Glycophorin B is the Erythrocyte Receptor of Plasmodium Falciparum Erythrocyte-Binding Ligand, EBL-1

Citation

Published Version
http://dx.doi.org/10.1073/pnas.0900878106

Permanent link
http://nrs.harvard.edu/urn-3:HUL.InstRepos:3630585

Terms of Use
This article was downloaded from Harvard University’s DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA

Share Your Story
The Harvard community has made this article openly available. Please share how this access benefits you. Submit a story.

Accessibility
Supporting Information

Mayer et al. 10.1073/pnas.0900878106

SI Text

This supporting information (SI) considers some issues of population genetics in regard to the hypothesis that the null allele of glycoporphin B confers a selective advantage because of reduced susceptibility to Plasmodium falciparum malaria. The estimated frequency of the null allele in the Ituri forest pygmies is 0.59. Are there plausible scenarios of selection that could account for the null allele attaining such a high frequency in the relevant time frame? The answer depends on the time available, the initial null allele frequency in the population, the fitness advantage of homozygous null genotypes, and the degree of dominance affecting the fitness of null heterozygotes.

The time frame is likely bracketed by 10,000–100,000 years. The older date is an estimate of when P. falciparum malaria was spread around the world, and the more recent date corresponds to an expansion of infection with the introduction of swidden agriculture into Africa and the diversification of the Anopheles gambiae complex of mosquitoes. Both dates are based on the estimated times to coalescence of mitochondrial DNA lineages in the parasite (1). Assuming 20 years per human generation, 10,000–100,000 years corresponds to 500–5,000 generations. The initial allele frequency depends on the size of the population because it is reasonable to assume that the null allele was originally present in a single copy. We will assume population sizes of 1,000–10,000, yielding initial allele frequencies of 1/(2N) for the null allele.

The two selective scenarios are overdominance (homozygote superiority) and overdominance (heterozygous null). Overdominance implies a selective advantage of the heterozygous genotypes, and the values of s in the parasite gene ebl-1 range from 0.12 to 0.17 are consistent with a selective advantage of 1–2%.

The other selective scenario is heterozygous superior. With q = 0.59 in contemporary populations, it is not clear whether this is the equilibrium value or only a point on the trajectory toward the equilibrium value. For concreteness, we shall assume that q = 0.59 is the equilibrium value. To this end, suppose that the relative fitnesses of null, heterozygous, and homozygous null are s:1:1 – t. With random mating in a large population without mutation or migration, the equilibrium frequency of the null allele is given by t(1 + t)/(2s + 1), which for q = 0.59 implies that t = 0.695. For the relevant values of q0 and t, the required magnitudes of s and therefore of t are given in the lower part of Table S1. These values are again quite modest, which reinforces intuition in recognizing that, with heterozygote superiority, the initial selection depends on the fitness advantage of the heterozygous genotypes.

Several issues also arise in relation to genetic changes in the parasite postulated to have arisen in response to the increasing allele frequency of the null allele of glycoporphin B. The first is the haploid state of the erythrocyte stages, which allows selection to occur with maximal efficiency. The second is the short sexual generation time of the parasite, estimated as approximately 6 generations per year, which affords ample time for evolutionary changes to occur.

In regard to the specific run of Ts in the parasite gene ebl-1 resulting in a shifted reading frame that abrogates glycoporphin B binding, replication slippage in microsatellites is a prominent feature of mutation in P. falciparum (4). Although the relatively high frequency of the frameshift allele could be accounted for by random genetic drift, especially in view of the population bottleneck that the parasite experienced ~10,000 years ago (1, 4), positive selection cannot be ruled out. In addition, the high rate of new gene duplications observed in eukaryotic genomes (5) would easily provide the raw material for the diversification of the parasite DBL-EBP gene family by duplication and divergence.

It is probably more plausible to assume some degree of dominance less than additivity. The upper part of Table S1 assumes a 10% selective advantage for the homozygous null, based on the protective effect in sickle-cell heterozygotes (3) and indicates that values of h = 0.12–0.17 are consistent with a current null allele frequency of 0.59 after 500 generations. With partial dominance, most of the initial selection occurs in heterozygous genotypes, and the values of h imply a selective advantage in heterozygotes of only 1–2%.

We have also explored models in which h = 0 (data not shown), which implies that the fitness advantage of the null homozygote is completely recessive. We find that models with completely recessive effects can be excluded because they require highly implausible values for the selective advantage of the homozygous null (e.g., s = 4.0).

Several issues also arise in relation to genetic changes in the parasite postulated to have arisen in response to the increasing allele frequency of the null allele of glycoporphin B. The first is the haploid state of the erythrocyte stages, which allows selection to occur with maximal efficiency. The second is the short sexual generation time of the parasite, estimated as approximately 6 generations per year, which affords ample time for evolutionary changes to occur.

In regard to the specific run of Ts in the parasite gene ebl-1 resulting in a shifted reading frame that abrogates glycoporphin B binding, replication slippage in microsatellites is a prominent feature of mutation in P. falciparum (4). Although the relatively high frequency of the frameshift allele could be accounted for by random genetic drift, especially in view of the population bottleneck that the parasite experienced ~10,000 years ago (1, 4), positive selection cannot be ruled out. In addition, the high rate of new gene duplications observed in eukaryotic genomes (5) would easily provide the raw material for the diversification of the parasite DBL-EBP gene family by duplication and divergence.

Fig. S1. Expression profile of EBL-1. EBL-1 is expressed only in the schizont stages of intraerythrocytic development. R, ring; T, trophozoite; S, schizont.
Table S1. Parameter values for directional selection and overdominance

Parameter values for directional selection

<table>
<thead>
<tr>
<th>Time = 500 generations</th>
<th>Additive case (h = 0.50)</th>
<th>Partial dominance (s = 0.10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0005</td>
<td>s = 0.032</td>
<td>h = 0.12</td>
</tr>
<tr>
<td>0.00005</td>
<td>s = 0.041</td>
<td>h = 0.17</td>
</tr>
<tr>
<td>Time = 5,000 generations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0005</td>
<td>s = 0.0032</td>
<td>h = 0.12</td>
</tr>
<tr>
<td>0.00005</td>
<td>s = 0.0041</td>
<td>h = 0.17</td>
</tr>
</tbody>
</table>

Parameter values for overdominance (t = 0.695 s).

<table>
<thead>
<tr>
<th>Initial frequency</th>
<th>Time = 500 generations</th>
<th>Time = 5,000 generations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0005</td>
<td>s = 0.027</td>
<td>s = 0.0032</td>
</tr>
<tr>
<td>0.00005</td>
<td>s = 0.035</td>
<td>s = 0.0040</td>
</tr>
</tbody>
</table>