ARTICLE IN PRESS

Blood Cells, Molecules and Diseases xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

Variability of homozygous sickle cell disease: The role of alpha and beta globin chain variation and other factors

Graham R. Serjeant[a,*], Elliott Vichinsky[b]

[a] Sickle Cell Trust (Jamaica), 14 Milverton Crescent, Kingston 6, Jamaica
[b] Hematology/Oncology, UCSF Benioff Children's Hospital Oakland, University of California San Francisco, 747 52nd Street, Oakland, CA 94609, United States

ARTICLE INFO

Editor: Mohandas Narla

Keywords:
Sickle cell disease
Beta globin haplotypes
Alpha thalassaemia
Fetal haemoglobin
Environmental factors

ABSTRACT

The single base molecular substitution characterizing sickle cell haemoglobin, β^6glu → val, might be expected to result in predictable haematological and clinical features. However, the disease manifests remarkable diversity believed to reflect the interaction with other genetic and environmental factors. Some of the genetic modifiers include the beta globin haplotypes, alpha thalassaemia, factors influencing the persistence of fetal haemoglobin and the effects of the environment are addressed in this review. It is concluded that much of the genetic data present conflicting results. Environmental factors such as climate and infections, and psychological, educational and social support mechanisms also influence expression of the disease. These interactions illustrate how the expression of a 'single gene' disorder may be influenced by a variety of other genetic and environmental factors.

1. Introduction

Sickle cell disease is a global public health problem affecting over 400,000 births annually [1]. The cause is a single point mutation which changes the behaviour of sickle haemoglobin (HbS) and has been designated as the first molecular disease [2]. The harmless carrier state for HbS known as the sickle cell trait has some protection from falciparum malaria during a critical period in early childhood [3] so that carriers are more likely to survive and pass on their genes. In the presence of falciparum malaria, the sickle cell trait has thus conferred a survival advantage which over the generations, has increased its prevalence to levels as high as 30% in some areas. The prevalence of the trait determines the frequency of sickle cell disease at birth, and the disease is widespread especially in sub-Saharan Africa and central India (Fig. 1). Sickle cell disease is characterized by increased haemolysis and blockage of flow in blood vessels and some of the marked variability in haematological and clinical expression is explained by the different genotypes of the disease resulting from the inheritance of HbS with other interacting haemoglobins. Focusing on homozygous sickle cell (SS) disease which is the single, most common genotype of sickle cell disease at birth, there is widespread diversity in features between different communities and sometimes between different patients in the same family. This report traces the search for the causes of this diversity within a 'single gene' disorder. It concludes that many other factors influence the haematological and clinical expression of the disease and although some of these are genetic, there are also important environmental determinants of severity. Genetic factors and their mode of operation may give valuable insights into new therapeutic approaches but environmental factors may be more readily manipulated. The evidence for these approaches is now presented.

2. Early observations

2.1. The first case reports

The first formal description of sickle cell disease was in a student from Grenada in the West Indies studying dentistry in Chicago between 1904 and 1907 [4]. Nearly 80 years later, the identity of this first patient was learnt from Herrick's original papers as Walter Clement Noel [5]. Although this case report long preceded the development of haemoglobin electrophoresis and more definitive diagnostic procedures, the blood film in Herrick's case leaves little doubt that the patient had homozygous sickle cell (SS) disease. Over the next 12 years, 3 more cases with similar features were reported and Mason [6] reviewed the features of these first four patients noting that all were of African origin (Fig. 2). This led to the common misconception that the disease was confined to persons of African origin and although consistent with the observed distribution of the disease throughout North and South America and the Caribbean, it was later recognized to be common in other racial groups.

* Corresponding author.
E-mail addresses: grserjeant@gmail.com (G.R. Serjeant), evichinsky@mail.cho.org (E. Vichinsky).

http://dx.doi.org/10.1016/j.bcmd.2017.06.004
Received 13 March 2017; Received in revised form 10 June 2017; Accepted 19 June 2017
1079-9796/ © 2017 Elsevier Inc. All rights reserved.

Please cite this article as: Serjeant, G.R., Blood Cells, Molecules and Diseases (2017), http://dx.doi.org/10.1016/j.bcmd.2017.06.004

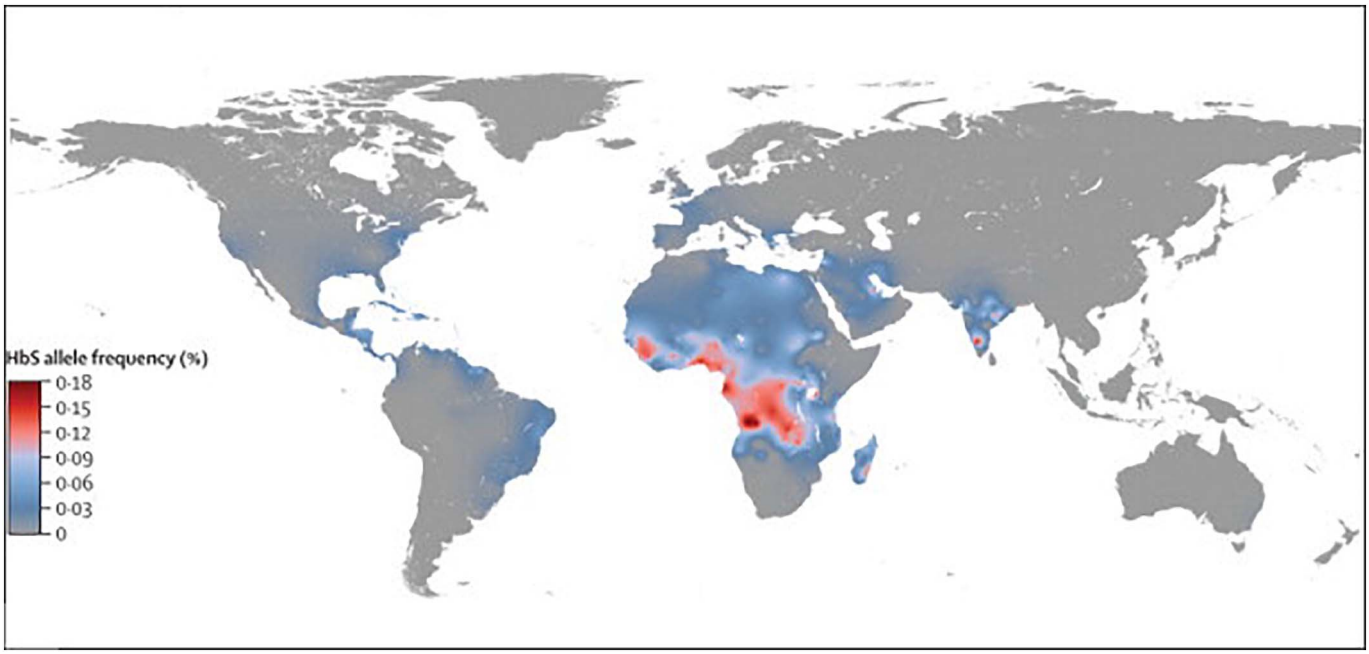
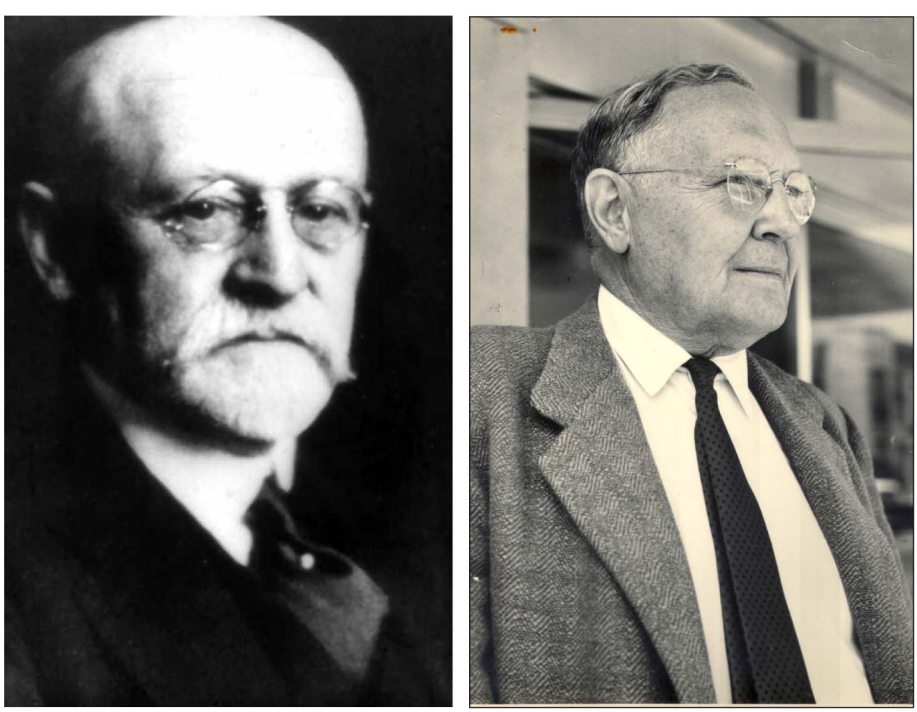


Fig. 1. Map of the distribution of the HbS allele frequency (adapted from the Lancet 2013 and kindly supplied by Dr. Frederic Piel).

2.2. Patterns of inheritance

Confusion emerged from the first studies of inheritance. In the third reported case [7], an early sickle cell test [8] was positive in the patient but also in the asymptomatic father leading to the concept of active and latent sickle cell disease [9]. It was not until 1949 that Neel and Beet working in totally different settings of the United States and the then Southern Rhodesia confirmed that the disease usually resulted from the inheritance of the sickle cell gene from both parents [10,11]. Asymptomatic carriers of the sickle cell gene were termed the sickle cell trait or AS genotype and persons with the disease as homozygotes or SS disease. This inheritance pattern which implied a simple relationship between the frequencies of the sickle cell trait and sickle cell disease in a population did not fit the observations in Africa where high trait frequencies occurred yet few cases of the disease were found [12–14] prompting the former to note that the early death of homozygotes in Africa would represent 'such a slaughter of the innocents that it would not have gone unnoticed'. It soon became clear that such an attrition was indeed occurring [15–17] and homozygous inheritance for much of the disease was confirmed. If both parents have the sickle cell trait, there is a 1 in 4 chance of an offspring with SS disease at each pregnancy (Fig. 3). Regardless of the outcome of each pregnancy, the risks



Dr. James Herrick **Dr. Verne Mason**

Fig. 2. Dr. James Herrick (1861–1954) described the first published case of sickle cell disease in 1910 and Dr. Verne Mason (1889–1965) described the 4th case (see text).

Download English Version:

https://daneshyari.com/en/article/8648044

Download Persian Version:

https://daneshyari.com/article/8648044

Daneshyari.com