

## Familial hypercholesterolemia in Brazil

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### Abstract

The Brazilian population has heterogeneous ethnic origins and is unevenly distributed in a country of continental dimensions. In addition to the Portuguese colonists until the end of the World War II Brazil received almost 5 million immigrants who settled mainly in the south and southeast. This features of the Brazilian population have two important consequences for the inherited diseases that are associated with an ethnic background: their frequencies are different in various regions of the country reflecting a variety of ethnic origins and variable degrees of admixtures. There was no report about the molecular basis of hypercholesterolemia in Brazil until our report in 1996 that the Lebanese allele is the most common cause of the disease in our country: 10 out of the 30 families were of Arab origin, and the Lebanese allele was detected in 9 of the 10 unrelated families of Arab origin. In addition, the abnormal gene is associated with the same haplotype at the LDL-R locus in all but one family, suggesting single origin for this mutation. Recently we described seven mutations in exons 4, 7, 12 and 14 and a new mutation in exon 15. In another region of our state, eight mutation already described and seven new mutations were described and interesting no common mutations were find. We can conclude that the complex history and structure of the Brazilian population, which was formed by the contribution of a large number of ethnic components that are in a state of increasing miscegenation, is reflected in the frequency and regional distribution of the more common hereditary diseases.

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The Brazilian population has heterogeneous ethnic origins and is unevenly distributed in a country of continental dimensions. In addition to the Portuguese colonists who settled in the country from the beginning of the 16th century, and about 2.5–4.0 million African Blacks brought as slaves, until the end of the World War II Brazil received almost 5 million immigrants who settled mainly in the south and southeast [1,2]. All those racial groups are gradually intermixing, although the regional differences are still notorious. The ongoing racial mingling was studied by Azevedo et al. [3] in the Island of Itaparica off the coast of Bahia, where the proportion of Mulattos has doubled and that of Whites has decreased to one-third in about 90 years. More recent studies on the basis of DNA markers also demonstrate the racial admixture of the Brazilian population. Although most of the original Amerindian population is now extinct, its genetic heritage has been in part preserved by the miscegenation with Whites and Blacks, especially in the north, where the contribution of Indian genes to the gene pool of the general population reaches 41% [4].

These features of the Brazilian population have two important consequences for the inherited diseases that are associated with an ethnic background: their frequencies are different in various regions of the country reflecting a variety of ethnic origins and variable degrees of admixtures, and no mutation can be contributed to understand the various aspects of anthropogenetic interest.

There was no report about the molecular basis of hypercholesterolemia in Brazil until our report in 1996 that the Lebanese allele is the most common (or one of the most common) cause of the disease in our country [5]. We expanded our study to 59 patients from 31 unrelated families and found a novel 4-kb deletion of the LDL-R gene in one; for the remaining 30 families, no gross abnormality of the LDL-R gene was detected [6]. However, 10 out of the 30 families were of Arab origin, and the Lebanese allele was detected in 9 of the 10 unrelated families of Arab origin [7]. In addition, the abnormal gene is associated with the same haplotype at the LDL-R locus in all but one family, suggesting single origin for this mutation [7,8]. The Lebanese allele, was described by Lehrman et al. in four unrelated Arab patients with familial hypercholesterolemia [9], is caused by a C (a nonsense mutation in exon 14 of the LDL-R gene) which creates a stop codon and leads to the production of a

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truncated receptor that is retained in endoplasmic reticulum. The mutation creates a *HinfI* restriction site that is the basis for a simple laboratory technique for its detection.

It is interesting that this mutation be so common at the cause of FH, since people of Arab origin constituted less than 1% of the immigrants to Brazil and their descendants still represent a small proportion of the country's population.

In 2000 we expanded our research and we described two new mutations in exons 7 and 14 and mutations already described in Italy, Netherlands and other European countries. [10]. On other hands Salazar et al. [11] in the city of São Paulo described in a population of hypercholesterolemic patients seven new mutations in exons 1, 10, 12, 14, 16 and 17 and others already described in European countries. The Lebanese mutation was not found.

We can conclude that the complex history and structure of the Brazilian population, which was formed by the contribution of a large number of ethnic components that are in a state of increasing miscegenation, is reflected in the frequency and regional distribution of the more common hereditary diseases. Although the population of Arab origin contributed with less than 1% for the present Brazilian population, the Lebanese mutation represents one of the most important (or the most important) cause of familial hypercholesterolemia in the country, probably owing to a founder effect and inbreeding among the first generations of immigrants.

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