Study tracks mutations causing CDA II back to the Roman Empire

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Many of you might know that Congenital Dyserythropoietic Anemia type II (CDA II) is a rare blood disorder, due to a failure in final part of erythropoiesis. What will surprise you is the fact that some mutations responsible for the disease can be tracked 3.000 years back. A study led by the ENERCA member Prof. Achille Iolascon, from CEINGE Advanced Biotechnologies (Naples, Italy) and the University of Naples Federico II, analyzes two mutations (E109K and R14W) of the SEC23B gene and discovers one of them is responsible for the higher frequency of CDA II in Italian population. The first mutation, E109K, may have originated in the Middle East about 2.400 years ago and may have spread in the heyday of the Roman Empire. The other one may have originated in Southern Italy about 3.000 years ago.

ENERCA is an acronym for European Network for Rare and Congenital Anaemias. It started back in 2002, funded by the European Commission and led by Dr. Joan Lluís Vives Corrons, an investigator from the Hospital Clínic of Barcelona and the Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Its purpose is offering an improved public health service to professional medical practitioners and patients in every aspect of rare anaemias.

As many other kinds of anemia, CDA II is characterized by ineffective erythropoiesis. It leads patients to a decrease in the number of produced reticulocytes and a low concentration of hemoglobin in the blood. This shortage prevents the blood from carrying an adequate supply of oxygen to the body's tissues, resulting in various symptoms of anemia including:

tiredness (fatigue), weakness, pale skin, and other similar complications. It was first described in 1968, and soon became clear that the condition was heterogeneous, and three forms became well known, with type II being the most frequent.

CDA II is an autosomal recessive condition caused in most of the cases by a mutation in the SEC23B gene. Although many different mutations have been described, only 4 mutations account for more than 50% of mutant alleles. The present study, published in the American Journal of Hematology with Dr. Roberta Russo as the first author and Prof. Achille Iolascon as the last one, compares the relative allelic frequency of SEC23B mutations in two cohorts of cases, 64 Italian and 45 non-Italian European cases. The work shows that two mutations, R14W and E109K, are relatively common in both cohorts. Nevertheless, R14W variant showed a higher recurrence in Italian CDA II patients when compared to the rest of European patients (26.3% vs 10.7%), while E109K substitution showed almost the same allelic frequency between both groups (28.0% in Italian and 25.0% in NIE).

The fact that the R14W variant is more common in Italy could be explained by a positively selected mutation, which would mean that the mutation gives some kind of genetic advantage to its carrier, or a genetic drift resulting from a so-called founder effect. The investigators explain that it is difficult to imagine that mutations that give no known phenotype in the heterozygous state, and cause a disease in the homozygous state, can be positively selected. Therefore they suggest the second option as the most likely to explain the higher presence of the R14W variant in the Italian population.

A founder effect implies that identical mutant genes we see today have a single ancestral origin. The spread of the mutant gene may have been greatly favoured if at some stage a small population in which the gene was present has undergone rapid expansion. With a genetic analysis,

called Haplotype analysis, it is possible to provide estimates for the time of origin of a founder mutation.

The cases analyzed by the present work suggest that the E109K mutation might have been originated in Italian population approximately 2.200 years ago. These results are consistent with another study that estimates its origin 2.400 years ago in Israeli Moroccan Jews. As E109K is particularly common in this population, the authors hypothesize it was born in the Middle East 2.400 years ago and arrived in European regions approximately at the time of Caesar Augustus when Roman Empire had the maximum expansion.

On the other hand, for the most frequent mutation in Italian CDA II patients, R14W, the investigators estimated that this mutation would be originated approximately 3.000 years ago, at the time when much of Southern Italy was a Greek colony, the Magna Graecia. The geographic distribution of CDA II, showing a concentration of this disease in Southern Italy and in Mediterranean countries, supports the idea that a particular CDA II mutation arose or was introduced in Southern Italy, from where it might have spread over the rest of the country.

Provided by IDIBAPS