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Genomics 2021: Cytochrome CYP2D6 gene polymorphism and effectiveness of antibacterial therapy in cystic fibrosis patients homozygous for the F508del-CFTR mutation: A Review Article- Novoselova O.G, Research Centre for Medical Genetics, Russian Federation

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Objectives: Cystic Fibrosis (CF) is a systemic hereditary disease caused by CFTR gene mutation and characterized by the chronic respiratory infections. The severity of CF clinical manifestations depends on the type of CFTR gene mutations, modifier genes, environmental factors, including the positive and negative effects of therapy. F508del is the most common mutation worldwide. Xenobiotic biotransformation genes determine the individual profile of drug metabolism.

Subjects and methods: To study the effect of the polymorphic variant CYP2D6 * 4 (1846G> A), on the effectiveness of antibiotic therapy in cystic fibrosis patients homozygous for the F508del-CFTR mutation. The number of examined cystic fibrosis patients homozygous for the F508del-CFTR mutation was 71. All examined children are residing in the European part of the Russian Federation, 87.7% - from Moscow region. The sex ratio - 1.00 M : 1.09 F (34 M: 37 F). Age - from 5 months up to 40 years (mean age 14.47, Std 9.97). Polymorphism c.1846G>A of the CYP2D6 gene was studied by RFLP-analysis.

The most genuine indications are identified with the respiratory plot. Sinusitis happens when thick bodily fluid gathers in the sinuses hindering suitable freedom of particles which can be a site for disease. This outcomes in impeded aviation routes which can be a repository for disease and eventually lead to respiratory disappointment. Lung illness is the main source of horribleness and mortality in patients with CF. CF patients experience regular pneumonic intensifications which can give hack, chest blockage, expanded sputum creation, wheezing, windedness, and dyspnea on effort. In 2018, the most widely recognized respiratory microorganisms were Staphylococcus aureus 70%, Pseudomonas aeruginosa 44.4%, mycobacterial species 13.6%, Stenotrophomonas maltophilia 12.3%, and Burkholderia cepacia 2.6%. Generally, the level of patients with positive Pseudomonas aeruginosa has declined over the long run probably because of the current treatments forestalling the securing. Additional time as patients experience deteriorating lung sickness, aggravation expansions in the aviation routes prompting tissue obliteration. There are a few morphological changes that happen in the CF lung. The soonest indication of aviation route illness in CF patients is bronchiectasis which is found in about 29.3% of CF patients by 90 days old enough and 61.5% at three years old. Because of the amassing of thick bodily fluid, CF patients regularly experience bodily fluid connecting the aviation routes. Lung sickness is observed with different tests and imaging modalities including aspiratory work testing, chest x-beam (CXR), registered tomography (CT), and attractive reverberation imaging (MRI). In particular, constrained expiratory volume in one second (FEV1) is estimated to decide illness movement and reaction to treatment.

A few organs in the gastrointestinal parcel are influenced by CF including the pancreas, gallbladder, liver, and digestion tracts. In CF, pancreatic brokenness ranges in seriousness. Patients are marked as pancreatic adequate (PS) and pancreatic lacking (PI). This is resolved dependent on the measure of exocrine pancreatic function. Studies uncovered that roughly 85% of patients with CF are PI, and patients who are PS can foster PI for the duration of their lives. Patients with exocrine pancreatic deficiency can encounter gas, bulging, weight reduction, dyspepsia, and steatorrhea. Youngsters will frequently give inability to flourish. Intestinal indications of CF are normal; the most punctual show is meconium ileus in an infant. As CF patients age, this equivalent marvel can happen in grown-ups and is called Distal Intestinal Obstructive Syndrome (DIOS) which brings about fractional or complete inside deterrent that should be treated with diuretics and additionally bowel purges. In the small digestive tract the brutal stomach corrosive isn't killed by pancreatic chemicals prompting little intestinal bacterial abundance (SIBO); this can cause loose bowels, stomach agony, and weight reduction.

Results: When comparing two groups of CF patients (40 patients receiving intravenous antibiotic therapy ≥2 times per year and 31 patients receiving intravenous antibiotic therapy sporadically or not receiving at all), there is an increasing frequency of the CYP2D6 * 4 allele in the group of patients with a low incidence of broncho-pulmonary exacerbations, which do not require repeated courses of intravenous antimicrobial therapy within one year ($p < 0{,}046$). When comparing two groups of CF patients (34 carriers of the highly pathogenic flora of the respiratory tract and 37 carriers of the etiologically insignificant flora), the higher frequency nonfunctional allele of CYP2D6 in the group of patients with nonpathogenic flora of the respiratory tract ($p < 0.02$) was also observed.

Conclusion: The CYP2D6*4 carrier status is associated with a favorable course of the disease in cystic fibrosis patients

homozygous for the F508del-CFTR mutation, with a lower incidence of broncho-pulmonary exacerbations and a reduced risk of chronic colonization of the respiratory tract by the highly pathogenic flora. This observation is consistent with the assertion that the therapeutic effect can be achieved at lower doses of the drug in the case of the "poor metabolizer" phenotype. The data suggest the possibility of optimization of dosing regimens of antibacterial drugs based on genetically determined level of xenobiotic metabolism in patients with CF.

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