Pathobiology of Atherosclerosis: Are There Racial and Ethnic Differences?

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Ethnic differences in the prevalence of complex diseases such as atherosclerosis are undoubtedly multifactorial. It is clear that there are social, environmental, biologic, genetic, and other determinants leading to disparities in the rate of coronary heart disease among different ethnic and racial groups. Many epidemiologic studies have characterized the social and environmental factors leading to these differences, but there has been relatively limited investigation of the potential biologic and genetic factors involved. In this review, we will summarize currently available data on ethnic differences in cardiac risk factors, vascular biology, and genetic determinants of atherosclerosis.

[Rev Cardiovasc Med. *2004;5(suppl 3):S14-S21*]

Key words: Ethnicity • Atherosclerosis • Cardiac risk factors • Vascular biology • Genetics

Coronary heart disease (CHD) affects African Americans disproportionately.[1] It is well documented that cardiovascular morbidity and mortality rates are higher among African Americans than in the general US population.[1,2] The most recent data from the Centers for Disease Control and Prevention (CDC) reveal that African Americans have earlier and higher mortality rates from CHD than do either Whites, American Indian/Alaska Natives, Asian/Pacific Islanders, or Hispanics (Figure 1).[2] Ethnic differences in the prevalence of complex diseases

such as atherosclerosis are undoubtedly multifactorial. It is clear that there are social, environmental, biologic, genetic, and probably other determinants leading to the disparities in CHD. Many epidemiologic studies have characterized the social and environmental factors leading to these differences, but there has been relatively limited investigation of the potential biologic and genetic factors involved. In this review, we will summarize currently available data on ethnic differences in cardiac risk factors, vascular biology, and genetic determinants of atherosclerosis. Exploration of differences among ethnic groups is a means of learning more about this complex disease and will ultimately lead to improved understanding, prevention, and treatments for all patients.

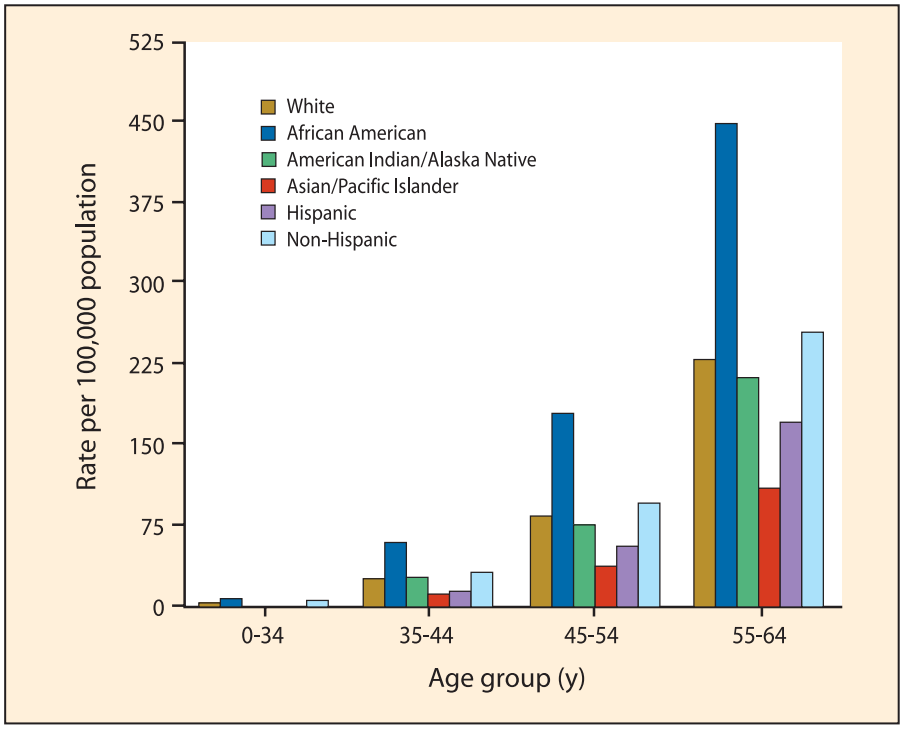


Figure 1. *Coronary heart disease mortality rates (2001) among persons < 65 years of age from different racial/ethnic groups. African Americans (dark blue bar) have higher CHD rates compared to all other groups. Reprinted with permission from Centers for Disease Control and Prevention.*[2]

Cardiac Risk Factors

Considerable information has been gathered about cardiovascular risk factors in ethnic populations. The major cardiac risk factors are the same in all ethnic and racial groups; however, the demographics and relative weight attributed to each factor may differ. Among African Americans, some of the excess CHD prevalence may be accounted for by the excess prevalence of known complicating risk factors such as hypertension, left ventricular hypertrophy (LVH), and diabetes mellitus. Differences in other risk factors, such as plasma lipoprotein profiles, may not explain disparities, but may lend insight into ethnic differences in the biology of atherosclerosis.

Hypertension

Compared with all other ethnic groups in the United States, hypertension in African Americans is more common, begins earlier, is more severe, and causes more target-organ damage.[3–6] Relative to Whites with hypertension, African Americans with hypertension demonstrate delayed sodium excretion, plasma volume expansion, lower plasma renin activity, elevated intracellular sodium concentration, and altered numbers and activities of sodium transporters (the Na+–H+ antiporter, Na+–K+ ATPase, and the Na+–K+–Cl- cotransporter).[7,8] Many of these differences may have a genetic basis. To possibly explain the greater prevalence and severity of hypertension in African Americans, several candidate genes have been explored. Genes encoding components of epithelial sodium channels,[9] the renin–angiotensin–aldosterone system,[10–12] α- and ß-adrenergic receptors,[13,14] endothelin,[15,16] kallikrein,[17] natriuretic peptides,[18] and the nitric oxide pathway[19] have all been investigated. To date, no compelling genetic explanations for ethnic differences have emerged.

Hypertension in part increases CHD risk by predisposing to LVH.[20] Left ventricular hypertrophy increases cardiac risk up to 4-fold and is more common in African Americans, even after adjusting for blood pressure.[1] The mechanisms by which LVH increases risk are poorly understood, but likely include predisposition to ischemia and arrhythmias.[21]

Insulin Resistance and Diabetes Mellitus

Type 2 diabetes is considerably more common in African Americans than Whites.[22–24] In the Atherosclerosis Risk in Communities (ARIC) study, the incidence of diabetes was 2.4-fold greater in African American women and 1.5-fold greater in African American men than in their white counterparts.[25] Excess adipose tissue accounted for almost half of the increased risk in African American women, but little of the excess risk

in African American men. African Americans with diabetes also have an increased risk of target-organ damage[26,27] and several studies have documented a higher prevalence of insulin resistance in African Americans, even after correction for obesity and lifestyle factors.[28]

It is clear that both genetic and environmental risk factors play critical roles in the development of type 2 diabetes; however, despite strong evidence of heritability, there has been little success in identification of specific genes. Numerous candidate genes have been investigated, and although some gene variants have been found that confer increased risk of type 2 diabetes,[29,30] many others have not been verified. No genes that explain genetic differences have been established.

Inflammation has been associated with diabetes by some investigators. Duncan and colleagues[31] examined the association between low-grade systemic inflammation and type 2 diabetes in 581 subjects with diabetes and 572 nondiabetic controls. An overall inflammation score based on inflammatory markers was assigned to each subject. The investigators found that an increased inflammation score predicted diabetes in Whites, but not in African Americans.

Due to the considerable cardiovascular risk conferred by diabetes, further studies exploring ethnic differences are essential in order to reduce disparities.

Lipoproteins

African Americans have similar or slightly lower total cholesterol levels, similar low-density lipoprotein cholesterol (LDL) levels, lower triglyceride levels, and higher high-density lipoprotein cholesterol (HDL) levels than Whites,[32,33] thus giving African Americans what would appear to be a more favorable lipoprotein profile. Despite this, African Americans have one of the highest CHD event rates of any ethnic/racial group in the United States. The more favorable lipoprotein levels do not appear to protect from CHD. The reasons for this remain unknown. One of the most striking differences regarding lipoprotein levels in African Americans is the higher HDL level. African Americans have HDL levels that are between 10% and 20% higher than Whites. This is likely due, at least in part, to the lower activity of the enzyme hepatic lipase in African Americans.[34] High-density lipoprotein protects against atherosclerosis by performing at least 3 functions: reverse cholesterol transport,[35] anti-inflammatory functions, and protection against LDL oxidation.[36–38] Despite the fact that HDL levels are higher in African Americans, little is known about HDL function in this population. Evaluating functional properties of HDL may help to explain the apparent lack of protection afforded by the higher HDL levels in African Americans.

Another lipid particle with significant racial variability is lipoprotein(a) [Lp(a)]. Lp(a) is structurally similar to LDL, with an additional disulfide-linked glycoprotein termed apolipoprotein(a) [apo(a)].[39] Apolipoprotein(a) shares extensive structural homology with plasminogen but varies in size due to variations in the number of plasminogen kringle-IV repeats. Several studies have shown that when Lp(a) levels are elevated, it is an independent risk factor for CHD in Whites.[40–43] Mean Lp(a) levels are more than twice as high in African Americans compared with Whites;[44] several studies have failed to establish a significant association between elevated Lp(a) levels and CHD in African Americans.[45,46] One explanation for this paradox may be in the size distribution of Lp(a). The size of an individual Lp(a) particle can vary substantially due to the genetic size polymorphisms of apo(a). The presence of small apo(a) isoforms (with fewer kringle-IV repeats) has been associated with CHD, regardless of total Lp(a) level.[47,48] The majority of Whites with elevated Lp(a) possess at least one small apo(a) isoform; however, the majority of African Americans with elevated Lp(a) do not.[49] When African Americans have elevated Lp(a) levels in conjunction with small apo(a) isoforms, a significant association with CHD has been found.[50]

Vascular Biology

A perplexing fact regarding CHD in African Americans is that despite suffering more cardiac events, African Americans have less coronary atherosclerotic lesions as detected by angiography[51] or autopsy,[52] and also appear to have less atherosclerotic plaque burden as detected by coronary artery calcium.[53] It appears that for a given plaque burden, acute atherosclerotic events are greater in African Americans, suggesting that the biology of the arterial wall and of the atherosclerotic plaque may be different. It is now recognized that atherosclerosis is a complex disease, adversely affected by a wide variety of processes including inflammation, oxidative stress, endothelial dysfunction, and abnormal vascular reactivity. These parameters may help explain the increased risk of atherosclerotic events in African Americans, despite their having less atherosclerosis.

Endothelium-dependent vasodilatation is significantly impaired in African Americans compared with Whites, even in healthy, young individuals.[54] Endothelin-1 (ET-1), the potent vasoconstrictor, may be involved. Plasma levels of ET-1 are higher in African Americans than in

Whites.[15] Furthermore, the relative density of endothelin-receptor subtypes A and B (ETA and ETB) on vessels has also been found to differ by race. Ergul and colleagues[16] detected the presence of both ETA- and ETB-receptor subtypes on vessels obtained from African American patients; in contrast only ETA receptors were found on vessels from white patients. These differences in endothelin and endothelin receptors may, in part, explain differences in vascular reactivity.

Plaque disruption (plaque rupture or erosion) and subsequent thrombosis causes the vast majority of acute coronary syndromes.[55] Inflammatory mediators influence several biological processes that can promote atherosclerotic plaque disruption.[56] C-reactive protein (CRP) and other markers of inflammation have been found to be elevated in African Americans as compared to Whites.[31,57,58] African Americans also have increased prevalence of pro-inflammatory cardiac risk factors. It is conceivable that increased inflammation might promote plaque disruption and lead to more acute coronary events in African Americans despite their having a lower burden of atherosclerotic plaque.

Oxidative stress also appears to represent a key phenomenon in vascular disease and is involved in all stages of atherosclerosis from its initiation to the acute manifestations.[59] The major cardiac risk factors lead to increased oxidative stress by causing production of reactive oxygen species (ROS) by vascular cells. Oxidative stress may be a common mechanism by which various cardiovascular risk factors induce vascular damage.[60] Some evidence suggests that for a given level of a risk factor, oxidative stress is increased to a greater degree in African Americans as compared to Whites. Lopes and colleagues[61] evaluated the degree of oxidative stress induced by hyperlipidemia in African American and white subjects. The investigators measured plasma F2-isoprostane levels as a biomarker of oxidative stress and discovered that although baseline levels were the same, during acute experimentally induced hyperlipidemia, F2-isoprostanes increased more in African Americans than in Whites. Figure 2 summarizes some of the known vascular differences between African Americans and Whites. Further research will likely show additional differences and lend greater insight into atherosclerosis.

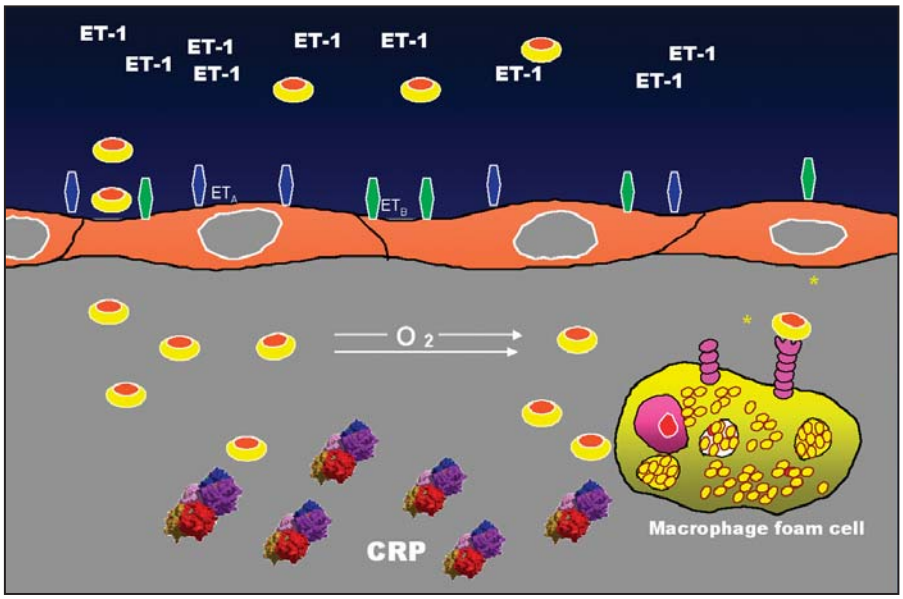


Figure 2. *Schematic representation of distinguishing vascular biology features in African Americans. Differences include elevated levels of circulating endothelin (ET-1), presence of both ETA- and ETB-receptor subtypes on the endothelial surface, increased reactive oxygen species (ROS) leading to increased levels of oxidized lipoproteins, and increased inflammatory mediators such as C-reactive protein (CRP).*

The recognized differences in vascular biology predict that there might also be differences in response to pharmacotherapies. To date there have been several reports of such differences, both in terms of efficacy and of toxicity.[62–64] A prominent example of this is angiotensin-converting enzyme (ACE) inhibitors. It is generally accepted that African Americans experience less blood-pressure lowering from ACE inhibitors than Whites. In the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT), African Americans randomized to the ACE inhibitors–based blood-pressure–lowering strategy had a systolic blood pressure that was 6 mm Hg higher than non–African American subjects allocated to this strategy.[64] It is also documented that African Americans have a higher incidence of angioedema to ACE inhibitors than do Whites.[65] This effect was verified in ALLHAT where the incidence of angioedema to ACE inhibitors was 0.7% in African Americans versus 0.3% in non-African American subjects.[64] Variations in drug concentrations, drug action, and receptor polymorphisms help explain why some patients respond well to certain medications, while others do not. Pharmacogenetics is the ability to identify genetic polymorphisms that alter drug responses and offers the potential to possibly

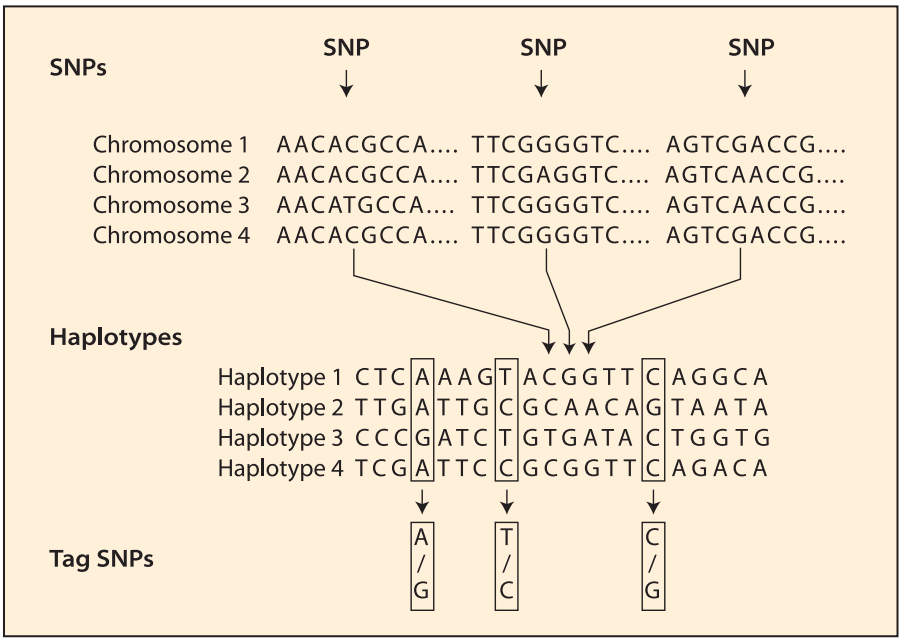


Figure 3. *Tagged SNPs marking distinct haplotypes. Reprinted with permission from The HapMap Consortium.*[72]

predict responses to medications. Unfortunately, our understanding of pharmacogenetics in African Americans is lacking, as is our understanding of genetic polymorphisms in general in this population.

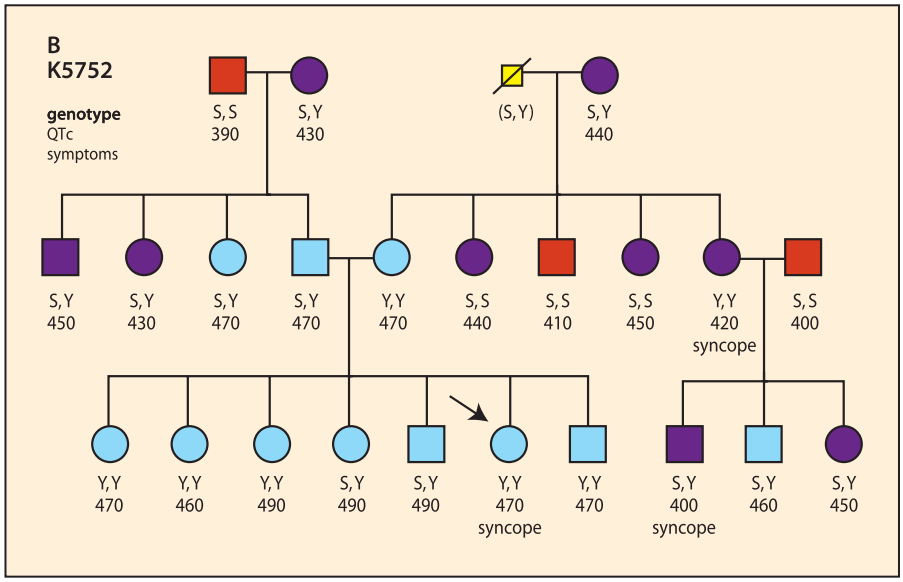
Genetics

Our lack of knowledge of specific predisposing genes for myocardial infarction (MI) and CHD among African Americans is particularly troubling. In recent months there has been a series of reports of genes and loci that underlie MI in Whites.[66–69] The first MI gene identified, a 21 base-pair deletion of myocyte-enhancing factor 2A (MEF 2A), was transmitted as autosomal dominant in a large white family.[66] Two papers that have published significant loci for MI on chromosomes 1 and 14 were in white populations.[67,68] Most recently, the first complex trait for MI, a gain-of-function haplotype of 5-lipo-oxygenase–activating protein (FLAP), was identified in Icelandic and confirmed in British white cohorts.[69]

In parallel to the work to decipher susceptibility genes in Whites, high throughput gene association work has been conducted in Japanese patients with MI. Ozaki and colleagues[70] studied over 65,000 single nucleotide polymorphisms (SNP) and identified 3 key SNPs on chromosome 6p21 in the lymphotoxin gene-α that are functionally pro-inflammatory. Yamada and associates[71] studied sporadic MI in over 4000 Japanese patients and found 4 SNPs that were gender specific, all related to inflammation pathways.

It is clear that in order to define the specific genes underpinning MI and CHD in African Americans, dedicated work will need to be performed to gather affected families. One of the helpful projects that will facilitate the ultimate identification of key genes is the current International Haplotype Map Project.[72] In this multinational, government-funded project, hundreds of individuals of all ethnicities and racial origins are undergoing complete genome sequencing and the essen-

Figure 4. *Pedigree structure and phenotypic classifications for African-American kindred 5752. The proband is indicated with an arrow. Individuals with prolonged QTc intervals (QTc ≥ 460 ms) are indicated by a blue circle (female) or blue square (male). Individuals with normal QTc intervals (QTc ≤ 420 ms) are indicated by red symbols. Individuals with uncertain phenotype (420 ms < 460 ms or QTc < 460 ms with symptoms) are indicated with purple symbols. Individuals without phenotypic data are indicated by the yellow squares and deceased individuals are indicated with a slash. Genotype, QTc, and symptoms are shown under each symbol. Genotype in parentheses is inferred. Reprinted with permission from Splawski et al.*[73]



tial tagged single nucleotide polymorphisms, which are the markers of distinct haplotypes, are being defined (Figure 3).

We are already aware of important interracial differences in a critical ion-channel gene associated with sudden cardiac death. The sodium-channel gene (SCN5A) is the basis of one of the channelopathies inducing long QT syndrome and sudden cardiac deaths. Recently, Splawski and colleagues[73] showed that a SNP in this gene (Y1102, a tyrosine substitution for serine S1102) is present in 13.2% of African Americans, but not present in Whites. From the initial kindred (Figure 4), it was shown how this sodium-channel SNP is linked to syncope and ventricular arrhythmias. It is estimated that 4.6 million African Americans[73] have this variant, making them susceptible to malignant ventricular arrhythmias. This is important in the context of MI and CHD. If an African American individual has an MI and also carries this common sodium-channel variant, there is the possibility that sudden cardiac death will be the initial presentation. In contrast, if an individual does not have concomitant genetic predisposition to a serious arrhythmia, the chance of surviving to present to a hospital would be enhanced. This type of reasoning is prototypic of racial- and ethnic-specific considerations in the new era of genomic, sequence-based medicine.

Conclusion

The various ethnic populations in the United States are far more similar with respect to many genetic and biologic traits than they are different. Nonetheless, observations of disease variation among ethnic groups can provide important keys to understanding the causes of complex genetic conditions like atherosclerosis. Dedicated studies are critically needed to assemble cohorts of African American individuals with MI and CHD in order to fully understand the specific susceptibility molecular basis of the disease. Such investigations can also lead to important advances in understanding pathophysiology and improving prevention and treatment. ■

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Main Points

- Among African Americans, some coronary heart disease may be accounted for by the excess prevalence of known complicating risk factors such as hypertension, left ventricular hypertrophy, and diabetes mellitus. Differences in other risk factors, such as plasma lipoprotein profiles, may not explain disparities, but may lend insight into ethnic differences in the biology of atherosclerosis.
- Relative to Whites with hypertension, African Americans with hypertension demonstrate delayed sodium excretion, plasma volume expansion, lower plasma renin activity, elevated intracellular sodium concentration, and altered numbers and activities of sodium transporters.
- African Americans with diabetes have an increased risk of target-organ damage and a higher prevalence of insulin resistance, even after correction for obesity and lifestyle factors.
- African Americans have HDL levels that are between 10% and 20% higher than Whites. Despite the fact that HDL levels are higher in African Americans, little is known about HDL function in this population. Evaluating functional properties of HDL may help to explain the apparent lack of protection afforded by the higher HDL levels in African Americans.
- It is conceivable that increased inflammation might promote plaque disruption and lead to more acute coronary events in African Americans despite their having a lower burden of atherosclerotic plaque.
- If an African American individual has a myocardial infarction and also carries a common sodium-channel variant, there is the possibility that sudden cardiac death will be the initial presentation. In contrast, if an individual does not have concomitant genetic predisposition to a serious arrhythmia, the chance of survival is enhanced. This type of reasoning is prototypic of racial and ethnic-specific considerations in the new era of genomic, sequence-based medicine.

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