GENETIC ANALYSIS FOR CYSTIC FIBROSIS (*CFTR* gene) CASE 1

First name: Andrej
Surname: Kovacs
Gender: Male
Ethnic origin: Slovakia
Sample type: DNA

Date of birth: 14/03/2022
Place of birth: Bratislava
Your reference: CF23-1
Our reference: 230637366
Sample received: 05/04/2023

Reason for referral: Andrej Kovacs, a one-year-old boy, is referred by the paediatrician for *CFTR* testing due to recurrent bronchiolitis and chronic diarrhoea. Newborn screening result was positive (elevated IRT) and the sweat test result was intermediate (55 mmol/L). Andrej's parents are both of Slovak origin. There is no family history of cystic fibrosis. Molecular analysis is requested to confirm or exclude the diagnosis of CF.

Methods: we have performed the molecular study of the *CFTR* gene using the Elucigene CF-EU2v1 kit and analyzed in an ABI3130 genetic analyzer.*

Result: highly likely compound heterozygous for c.1521_1523delCTT, p.Phe508del, (traditional name: F508del) and c.3718-2477C>T, p.? (traditional name 3849+10kbC>T)
Genotype in HGVS: c.1521_1523delCTT(;)3718-2477C>T
Reference sequence: NM_000492.4

Interpretation: this result detects the presence of two pathogenic variants in heterozygosis in the proband. **The result confirms the clinical diagnosis of cystic fibrosis (CF).**
F508del is considered as CF causing mutations and associated with pancreatic insufficiency[1].
3849+10kbC>T is considered a pathogenic variant and associated with less severe disease. It has residual function and has been associated with normal sweat chloride values (this could explain the intermediate sweat test in the patient), and pancreatic sufficiency (IDuguépéroux and De Braekeleer. European Respiratory Journal 2005 25: 468). Symptom onset generally occurs at a later age than in people with null pathogenic variants in homozygosis (i.e. F508del homozygotes).
The patients with this combination of variants are expected to have lung disease from mild to severe and they are likely to be pancreatic sufficient. The sweat chloride concentration can be within the normal/borderline values.
He should be referred to a CF Unit to enrol the patient in a correct programmed clinical follow up.
The patient could be eligible for elexacaftor-tezacaftor-ivacaftor (Trikafta or Kaftrio) therapy.
Genetic counseling: Cystic Fibrosis is an autosomal recessive disease caused by mutations in the *CFTR* gene. Andrej's parents are obligate carriers and they have a risk of 25% to have affected offspring in each pregnancy. Nevertheless, it is recommended to test Andrej's parents in order to confirm their carrier status and refer them to genetic counseling, where reproductive options can be discussed for future pregnancies. Prenatal diagnosis for CF on future pregnancies can be offered.
It is also recommended to Refer Andrej to genetic counselor when of age, for reproductive options discussion.
Cascade molecular screening in at risk relatives in the framework of genetic counseling is recommended.

Molecular Geneticist 1
ID 20231149

Molecular Geneticist 2
ID 20231149

*Mutations screened for in traditional nomenclature:
CFTRdel2,3, I507del, 2789+5G>A, E60X, F508del, Q890X, P67L, 1677delTA, 3120+1G>A, G85E, V520F, 3272-26A>G, 394delTT, 1717-1G>A, R1066C, 444delA, G542X, Y1092X(C>A), R117C, S549N, M1101K, R117H, S549R T>G, D1152H, Y122X, G551D, R1158X, 621+1G>T, R553X, R1162X, 711+1G>T, R560T, 3659delC, L206W, 1811+1.6kbA>G, 3849+10kbC>T, 1078delT, 1898+1G>A, S1251N, R334W, 2143delT, 3905insT, R347P, 2184delA, W1282X, R347H, 2347delG, N1303K, A455E, W846X
In traditional nomenclature nucleotide +1 is 132 base pairs before ATG codon.
The mutation detection rate for the kit is about 86.54% for Slovak population (Soltysova *et al*, Clin Respir J 2018, 12:197).
The CF carrier frequency for Slovak population is 1/40-1/45 (Soltysova et al, Clin Respir J 2018, 12:197)
[1]Clinical and Functional Translation of CFTR (CFTR2) website (http://www.cftr2.org/index.php)