GENETIC ANALYSIS FOR CYSTIC FIBROSIS (*CFTR* gene) CASE 2

First name: Charlotte
Surname: Hofmann
Gender: Female
Ethnic origin: Austria
Sample type: DNA

Date of birth: 25/03/1998
Place of birth: Vienna
Your reference: CF23-2
Our reference: 230637367
Sample received: 05/04/2023

Reason for referral: Charlotte Hofmann is a 25-year-old woman. She is referred for *CFTR* analysis by the gastroenterologist due to recurrent idiopathic pancreatitis. A history of cystic fibrosis is reported in her family but no genetic analysis was performed on the CF patient (deceased prior to 1989).

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.254G>A, p.Gly85Glu, (traditional name: G85E) and c.3454G>C, p.Asp1152His (traditional name D1152H)
Genotype in HGVS: c.254G>A(;)3454G>C
Reference sequence: NM_000492.4

Interpretation: this result detects the presence in heterozygosis of two variants in the proband, one is a pathogenic variant and the other is associated to varying clinical consequence. **The pancreatitis could be explained by this result** (other causes of pancreatitis should have to be ruled out).
Pathogenic variant G85E is associated to classical CF phenotype and pancreatic insufficiency[1], while variant D1152H has a highly variable phenotype that can range from no symptoms to mild lung disease. This variant is likely to be pancreatic sufficient (<30% of patients are pancreatic insufficient) (Burgel et al 2010, Clin Genet 77:355).
The expected phenotype for G85E/D1152H individuals varies from no symptoms to CFTR related disorders, such as pancreatitis (as in the patient), bronchiectasis, CBAVD in males and very rarely to classical CF. Due to the fact that the patient could develop pulmonary symptoms later, she should be referred to a CF Unit where it would be considered if she should be enrolled in a programmed clinical follow up.
Genetic counseling: Cystic Fibrosis is an autosomal recessive disease caused by mutations in the *CFTR* gene. Charlotte's parents are obligate carriers, and they have a risk of 25% of having a child with the heterozygote genotype (G85E and D1152H) in each pregnancy: 25% of the offspring will be heterozgyous carriers of G85E mutation and 25% heterozygous carriers of D1152H, 25% will be no carriers. Nevertheless, it is recommended to test Charlotte's parents in order to confirm their carrier status and also siblings (if any) and refer them to genetic counseling.
We encourage Charlotte to refer to genetic counseling. All Charlotte's descendants will be carriers of a *CFTR* pathogenic variant, so the risk of having an affected child would depend on the carrier status of his partner. We recommend testing her partner for mutations in the *CFTR* gene in order to give an accurate genetic counseling and discuss if prenatal diagnosis in the future will be needed. The initial risk of her partner being a carrier is 1/30 (Austrian population, Farrel, J Cystic Fibrosis 2008, 7:450), and the initial risk of CF or CFTR related disorders affected offspring is 1/60.
It is also advisable to perform cascade molecular screening in at risk relatives in the framework of genetic counseling.

Molecular Geneticist 1
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*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 95% for Austrian population (Zeyda *et al* Diagnostics (Basel) 2021,11:299).
[1]Clinical and Functional Translation of CFTR (CFTR2) website (http://www.cftr2.org/index.php)