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Research Article

Smith - Lemli - Opitz Syndrome: A Comparative Study Between the Mutations Found in Portugal and Other Countries and Correlation Genotype/Phenotype

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Abstract

Smith - Lemli - Opitz syndrome (SLO), is an autosomal recessive disease of the cholesterol synthesis, with 7 - dehydrogenase reductase deficiency.

Is characterized by craniofacial dysmorphism, 2 - 3 toes syndactyly, multiple congenital anomalies and psychomotor retardation.

The purpose of this study was compare mutations of Portuguese patients with SLO and other countries and also verify if any correlation between genotype/ phenotype and clinical severity with the cholesterol levels.

The others countries mutations were obtained after searching for the most recent manuscripts of medical journals.

The results showed predominance of the T93M mutation in Southern European countries and R352Q mutation only in Japan.

There is a heterogeneity of mutations in different countries.

Haplotypes in different ethnic populations may identify the origin and spread of mutations of the DHCR7 gene and perhaps explain the reason for the low frequency of SLO in non-Caucasians compared to Caucasians.

It may also explain why some of the mutations in the DHCR7 gene are more common in certain countries.

There is no correlation between the phenotype and the genotype.

The clinical severity is related to the plasma levels of 7 – dehydrocholesterol.

Keywords: *Smith-Lemli-Opitz; Mutations; Genotype/Phenotype*

Introduction

Smith - Lemli - Opitz syndrome (SLO), is an autosomal recessive disease of the cholesterol synthesis, with 7 - dehydrogenase reductase deficiency.

Is characterized by craniofacial dysmorphism, 2-3 toes syndactyly, multiple congenital anomalies and psychomotor retardation.

The incidence is around 1/20000, with more than 90 mutations described [1].

Purpose

Compare the mutations between Portuguese children with SLO and other countries and study if any correlation of genotype/phenotype.

Material and Methods

The mutations of Portuguese children (8 cases) with SLO were compared with those of other countries: Spain (20), Italy (12), Canada (30), United States of America (32) and Japan (7), with a total of 109 cases.

The results of the mutations of the other countries were obtained through the most recent studies found in international medical journals.

The genotype/phenotype correlation of the studied cases was also evaluated.

The phenotype was classified in:

• Mild (minor malformations, no mental retardation or slight mental retardation);
• Moderate (multiple malformations with mild to moderate mental retardation);
• Severe (multiple malformations with severe mental retardation).

The relationship between clinical severity and cholesterol levels were also study.

Results

- Portugal: 8 cases - 16 alleles. The mutations were: T93M - 31% and IVS8-1G> C - 25%.
- Spain: 20 cases - 40 alleles. Most frequent mutations were: IVS8-1G > C - 30% and T93M - 23%.
- Italy: 12 cases - 20 alleles. The common mutations were: T93M - 45% and IVS8 > C - 20%.
- Canada: 30 cases - 60 alleles with the most frequent mutations: IVS8-1G > C-4 0% and T93M - 8%.
- United States: 32 cases - 64 alleles with the most frequent mutations: IVS8-1G> C-34%. The other one is T93M - 12.5%.
- Japan: 7 cases - 13 alleles and the most frequent mutation was R352Q - 69% (Figure 1).

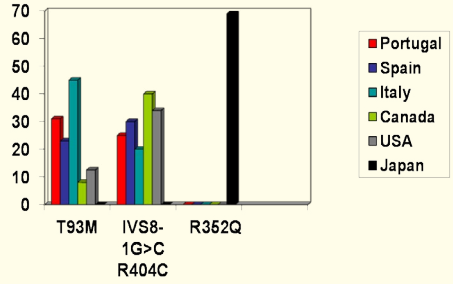

Figure 1: *Percentage of Mutations Prevalence in Portugal, Spain, Italy, Canada, USA, Japan.*

The correlation between genotype/phenotype and clinical severity and cholesterol levels are resumed in Figures 2 and 3 respectively.

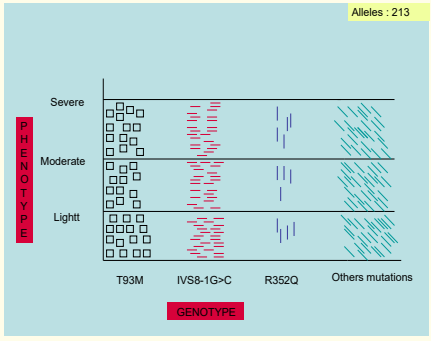

Figure 2: *Genotype/Phenotype Correlation.*

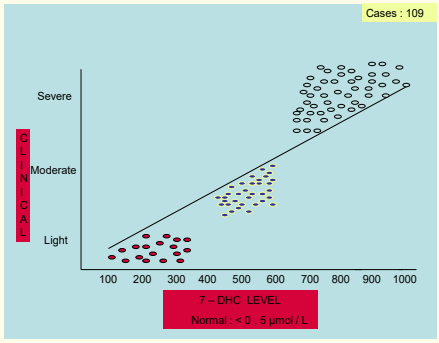

Figure 3: *Relation 7- DHC/Clinical Severity.*

Discussion

The T93M mutation in Portugal was the most frequent as in Italy. It is the second most identified in Spain and United States and third in Canada. This result confirms the predominance of the T93M mutation in Southern European countries.

The IVS8 - 1G> C mutation was the most frequent in the United States, Canada and Spain and only the second found in Portugal. However, the percentage found in Portugal is higher than in Italy.

The mutations found in Japan are different from those of the other countries, the most frequent being R352Q.This mutation appears to be specific to this country.

These results showed the heterogeneity of the mutations in the different countries [2-5].

Further investigation of the mutation spectrum and association of haplotypes in different ethnic populations may identify the origin and spread of mutations of the DHCR7 gene and perhaps explain the reason for the low frequency of SLO in non-Caucasians compared to Caucasians.

It may also explain why some of the mutations in the DHCR7 gene are more common in certain countries.

There is no correlation between the phenotype and the genotype. We can see in the Figure 2, that if we compare the three main mutations, IVS8-1G>C, T93M and R352Q, with the grade of severity of the phenotype is practically the same. We can have IVS8-1G>C or other genotype with light, moderate and severe phenotype.

The clinical severity is related to the plasma levels of 7 – dehydrocholesterol. In the Figure 3, we can observe that the phenotype is more severe, if the levels of 7- dehydrocholesterol are much higher. On the other hand, if the levels are low the phenotype is more atypical, with only few features on the clinical presentation.

Conclusions

We concluded that there is a heterogeneity of mutations in different countries. We didn't found correlation between phenotype and genotype in SLO children.

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