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Title:

THE Q359K/T360K MUTATION CAUSES CYSTIC FIBROSIS IN GEORGIAN JEWS

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What was your research question?

The Q359K/T360K mutation, described in Jews of Georgian descent is currently not recognized as a CF causing mutation by the CFTR2, the CF mutation database. We aim to establish this mutation as CF causing by describing its clinical characteristics and by exploring the mechanism of the development of disease (pathogenicity) of this mutation.

Why is this important?

Late diagnosis of CF is one of the causes of a more severe course of disease. Recognizing this mutation as CF causing will facilitate early diagnosis in this ethnic group. It will also enable pre-natal diagnosis in this population. New therapies for CF are mutation- specific. In order to find a cure for patients with

this mutation it is crucial to establish it as a CF causing mutation and to understand its mechanism of action.

What did you do?

We reviewed clinical records of all CF patients with the Q359K/T360K mutation from three CF centers in Israel. We collected data regarding their diagnosis, as well as their pulmonary and nutritional status. Computer models of the protein affected in CF - the CFTR, enable us to understand its 3-dimensional structure and its normal activity. In order to understand the mechanism of pathogenicity of the Q359K/T360K mutation we constructed computer models of the CFTR with this mutation and assess the changes in its structure caused by this mutation and its effect on chloride transport.

What did you find?

We found 9 patients of Georgian Jewish origin with this mutation. Four of them carrying a double mutation (homozygous). These patients were diagnosed with CF relatively late - median age of diagnosis- 9.4 years, range 0.25-38.2 years. All had abnormal sweat chloride. All had pulmonary symptoms since early childhood with typical CF bacteria in their airways. This mutation is associated with pancreatic insufficiency. The patients started pancreatic enzyme supplementation relatively late suggesting some early residual function of the CFTR in this mutation. Structural models of the mutant CFTR suggest that this mutation interferes with chloride transport through the cell wall (membrane).

What does this mean and reasons for caution?

Our results clearly demonstrate that the Q359K/T360K mutation is CF causing. The symptoms of patients carrying this mutation suggest that although it has features of a mutation with minimal function, some residual function of the CFTR exists in early childhood. Together with the structural models of the mutant CFTR we assume that this mutation is associated with interference of chloride transport through the chloride pore of the CFTR. Limitations of this study are the small sample and the fact that all data was collected retrospectively.

What's next?

We believe this mutation should be recognized as CF-causing mutation. Further investigation should be conducted to better characterize the class of this mutation. After being classified, patients with this mutation should be considered for the appropriate new generation medications

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