GENETIC ANALYSIS FOR CYSTIC FIBROSIS (*CFTR* gene) CASE 3

First name: Aideen
Surname: Brennan
Gender: Female
Ethnic origin: Ireland
Sample type: DNA

Date of birth: 05/03/2023
Place of birth: Galway
Your reference: CF23-3
Our reference: 230637369
Sample received: 05/04/2023

Reason for referral: Aideen Brennan is a one-month-old baby with a positive newborn screening (Day 3 IRT: > 99th percentile). *CFTR* gene analysis for 38 common CF variants showed that Aideen is heterozygous for c.1521_1523delCTT p.(Phe508del). Her sweat test was positive and extended DNA sequencing is requested to search for a second *CFTR* variant and confirm 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.350G>A, p.Arg117His (traditional name R117H). Intron 8 result: heterozygous for 5T(12TG) and 9T alleles
Genotype in HGVS: c.1521_1523del(;)350G>A with variants c.1210-12T[5];[9]
Reference sequence: NM_000492.4

Results: this result detects the presence in heterozygosis of variants:

1-Pathogenic variant c.1521_1523del (traditional name F508del) is associated to classical CF phenotype and pancreatic insufficiency[1].

2- Pathogenicity of variant c.350G>A (traditional R117H) depends on the T tract length in intron 8. Individuals with R117H and the 5T variant in the same allele (in *cis*) have a more reduced CFTR activity and more severe phenotype compared to patients with R117H in *cis* with variants 7T or 9T. The patient has a 5T(12TG) and 9T alleles. 9T allele is usually in *cis* with F508del, so it is expected that R117H would be in *cis* with 5T(12TG), and be thus classified as a CF pathogenic variant (nevertheless, it has to be confirmed by segregation analysis). If this is the case, the expected phenotype for F508del-9T/R117H-5T(12TG) will be cystic fibrosis, which in some cases can be severe, but likely to be pancreatic sufficient (Massie et al, Eur Respir J 2001; 17: 1195-120).

Interpretation: this result detects the presence of two pathogenic variants in the proband. She is highly likely to be a compound heterozygote of both pathogenic variants and **this result confirms the diagnosis of CF**.

She 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) therapies.

Genetic counseling: Cystic Fibrosis is an autosomal recessive disease caused by mutations in the *CFTR* gene. Aideen'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 Aideen's parents in order to confirm their carrier status and to determine if variant R117H is in *cis* with allele 5T(12TG). Aideen's siblings, if any, should also be tested. Parents should be referred 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 Aideen 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
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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 is about 90% for Caucasian population (WHO report 2004, http://www.genet.sickkids.on.ca/cftr/).
Carrier frequency in Ireland (1/19, Mirtajani et al, Biomed Biotechnol Res J 2017;1:105)
[1]Clinical and Functional Translation of CFTR (CFTR2) website (http://www.cftr2.org/index.php)