Beta thalassemia causes and symptoms

Beta-thalassema is an inherited autosomal-recessive blood disease affecting red blood cells. A mutation or deletion in the gene that codes for the beta chain of the hemoglobin molecule causes reduced (or in more severe cases, no) synthesis of the hemoglobin beta chain. This can cause anemia or other related symptoms in the patient. Beta-thalassemia is most prevalent in the region of the world surrounding the Mediterranean Sea (including Italy, Greece, Turkey, North Africa, and the Middle East), and also in areas of Southeast Asia (including India and southern China) and Melanesia (Galanello & Origa, 2010, p. 2). Beta-thalassemia is thought to be similar to sickle-cell anemia in that while the allele results in a highly problematic condition in the homozygous recessive state, it is thought to confer some resistance to malaria in the heterozygous state. Malaria was (and in some cases still is) highly prevalent in the warm, humid climate of subtropical regions such as those listed above, so the parasite could have exerted selective pressure on populations living in these areas, leading to many carriers of the beta-thalassemia allele. Thus, selective pressure exerted on subtropical populations leading to selection for beta-thalassemia alleles in the population and heterozygote advantage due to the malaria resistance conferred by having one normal and one beta-thalassemia allele can serve as an evolutionary, or ultimate, explanation for beta-thalassemia. The questions that must be answered about this hypothesized evolutionary explanation are: Does the beta-thalassemia trait confer some resistance to malaria? If so, what is the mechanism by which this occurs?

There are three clinically-recognized subtypes of beta-thalassemia that vary in terms of the severity of the disease. Which subtype an individual has

depends on their genotype: i. e. whether they are heterozygous or homozygous recessive for the beta-thalassemia allele and what, if any, modifier genes they possess. If a patient has one abnormal allele and one normal allele (that is, if they are heterozygous), they may not manifest any symptoms. If they do show symptoms, it is usually just a mild anemia, and is referred to as beta-thalassemia minor. Even if the individual is asymptomatic, however, they are still a carrier of the beta-thalassemia allele and can pass it on to their offspring. If an individual has two abnormal alleles (if they are homozygous recessive), they are said to have beta-thalassemia major. This form of the disease, as the name implies, is more severe and require more intensive treatment. Depending on the specific mutation or deletion involved in the disease, heterozygous or homozygous recessive individuals may also exhibit a form of the disease called beta-thalassemia intermedia. The severity of this form is in between that of the minor and major forms and is generally treated by blood transfusions as needed, although more severe symptoms may be present in some cases (Galanello & Origa, 2010, p. 2-3). Severity of symptoms is also mediated by modifier genes (Galanello & Origa, 2010, p. 4).

Beta-thalassemia major usually makes its presence known between the ages of 6 months and 2 years with severe anemia accompanied by other symptoms. “ Affected infants fail to thrive and become progressively pale. Feeding problems, diarrhea, irritability, recurrent bouts of fever, and progressive enlargement of the abdomen caused by spleen and liver enlargement may occur” (Galanello & Origa, 2010, p. 2). Untreated, beta-thalassemia major can lead to a variety of serious health problems, including

“ growth retardation, pallor, jaundice, poor musculature, genu valgum, hepatosplenomegaly, leg ulcers, development of masses from extramedullary hematopoiesis, and skeletal changes resulting from expansion of the bone marrow” (Galanello & Origa, 2010, p. 2). Individuals with beta-thalassemia intermedia generally do not develop symptoms until later in life, ranging from between 2 and 6 years of age for more severe beta-thalassemia intermedia to adulthood in less severe cases. Besides anemia, the health concerns associated with beta-thalassemia intermedia include enlarged spleen, leg ulcers, thrombosis, and bone deformities (Galanello & Origa, 2010, p. 3).

Treatment for beta-thalassemia varies depending on the subtype of the disease. It is generally not necessary to treat beta-thalassemia minor, as only slight anemia is present. Beta-thalassemia intermedia is treated with blood transfusions as necessary. Iron chelation therapy may be necessary due both to increased gastrointestinal absorption of iron and iron buildup from blood transfusions. Splenectomy may also be necessary in cases of enlarged spleen (Galanello & Origa, 2010, p. 11). Individuals with beta-thalassemia major require regular blood transfusions, along with iron chelation therapy to prevent the damage to organs associated with iron overload (Galanello & Origa, 2010, p. 7-9).

As stated above, beta-thalassemia is the result of a mutation or deletion in the gene that codes for the beta chain of the hemoglobin protein. Over 200 different mutations in this gene have been shown to cause beta-thalassemia, with symptoms of varying severity. The mutation may either cause reduced synthesis of beta-globin, or a complete absence of it. This, obviously,

determines the severity of the disease that the affected individual will experience (Galanello & Origa, 2010, p. 4). Also mediating disease severity are “ modifier genes.” “ In homozygous beta-thalassemia, primary genetic modifiers, affecting the clinical severity of the disease, include genetic variants able to reduce the globin chain imbalance, therefore resulting in a milder form of thalassemia. These factors are the presence of silent or mild beta-thalassemia alleles associated with a high residual output of beta globin, the co- inheritance of alpha-thalassemia and/or of genetic determinants able to sustain a continuous production of gamma globin chains (HbF) in adult life” (Galanello & Origa, 2010, p. 4). The frequency of specific mutant beta-globin genes differs between geographic regions where thalassemia is present, so that, for example, the actual alleles causing the disease may be different in someone of Mediterranean descent versus someone of Southeast Asian descent, even though their symptoms may be similar (Galanello & Origa, 2010, p. 4-5).

The beta-globin gene is found on the short arm of chromosome 11 (11p15. 4) (Thein, 2005, p. 650). “” Although more than 200 beta-thalassemia alleles have been characterized, population studies indicate that about 40 account for 90% or more of the beta-thalassemias worldwide. This is because in the areas in which it is prevalent, only a few mutations are common, with a varying number of rare ones, and each of these populations has its own spectrum of beta-thalassemia alleles” (Thein, 2005, p. 651). According to Thein (2005, p. 651), beta-thalassemia is rarely caused by deletions. “ The vast majority of beta-thalassemias are caused by point mutations within the [beta-globin] gene or its immediate flanking sequences” (Thein, 2005, p.

652). “ Approximately half of all beta-thalassemia mutations interfere with translation” (Olivieri, 1999, p. 101). The actual anemia of beta-thalassemia is caused by ineffective erythropoiesis due to a high ratio of alpha-globin chains to beta-globin chains (Olivieri, 1999, p. 101).

As stated earlier, beta-thalassemia is most common in the subtropical populations of the Mediterranean region, the Middle East, and Southeast Asia. “ In 1949, [J. B. S.] Haldane proposed the malaria hypothesis to account for the high frequency of thalassemic blood disorders observed in Mediterranean populations. He suggested that carriers of thalassemic genes might enjoy protection against malaria, which exacted a very high mortality in Southern Europe right up to the end of the Second World War” (Penman et al., 2009, p. 21242). This hypothesis bears a resemblance to the heterozygote advantage enjoyed by carriers of the sickle-cell gene in Africa, who also enjoy increased resistance to malaria at the expense of potentially passing on a deleterious allele to their offspring. The protective effect against malaria of another thalassemic disorder, alpha-thalassemia, has been more thoroughly studied, but several potential mechanisms and evidence for a protective effect of beta-thalassemia genes against infection by Plasmodium falciparum malaria have been proposed.

The “ adaptationist program,” proposed by Nesse and Williams (1994, p. 21-25), provides a useful paradigm to examine the possible evolutionary origins of beta-thalassemia. The adaptationist program can be used to deduce convincing evolutionary explanations for a variety of human diseases and medical conditions. The adaptationist program will now be applied to test the

hypothesis that beta-thalassemia alleles persist in subtropical populations because they confer heterozygote advantage.

As Haldane noted, the distribution of populations with beta-thalassemia alleles and the frequencies of the alleles in these populations correspond well with areas where malaria either currently is or historically was endemic. It is known that malaria parasites spend a stage of their lives in human red blood cells, and so, taking these two pieces of data into account, it can be surmised that the continued incidence of a genetic disease affecting red blood cells in areas where humans are frequently infected by parasites that invade red blood cells means that there is a connection between the two phenomena. There is also widely-known evidence that another disease affecting red blood cells, sickle-cell disease, persists in African populations because it confers some malaria resistance to heterozygotes. A study by Hill et al. (1988, p. 9) found that rates of beta-thalassemia in Melanesian populations were markedly higher in populations living in low-lying and highly malarious coastal areas as opposed to populations living in highland areas where malaria is less prevalent, and that the distribution of beta-thalassemia alleles showed an increasing gradient from the highland to the lowland populations.

Indeed, the relative absence of the sickle-cell allele in populations where beta-thalassemia is present offers more evidence in support of the hypothesis that carriers of the trait are protected from severe malarial infection in a manner similar to carriers of the sickle-cell allele. According to a study by Penman et al. (2009, p. 21242-21243), epistatic interactions between alpha-thalassemia alleles and sickle-cell alleles (which, like beta-

thalassemia, affect the beta-globin locus) can negate the malaria-resistance properties that each of these alleles alone would provide. However, no such negative epistatic interaction exists between alpha-thalassemia and beta-thalassemia alleles, and in fact individuals who are heterozygous for both thalassemia alleles have reduced thalassemia symptoms without reduced protection against malaria, so these alleles are more likely to co-exist in a population (Penman et al., 2009, p. 21246). Thus, in a population in a malarious area where alpha-thalassemia alleles are initially prevalent, beta-thalassemia mutations will be more likely to contribute to genetic fitness and thus persist in the population, whereas a malaria-prone population where alpha-thalassemia alleles are not initially prevalent will be more likely to contain a large prevalence of sickle-cell alleles (Penman et al., 2009, p. 21244). Beta-thalassemia alleles were historically maintained in Mediterranean populations alongside relatively lower rates of alpha-thalassemia alleles, while alpha-thalassemia alleles are virtually absent in areas of African (such as sub-Saharan Africa) where sickle-cell alleles are common and are generally only found in parts of Africa with lower prevalences of sickle-cell alleles (Penman et al., 2009, p. 21245). The fact that both sickle-cell disease and beta-thalassemia are present in populations in malarious areas but that they are prevalent in different malaria-prone populations provides evidence that beta-thalassemia alleles, like sickle-cell alleles, offer protection against malaria in the heterozygous state.

The exact mechanism by which beta-thalassemia heterozygosity protects against severe Plasmodium falciparum malaria infection is currently not known, but several hypotheses have been advanced. One is that the

abnormal beta-globin genes coded for by the beta-thalassemia allele cause premature death of red blood cells, which causes anemia (in symptomatic carriers, at least) but which also kills red blood cells containing malaria parasites before the parasites have a chance to mature and kill the cells themselves to continue their life-cycle. “ The [P. falciparum malaria] pathogen induces oxidative stress to the host erythrocyte, which triggers eryptosis, the suicidal death of erythrocytes” (Föller et al., 2009, p. 133). The malaria-infected red blood cells of a beta-thalassemia heterozygote undergo oxidative stress and age very rapidly, which causes them to be destroyed while they are still in the “ ring stage” of the infection, and this is thought to contribute to “ the partial resistance to malaria of the carriers of these erythrocytes” (Föller et al., 2009, p. 136). The mild anemia that this increased eryptosis of red blood cells may cause in a beta-thalassemia carrier thus appears to be an evolutionary trade-off for an increased resistance to malarial infection.

Another means by which carriers of beta-thalassemia alleles are hypothesized to be protected against severe malaria infection is by the increased expression of neoantigens against the malaria parasite on the surfaces of beta-thalassemia carriers’ red blood cells as opposed to homozygous dominant (i. e. non-thalassemic) individuals. This increased expression of neoantigens in turn causes increased binding of anti-malarial antibodies to the infected red blood cell, which of course will more rapidly trigger the immune system to fight the infection. Luzzi et al. (1991, p. 786) conducted a study in which cultures of red blood cells of beta-thalassemia heterozygotes and non-thalassemic individuals were infected with P.

falciparum malaria and exposed to serum from humans living in a malaria-endemic area (and thus likely to contain antibodies against malaria). The researchers “ found that P . falciparum-parasitized … beta-thalassemic red cells bind greater levels of antibody from endemic serum than controls” and that “[b]inding of antibody increased exponentially during parasite maturation” (Luzzi et al., 1991, p. 785). The researchers also hypothesized that, since beta-thalassemia carriers express more antibodies on the surfaces of their malaria-parasitized red blood cells, their “ degree of protective immunity or its rate of acquisition may be enhanced” compared to non-thalassemic individuals (Luzzi et al., 1991, p. 789). It appears that the abnormalities in the structure of the red blood cells of beta-thalassemia carriers causes increased expression of anti-malarial antigens and thus increased binding of antibodies and increased immune system activity against the parasite.

A third explanations for the increased malaria resistance of beta-thalassemia carriers include the red blood cells of beta-thalassemia carriers simply not being a very hospitable environment for malaria parasites to replicate in due to the cells’ structural abnormalities. A study by Pattanapanyasat et al. used a novel method of cell culturing involving biotin labeling and found that, although the red blood cells of beta-thalassemia carriers are as susceptible to infection by P. falciparum malaria as the red blood cells of non-carriers, “ in subsequent growth cycles, [beta-]thalassemia [red blood cells] were significantly less supportive of parasite growth than were normal [red blood cells]” (Pattanapanyasat et al., 1999, p. 3118). The abnormalities present in beta-thalassemic red blood cells, and possibly also simply the smaller size of

the cells, creates an environment that is less conducive to the reproduction of malaria parasites and thus allow the disease to be less severe in beta-thalassemia carriers. The red blood cells of beta-thalassemia carriers also contain higher than average levels of the heme analog zinc protoporphyrin IX, and the presence of this heme analog was found to inhibit the heme-detoxification process carried out by the malaria parasite inside the red blood cell and therefore could be another potential mechanism by which beta-thalassemia alleles reduce the severity of malaria infections in carriers (Martiney, Cerami, & Slater, 1996, p. 242-243). A final hypothesis, proposed by Wood et al. (1982, p. 286) holds that “[t]he low mean cell hemoglobin, elevated [fetal hemoglobin] level, and increased susceptibility to oxidant damage which characterize the red cells of heterozygous beta-thalassemia infants may combine to protect these infants against P. falciparum malaria.”

Applying the adaptationist program to beta-thalassemia, it seems likely that all the hypotheses proposed above are correct, at least on some level. The disease is most common in populations in subtropical areas of the world, the same areas in which malaria once was or still is endemic. It is also found in malarious areas that do not have a significant presence of the sicke-cell allele, thus hinting that beta-thalassemia alleles must serve as the inherited protection against malaria in these parts of the world in the absence of sickle-cell alleles. All of the factors posited above, or at least a combination of some of them, could combine to create in carriers of the beta-thalassemia allele a phenotype that inhibits the growth of Plasmodium falciparum malaria via several biological pathways and causes the individual to have increased resistance to malaria when compared to a non-carrier. Characteristics of

hemoglobin and red blood cells in early life could protect infant carriers when they are most vulnerable, and the other factors that make beta-thalassemia carriers' red blood cells inhospitable to malaria parasites combine to confer increased resistance to malaria in later life. It is also possible that the hypotheses presented above are each true for different populations that experience beta-thalassemia, since the number of different mutations that causes the disease is so large and since the P. falciparum parasites encountered in different regions of the world are also likely to have differing mutations to facilitate their survival in divergent environments. Perhaps the number of the above factors that a given beta-thalassemia carrier has " working for them," so to speak, in their fight against malaria is directly proportional to the severity of their disease symptoms. Beta-thalassemia appears to stand alongside sickle-cell disease in the ranks of genetic diseases that show a clear incidence of heterozygote advantage, which allows the disease to persist in a population, despite the problems associated with the homozygous-recessive state, because the heterozygous state provides a significant increase in survival and thus reproductive success and genetic fitness when compared to the homozygous-dominant " wild-type" state.

In summary, beta-thalassemia is a recessively-inherited autosomal blood disease that is caused by a mutation or deletion in the gene that codes for the beta chain of the hemoglobin molecule. This results in reduced or absent production of the beta-chain of hemoglobin and leads to red blood cells with structural abnormalities and creates anemia and associated symptoms in the patient. The disease presents in three distinct subtypes, which are

associated with different genotypes. There appears to be ample evidence that beta-thalassemia alleles persist in subtropical populations because they confer a partial resistance to infection by Plasmodiun falciparum infection in individuals heterozygous for the allele. Several mechanisms have been posited for this resistance, and it is possible that the collective presence of these mechanisms confers carriers with increased malaria resistance, or that certain effects are more predominant with certain alleles found in specific populations. This increased resistance to malaria thus confers greater genetic fitness to heterozygotes and allows the alleles to persist in subtropical populations. The adaptationist program of Nesse and Williams serves as a useful model for exploring the evolutionary causes of beta-thalassemia and the seeming paradox of the continued existance of a mutation that can be very harmful. It seems that beta-thalassemia is yet another one of the evolutionary compromises that has occurred during the long history of the human species as we adapt to the challenges of sharing our environments with pathogens.