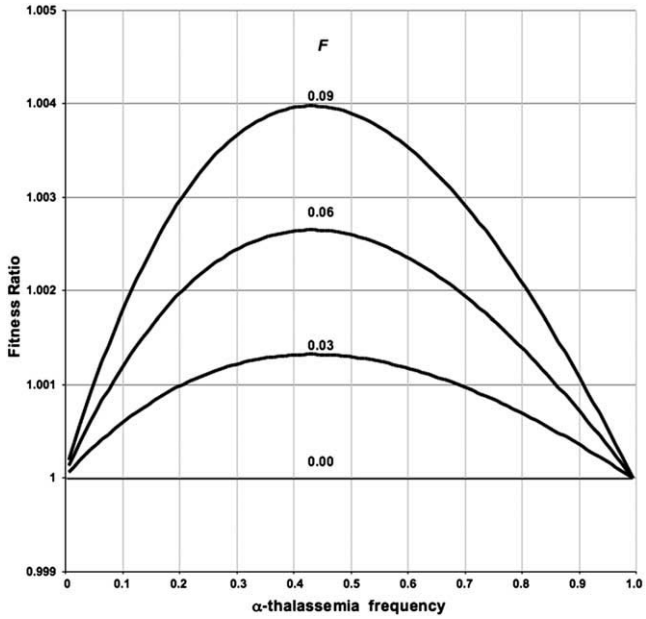


Fig. 2. Ratio of relative fitness of inbred ($F$=0.03, 0.06, and 0.09) vs. non-inbred ($F$=0) population (fitness ratio) at different frequencies of $\alpha^+$-thalassemia allele. The gain in fitness is for per one generation only.

## 4. Discussion

The overall consequence of consanguinity in a population, a sum-total of its harmful and beneficial genetic effects, cannot be precisely determined. This study was an attempt to gain an insight into the possible effects of human inbreeding by simulating relative fitness of a malaria-endemic population with both $\alpha^+$- thalassemia and hemoglobin S mutations. Our results suggest that the practice of consanguineous marriages, theoretically, could be beneficial for some populations with endemic malaria. The benefits of inbreeding are produced by the change of the speed of allele selection, i.e., the speed of adaptation which is increased for $\alpha^+$- thalassemia and decreased for hemoglobin S. This beneficial effect is most likely to occur when the frequency of $\alpha^+$-thalassemia allele is in the vicinity of 0.5 and the frequency of hemoglobin S allele is relatively low. Although the effect of inbreeding on relative fitness appears to be small, it compounds over generations —every next generation is bigger with a higher allele frequency. For $\alpha^+$-thalassemia, these results are in agreement with the findings that we have obtained using alternate methodology (Denic et al., 2007).

Any complex natural phenomenon is difficult to fit into a simple model. Here, we have ignored the effect of other recessive lethal genes that lower fitness of inbred populations. We have also ignored many beneficial recessive and codominant genes, which could increase the fitness of inbreeding populations. Further, we have assumed that selection of one allele is independent from another allele, which may not be true. The results of any simulation study depend of the values of parameters used. The value of *h* and *s* parameters were estimated for populations highly endemic for malaria, although the mortality from malaria varies between the regions and, in the same population, often changes from one generation to another (Carter & Mendis, 2002). Therefore, our results should be viewed as evidence that consanguinity, in addition to being genetically harmful, could have some beneficial effects that could ameliorate, at least partially, some of the harmful effects of inbreeding.

Consanguineous populations in regions with endemic malaria often have other genes protective against malaria like the β-thalassemia allele (Weatherall et al., 2002). This is exemplified by the native population of United Arab Emirates, where the rate of consanguineous marriages is 50% and the frequency of carriers with $\alpha^+$-thalassemia, hemoglobin S, and β-thalassemia gene is 50%, 2% and 8%, respectively (Al-Gazali et al., 1997; Baysal, 2001). β-Thalassemia is a lethal recessive gene; it may be reasonable to assume that an inbred population with β-thalassemia loses in relative fitness as much as it does with hemoglobin S. Thus, from Fig. 1, it follows that the net effect of inbreeding (that for $\alpha^+$-thalassemia minus twice the effects for hemoglobin S) could still be positive when the frequency of $\alpha^+$-thalassemia is around 0.5. Therefore, this native UAE population with a mean single-generation *F* of 0.022 may have benefited from the practice of consanguineous marriages in earlier times, before malaria was eradicated in the country by modern advancements.

Consanguinity is also practiced in West African populations with hemoglobin C (codominant protection against *P. falciparum*) and Duffy antigen negative blood group (recessive protection against *P. vivax*), which protect homozygotes better than heterozygotes and wild type homozygotes (Denic & Nicholls, 2007; Weatherall et al., 2002). These populations could have experienced an enhanced selection of hemoglobin C and Duffy antigen negative blood group.

However, multiple diverse historical scenarios are possible in the various populations in terms of the time and type of allele introduction, the intensity of selection pressure of malaria, the rate of inbreeding, and other factors that affect selection (Fig. 3). This causes difficulty of analyzing the net effect of inbreeding in populations with malaria. Furthermore, $\alpha^0$-thalassemia (deletion of both α-chain alleles on chromosome 16) is lethal in homozygotes, rare or absent in many consanguineous populations, and, thus, was not considered in this analysis (Denic & Nicholls, 2007; Weatherall & Clegg, 2001). Consequently, the overall effects of inbreeding on fitness will vary between populations and, in the same populations, will vary over time.

The coexistence of consanguineous marriages in many malaria-infested populations fit into a broader historical context of emergence of and human adaptation to malaria. The relative health of a population depends on the frequency

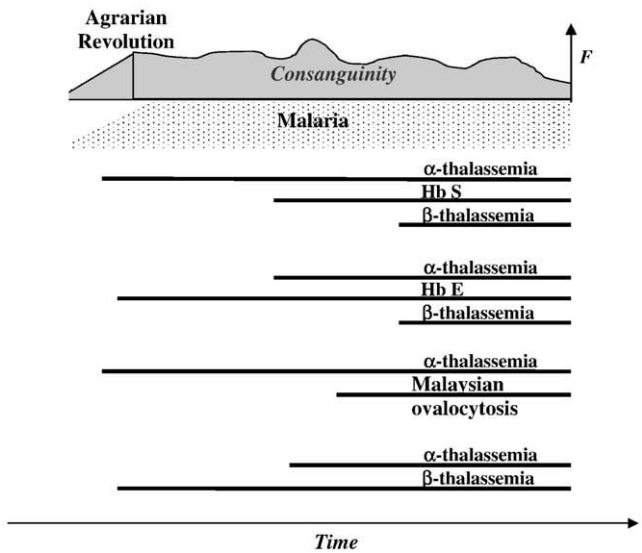


Fig. 3. Schema of possible historic scenarios showing the main variables that could affect population fitness: number and time of introduction of different genes protective against malaria, intensity of malaria infestation, and coefficient of inbreeding (*F*). Surge in malaria infestation is linked to the beginning of agriculture (ca. 10,000 years ago), which has caused population explosion and likely an increase in the rate of inbreeding, which may have accelerated selection of some antimalaria genes.

of protective mutation. When a single mutation was introduced into a big and expanding population of first agriculturalist, this initial boost in fitness was low due to its very low initial frequency. An increase in inbreeding decreases effective size of a population, and this increases the speed of mutation selection, frequency of allele, and, thus, the relative fitness. In growing populations of early human settlements, it made more sense for the kin, who survived the recurrent and deadly epidemics of malaria, to inter-marry; an outsider was less likely to carry the protective gene than the survivor of epidemic. In larger populations, this mating strategy produces relatively fitter offspring (homozygotes) than in smaller populations, e.g., the earlier hunter-gatherers. In the latter, the small size causes more inbreeding than in larger populations (Caballero & Hill, 1992; Denic et al., 2007). Indeed, an increase of inbreeding has been noted in animal and human populations under stress, e.g., after a cholera epidemic (Bittles & Smith, 1994; Madrigal & Ware, 1997; Marr, Arcese, Hochachka, Reid, & Keller, 2006). Therefore, the rate of consanguinity in growing human settlements most likely increased with an emergence of malaria because, under the new conditions of life, this mating strategy had a greater adaptive value.

Today, the selection pressure of malaria has partially abated. Yet, consanguineous marriages persisted and have even increased in some regions (Al-Gazali et al., 1997; Jurdi & Saxena, 2003). The reasons are unclear, but there may be several possibilities. First, more time may be needed to change the deeply entrenched cultural norms as "old habits die hard"; potential harms and benefits of inbreeding are differently appreciated in populations, for example, consanguinity rate in Japan has dramatically decreased in the last two generations (Saito, 1988). Second, consanguinity might persist after the burden of malaria has been lifted if the population is exposed to environmental pressures against which other recessive or codominant alleles provide protection. For example, active tuberculosis is up to six times less likely in homozygotes of the *MCP-1* allele variant and three times less likely in heterozygotes than wild-type homozygotes (Flores-Villanueva et al., 2005).

In order to determine the overall genetic effect of consanguinity, all lethal recessive genes must be taken into consideration. Additional anti-malarial genes and all other recessive and codominant genes protective against other major infections and other selection pressures must be factored in the final cost–benefit analysis of consanguinity. Simulation studies could help us address some of these issues, helping to create better insight on the opposing effects of inbreeding on population fitness, although we cannot be absolutely sure that these models adequately mimic reality.

Our findings provide a plausible hypothesis for explaining the confinement of consanguineous marriages to the tropical and subtropical regions where malaria is endemic and explain their absence in other parts of the World. As such, they complement the socioeconomic benefits theory of consanguinity (Alwan & Modell, 1997; Bittles, 2001; Khlat, 1997). If consanguinity produces more surviving offspring (higher fitness) in some malarious populations, then a better protection of these survivors of malaria, as per socioeconomic theory of consanguinity, would further add to family fitness. Although neither theory is experimentally testable, the theoretical arguments underpinning both, as well as their complementing picture, will further insight into the causes and effects of customs regarding human reproduction.

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