

The Genetics of Benign Neutropenia

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ABSTRACT: In Israel, Yemenite Jews and other populations including Ethiopian Jews and Bedouins have a low neutrophil count. This phenomenon has been called “benign neutropenia” since it has not been associated with any increased risk of infection and has also been described in other populations around the world including Africans, African Americans and Afro-Caribbeans. Here we describe the recent success in mapping the gene that underlies benign neutropenia in African American populations. We discuss the known function of the gene and consider potential mechanisms for the effect on neutropenia. We also consider the possibility that this gene underlies the same effect observed in Yemenite Jews, Ethiopian Jews and Bedouins in Israel.

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Neutrophils normally comprise most circulating leukocytes and are a critical part of the innate immunity against bacteria and fungi. When the neutrophil count decreases in patients undergoing myelosuppressive therapy or in patients diagnosed with bone marrow malignancies, the risk of infection is increased. The risk for infection is highest when the neutrophil count is less than 500/mm³ for a prolonged period.

Traditionally, an absolute neutrophil count < 1500 cells/mm³ in persons over 1 year old is defined as neutropenia, regardless of ethnicity. The severity of neutropenia is categorized as mild when the absolute neutrophil count is 1000–1500 cells/mm³, moderate when 500–1000 cells/mm³, and severe when less than 500 cells/mm³. The risk of infection is related to both the severity and duration of the neutropenia. There is some controversy about the definition, especially since some ethnic groups are known to include healthy individuals with low neutrophil counts [1].

Benign neutropenia, defined as neutropenia in otherwise healthy subjects, has been observed in different groups, such as Africans [2], African Caribbean people [3], Ethiopians, Yemenite Jews [4,5] and certain Arab

populations [4]. Since it is much more common in specific ethnic groups, benign neutropenia is also defined as “ethnic neutropenia.”

EPIDEMIOLOGY OF BENIGN NEUTROPENIA

Several studies have recorded the relative rates in healthy individuals from different ethnic groups. In the United States, data from the 1999 to 2004 National Health and Nutritional Examination Survey (NHANES) were used to describe differences in blood counts related to age, gender, ethnicity and smoking, focusing on the neutrophil counts in African Americans [6]. Using a cutoff of < 1500 neutrophils/mm³, the authors reported that the prevalence of neutropenia was 4.5% among black participants, 0.79% among white participants, and 0.38% among Mexican American participants. The prevalence of neutropenia was higher among males and children younger than 5 years old. Neutrophil counts lower than 1000/mm³ were observed in less than 1% of the overall sample (0.57%, 0.11% and 0.08% in black, white and Mexican American participants respectively).

Comparing the prevalence of neutropenia between different studies is difficult since the definition of neutropenia varies among studies. However, a number of studies in Israel have systematically tested several populations. Weingarten et al. [5] reported a prevalence of 15.4% neutropenia, using a cutoff of < 2000 neutrophils/mm³ in both Ethiopian Jews and Bedouin Arabs.

CLINICAL FEATURES OF BENIGN NEUTROPENIA

Patients with benign ethnic neutropenia do not appear to have any difference in outcomes from infection when compared to patients without neutropenia from the same ethnic population [7]. In addition, they appear to have normal bone marrow morphology and their other leukocyte counts are normal [7–9].

INSIGHTS INTO THE MECHANISM OF NEUTROPENIA

Some authors have suggested that benign neutropenia may be from a possible diminished bone marrow neutrophil reserve, while others point to a defect in release of mature white blood cells from the bone marrow to the peripheral circulation. The number of granulocyte plus granulocyte-macrophage colony-forming units was lower in the bone marrow of healthy African and Afro-

Benign neutropenia is prevalent among Yemenite Jews, Ethiopian Jews and Bedouins as in other populations around the world including Africans, African Americans and Afro-Caribbeans

Caribbean subjects compared to healthy age and gender-matched Caucasians [10]. However, there was no evidence of any qualitative difference between the colony-forming units of the two ethnic groups and there was similar sensitivity to granulocyte-monocyte colony stimulating factor and similar enhancement of growth when cultured with a larger range of cytokines. These observations suggest that ethnic neutropenia may be a result of reduced numbers of bone marrow progenitor cells.

Phillips and co-authors [11] compared the neutrophil response among African American and Afro-Caribbean to that of European American healthy volunteers challenged with 10 minutes of exercise. The absolute increase was lower among the African American and Afro-Caribbean participants [11]. Shoenfeld et al. [12] compared the response to an intravenous injection of 200 mg hydrocortisone sodium succinate in Yemenite Jews (with and without neutropenia) and 18 non-Yemenite Jews [12] and found a smaller increase in neutrophil count in the Yemenite Jews. In another study, Shoenfeld and team [13] assessed the magnitude of labor-induced leukocytosis in 44 Yemenite Jewish women by comparing their hematological values during labor with those of 27 non-Yemenite women. A significant difference was found in the absolute counts of the white blood cells during delivery between the two groups, the values being lower among Yemenite Jews, and similar findings were detected among their infants. The low white blood cell counts in the Yemenite group at parturition were also associated with significantly lower plasma cortisol. The results from these studies – namely, the relationship of exercise, steroid administration and labor to a marginal pool of neutrophils – suggest a lowered bone marrow response to stressful stimuli. It has been suggested that a low grade of inflammation is the reason for this relative neutropenia, but Yemenite Jews do not have a low grade of inflammation compared with other populations [14]. Thus, the effect involves both bone marrow production and the migration process out of the margination pool.

Since molecular genetic and statistical techniques for gene mapping have advanced substantially, new insights have recently been gained about the etiology of benign neutropenia. Although benign neutropenia is not associated with any clearly reported negative consequences, better insight into the cause of benign neutropenia may help us understand the normal physiology of neutrophil production and circulation, which may ultimately help us to more effectively treat neutropenia resulting from chemotherapy and/or immune deficient diseases.

EVIDENCE FOR A GENETIC EFFECT OF ETHNIC NEUTROPENIA

To determine what proportion of a disease is due to genetic factors, researchers often use family studies, particularly twin

studies. Twin studies compare the correlation of a trait between monozygotic twins and dizygotic twins. Assuming that monozygotic and dizygotic twins share the same environmental influences, a stronger correlation in the monozygotic twins implies a genetic contribution to the trait. Using these assumptions, one can calculate “heritability” – the proportion of variability in the trait that is attributable to genetic factors. Garner and collaborators [15] evaluated the heritability of various hematological parameters using a twin study. They commented that a relatively high proportion of the variation in white blood cell count (~64%) could be attributable to heritable factors.

In addition, few studies of benign neutropenia demonstrated a familial recurrence. Shoenfeld et al. [4] reported an excess of neutropenia among relatives of Yemenite Jews with neutropenia and also noted a higher rate of neutropenia among relatives of both Ethiopian Jews and Bedouin Arabs with neutropenia [4].

SEARCHING FOR GENES IN POPULATIONS OF MIXED ANCESTRY: ADMIXTURE MAPPING

We recently identified the gene for benign neutropenia in African Americans [16,17]. The approach, admixture mapping, is a unique method of mapping genes in admixed populations [18]. Admixed populations are populations in which two or more different populations have been mixing over several generations [19]. For example, African Americans who have mixed African and European ancestry are considered an admixed population [20].

In order to have a context for understanding how admixture mapping works, it is useful to briefly review some of the basic factors underlying human population genetics. Anthropological and genetic studies support the view that all human populations are descended from African populations that migrated out of Africa less than 100,000 years ago [21]. As a result, human populations around the world share most of the same genetic variations (polymorphisms) [22]. However, some polymorphisms are unique to one racial or ethnic population, and others may have a very high frequency in one population but very low frequency in others. Such polymorphisms are referred to as ancestry informative markers [20,23]. The vast majority of polymorphisms, including the ancestry informative markers, are thought to be biologically and medically irrelevant. However, a subset of polymorphisms affect or are associated with either protein function or expression and some of these changes lead to differences in susceptibility to disease, disease outcomes, and response to medications. The ancestry informative markers that are biologically significant may lead to some of the clinically relevant differences we observe among members of different populations [18].

Admixture mapping, is a unique method of mapping genes in admixed populations. In admixed populations the disease-related gene and the genetic polymorphism are in enhanced linkage disequilibrium

To locate the genes that underlie differences between populations in health-related traits it is sometimes useful to focus on populations of mixed ancestry. The advantage of recently admixed populations can be seen in Figure 1. After several generations of admixture, recombination between chromosomes from the different ancestral populations leads to chromosomes that are a mosaic of mixed ancestry [Figure 1]. If a polymorphism that causes disease is more common in one of the ancestral populations, the cases will share the same genetic ancestry at the locus for this polymorphism [Figure 2]. Thus, by looking for regions where cases share the same genetic ancestry in an admixed population, we can identify polymorphisms that underlie disease.

The rationale for focusing on recently admixed populations is that the disease-related gene and the genetic polymorphism

Figure 1. Chromosomes in an admixed population. Each generation represents a schematic representation of the ancestry of chromosomes. After one generation of admixture, some individuals have ancestry from both population 1 and population 2. In subsequent generations, due to recombination, the chromosomes become mosaics with ancestry from both population 1 and population 2.

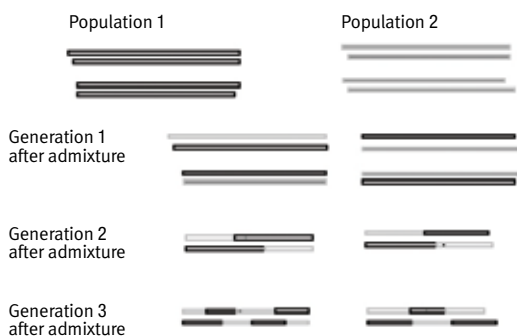
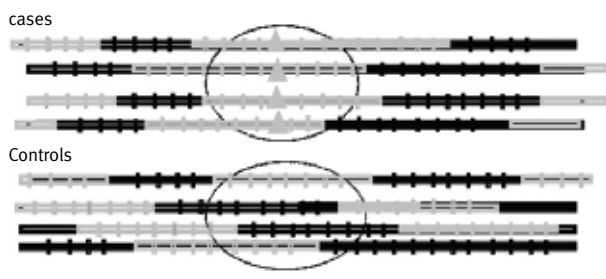


Figure 2. Schematic of admixture mapping. A polymorphism that causes disease has an allele that is more common among one population (represented by the gray triangle). This allele is found more commonly in cases than in controls since it increases the risk of disease. The cases then tend to share ancestry at the region around this polymorphism. Therefore, by typing ancestry informative markers (solid gray and black lines), geneticists can find a region of shared ancestry (circled in cases), which should harbor the causative marker, without knowing anything about the position of the causative marker.



are in enhanced linkage disequilibrium. Linkage disequilibrium is useful in genetic mapping since the causative polymorphism, which is not likely to be directly genotyped, can be “tagged” by other markers. The more linkage disequilibrium there is, the fewer markers are needed to be typed to cover all the potential causative markers. In recently admixed populations, since the admixture occurred only several generations ago the ancestry informative markers are likely to be in linkage disequilibrium over large distances. This means that few markers can be used to span very large distances. Once a particular region (or locus) has been associated with a trait, additional markers can be typed within the region until the causative marker is identified.

African Americans are considered an admixed population since they are known to have both African and European ancestry. It has been shown that relatively few markers (~1000–2000) can be used for admixture mapping in African Americans. Since benign ethnic neutropenia is known to be common in populations of African descent, but less so in European populations, admixture mapping would be a natural approach to search for the genetic determinants of benign ethnic neutropenia.

ADMIXTURE MAPPING OF BENIGN ETHNIC NEUTROPENIA

We studied African Americans to identify the genetic locus that determines the lower white blood cell count in this population [16]. We genotyped approximately 1300 markers that were known to be informative for European as compared to African ancestry.

The evidence overwhelmingly pointed at a locus on chromosome 1q22. One polymorphism could explain all the differences in the white blood cell count between African Americans and European Americans [Table 1]. This polymorphism was selected because it was known to have a high allele frequency difference between Africans and Europeans and thus is helpful in admixture mapping. However, subsequent investigation demonstrated that this polymorphism appears to be the causative marker in this population [17]. The effect of this polymorphism appeared to be the only marker in the region that

Table 1. White blood cells among African Americans and Caucasians in the Health ABC study

	WBC in African Americans		WBC in Caucasians	
All participants	N=448	5.1 (1.5)	N=1350	6.1 (1.4)
DARC null homozygote (FY-/-)	N=308	4.7 (1.1)	N=0	–
DARC heterozygote (FY+/-)	N=120	5.9 (1.4)	N=26	5.8 (1.2)
DARC + homozygote (FY+/+)	N=20	6.8 (1.1)	N=1324	6.1 (1.3)

The first row demonstrates the difference among all African American and Caucasian participants ($P < 0.0001$). The second through fourth rows demonstrate the white blood cell (WBC) count stratified by Duffy genotype. When comparing individuals of the different groups with the same genotype, there is no significant difference. Therefore, the lower WBC count among African Americans is due to the higher frequency of the FY-/- genotype. (Adapted from Nalls et al. [16])

could explain the association with ancestry, even after many additional markers were typed in the region.

The polymorphism mapped in this population is within the Duffy antigen receptor chemokine (*DARC*) gene. This gene encodes the Duffy antigen, a chemokine receptor found on red blood cells [24]. This allele, most common in African Americans, results in absence of expression of the gene product on red blood cells and is therefore called the “null allele” (Fy-). The Duffy antigen is used by the parasite *Plasmodium vivax* to enter the red blood cell [25]. Thus, carriers of two of the null alleles of the Duffy antigen are immune to *P. vivax* infection, and it has been proposed that the null allele underwent positive selection in West Africa due to this protective effect [26].

The Duffy antigen is expressed on red blood cells, capillary and post-capillary venular endothelial cells, but not on neutrophils or other mature white blood cell subtypes [27,28]. However, experimental evidence suggests that the Duffy antigen is involved in neutrophil localization and chemotaxis. The Duffy antigen promotes translocation of neutrophils across the endothelium in an in vitro experimental system [28]. In addition, interleukin-8/CXCL8 driven chemotaxis of neutrophils into infected lung tissue was reduced in transgenic mice without *DARC* gene expression [29], signifying the role of Duffy antigen in neutrophil response to chemotaxis. Plasma chemokine levels, particularly CXCL8 and CCL2, were higher in patients who were homozygous for the null allele vs. patients who were heterozygous following lipopolysaccharide stimulation of their whole blood in vitro [29]. Thus, the Duffy antigen appears to modulate chemokine levels, and, through that, neutrophil migration.

The effect on neutrophil count among homozygous carriers of the null allele is profound: the mean neutrophil count among homozygous carriers of the null allele is ~2.5, while the mean neutrophil count among heterozygous individuals or homozygous carriers of the allele associated with normal expression on red blood cells (Fy+) is ~4.0 [17]. This polymorphism explains the difference in mean neutrophil count between the African Americans who are homozygous carriers of the null allele and European Americans; there is no difference in neutrophil count among European Americans compared to African Americans who were heterozygous or homozygous for the Fy+ allele. However, while nearly everyone with neutropenia (neutrophil count < 1500 cells/mm³) is homozygous for the Fy- allele, most people who are homozygous for the Fy- allele are not neutropenic. Instead, the effect of Fy- homozygosity is to shift the mean neutrophil count down. Since the standard deviation of neutrophil count is relatively large, approximately 10–15%,

patients who are homozygous for Fy- have a neutrophil count < 1500 cells/mm³. There is substantial variation in neutrophil count in any individual over time; therefore, it is likely that many individuals with an Fy- allele cycle in and out of neutropenia.

RELEVANCE TO YEMENITE JEWS

Benign ethnic neutropenia among Yemenite Jews may also be attributable to the same gene. The null allele of the Duffy antigen is found in Yemenite Jews at a relatively common frequency of ~58% [30]. However, this is considerably lower than the allele frequency in African Americans (~80%). Since the effect on neutrophil count is only found in homozygotes, it is predicted that only ~36% of Yemenite Jews would be homozygous for the allele, and only these individuals would be at risk for neutropenia. The remainder of Yemenite Jews should have a neutrophil count that is no different than that found in other populations.

POTENTIAL MECHANISM

The mechanism by which the Duffy antigen affects the neutrophil counts remains unclear. Although neutrophils are known to adhere to endothelial cells and endothelial cells express the Duffy antigen, the Duffy null allele affects the expression on red blood cells but not on endothelial cells [31]. Transgenic mice with a complete knockout of the *DARC* gene have been produced, and they demonstrate a defect

in neutrophil translocation but no change in neutrophil counts [32]. However, these mice lack expression of any Duffy antigen on endothelial cells as well, and therefore the mice are not a good model for benign neutropenia in humans. Transgenic mice have also been created with an identical defect that eliminates expres-

sion on red blood cells, but there are no reported data on neutrophil levels or white blood cells in these mice [33].

Since the Duffy antigen on red blood cells can bind chemokines circulating in blood and thus reduce the level of chemokines circulating in blood, the Duffy antigen on red blood cells may act as a “sink” for circulating chemokines. The change in circulating levels of these chemokines may affect bone marrow recruitment and/or maturation of neutrophils. If this were the mechanism, then normal neutrophil counts may be restored among individuals with higher circulating chemokine levels, which override this “sink” effect.

Regardless of the mechanism, important questions remain. For example, although there is no evidence of a substantial defect in neutrophil function in patients with benign neutropenia [7], a more subtle effect that can be unmasked in the setting of severe infection/sepsis has not been ruled out

The polymorphism mapped in the neutropenic population is within the Duffy antigen receptor chemokine (DARC) gene. Duffy antigen appears to modulate chemokine levels, and, through that, neutrophil migration. We suggest that the absence of Duffy antigen is the cause of the observed neutropenia

[34]. Furthermore, some studies suggest that Duffy antigen is also important for neutrophil involvement in chronic autoimmune diseases such as rheumatoid arthritis [35]. Thus, it is possible that lack of Duffy expression may modify the progression of autoimmune diseases.

By understanding the involvement of Duffy antigen in orchestrating neutrophil function, we could learn more about both proper and improper function of the immune system. In addition, understanding the precise mechanism of neutropenia due to Duffy null allele status may lead to novel insights in the search for treatments for more severe types of neutropenia.

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“The art of being wise is the art of knowing what to overlook”

William James (1842-1910), American psychologist and philosopher who was trained as a physician. He wrote influential books on the young science of psychology, educational psychology, psychology of religious experience and mysticism, and on the philosophy of pragmatism. He was the brother of novelist Henry James