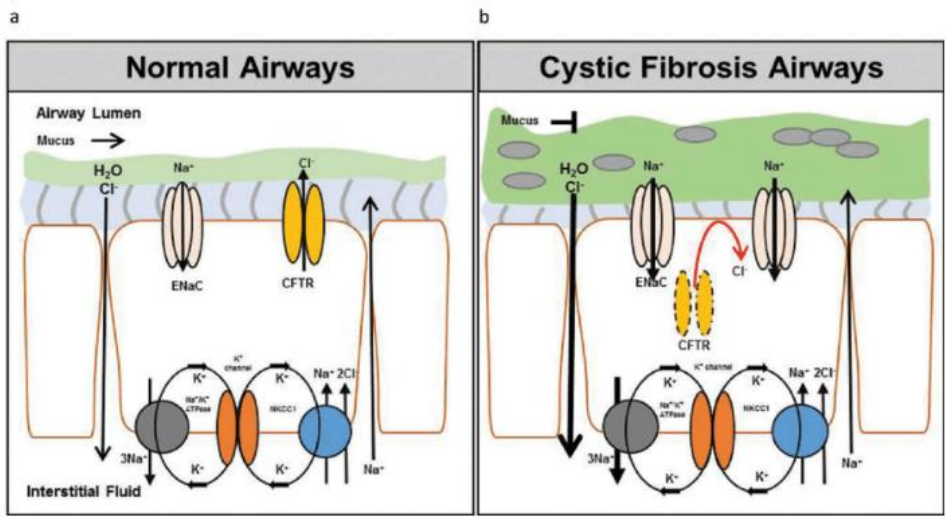
Three Pathogenic CFTR Variants In an Asymptomatic Child

Alya Qari, Zuhair Al-Hassnan
Department of Medical Genomics,
King Faisal Specialist Hospital& Research Center, Riyadh, Saudi Arabia

Background

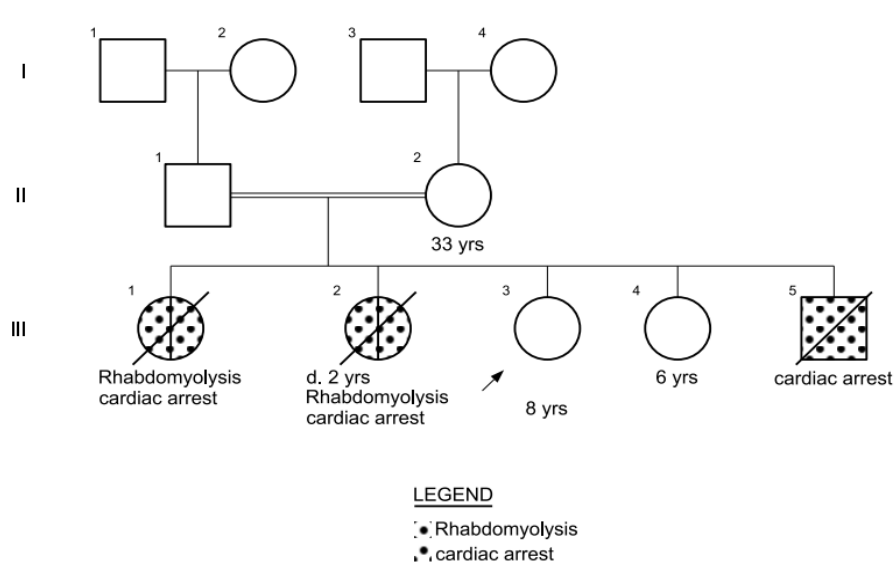
Cystic fibrosis is an autosomal recessive disease characterized by the buildup of thick mucus. It is caused by mutations in the Cystic fibrosis transmembrane conductance regulator (CFTR) gene (OMIM 219700). Although Cystic fibrosis is a monogenetic disease, its phenotypic variability is substantial as shown by the broad range of disease severity observed in patients with the same genotype (1).



Ion transport in the cystic fibrosis airway. In normal airways (A), the ASL is hydrated by a combination of Cl − secretion and Na + absorption and in CF airways (B), reduced Cl − secretion and Na + hyperabsorption causes ASL dehydration that favor mucostasis.

Case

We present here a 33-year-old lady who was referred to King Faisal Specialist Hospital & Research Center for evaluation. Two of her daughters and her only son passed away due to cardiac arrest. The two daughters had Rhabdomyolysis. Her first daughter was a product of full-term normal spontaneous vaginal delivery (NSVD). She was born healthy, with no NICU admissions. Her symptoms first appeared at age of 3 years when she started to have body ache and tea-colored urine CK and elevated myoglobin enzymes. She passed away at age of 4 years due to cardiac arrest. Her second daughter was also a full-term NSVD. She had the same symptoms as her sister; however, the presentations were earlier. It first occurred at age of 2 years, and she passed away at age of 3 years due to cardiac arrest. Her son was also a full-term NSVD. He was born healthy, with no NICU admissions. He passed away at age of 2 years due to cardiac arrest. The lady also had two other normal daughters.



Results

- The lady's WES result showed a heterozygous pathogenic mutation c.2768+1G>A in the LPIN1 gene associated with autosomal recessive acute Myoglobinuria.
- The lady was also heterozygous for two other pathogenic variants in the CFTR gene associated with Cystic fibrosis. Both on the same haplotype as a part of complex allele c.220C>T (p. Arg74Trp) and c.3808G>A ; (p. Asp1270Asn).
- The husband's WES result showed that in the LPIN1 gene he was also heterozygous for the same pathogenic mutation C.2768+1G>A that is associated with Myoglobinuria.
- In the CFTR gene he was confirmed to be heterozygous for a different pathogenic variant that is associated with autosomal recessive Cystic fibrosis c.416A>T (p. His139Leu).
- The 8 years old asymptomatic daughter's genetic testing results showed that she was confirmed to be heterozygous for all the 3 pathogenic variants in the CFTR gene with normal chest and sweat chloride.
- She was confirmed to be wild type for any mutation in the LPIN1 gene.
- The other asymptomatic 6 years old daughter was heterozygous for only the two pathogenic variants in the CFTR gene associated within the same haplotype and heterozygous for the LPIN1 gene pathogenic mutation (Table 1).

Gene	cDNA	Amino acid	Classification	Type	Mother	Father	6-year Normal Daughter	8-year Normal Daughter
CFTR	c.220C>T	P.Arg74Trp	pathogenic	Missense	+/-	-/-	+/-	+/-
CFTR	c.3808G>A	p.Asp1270Asn	pathogenic	Missense	+/-	-/-	+/-	+/-
CFTR	c.416A>T	p.His139Leu	pathogenic	Missense	-/-	+/-	-/-	+/-

Table 1 Mutations detected in CFTR gene in six families

Discussion

The lady was confirmed to be heterozygous for two pathogenic variants in the CFTR gene associated to the same haplotype as a part of complex allele. c.220C>T(p.Arg74Trp) and c.3808G>A (p.Asp1270Asn). According to the HGMD professional 2020.3, the two variants have previously been described as disease causing for Cystic fibrosis and possibly disease causing, respectively, by Clusters *et al.*, 2004 (PIMD: 15287992), and Brugnon *et al.,* 2008 (PIMD: 18703181) (2). The husband was confirmed to be heterozygous for c.416A>T (p. His139Leu). According to the HGMD professional 2020.3, this variant has previously been described as disease causing for Cystic fibrosis by Banjar *et al.,* 1999 (PIMD 10605524) (3). This variant was first described in Saudi Arabia as novel variant, and was of native Saudi descent, and affected individuals showed symptoms early in life with severe lung disease and pancreatic insufficiency. The 8 year old daughter was confirmed to be heterozygous for all the 3 pathogenic variants in the CFTR gene. with normal chest and sweat chloride. The findings are different than what Savov has described in 1995 that double mutant alleles could account for some of the problems in phenotype-genotype correlations (4). Banjar has described in 2020 that the clinical pictures in double homozygous was of the severe type (5).

Conflict of interest and acknowledgment

1. The author has no conflict of interest to declare
2. No acknowledgment

References

1. Banjar, H., Moghrabi, N., Alotaibi, T., Alotaibi, S., & Gamalmaz, H. (2017). The first case report of double homozygous of 2 different mutations in the CFTR gene in Saudi Arabia. *International Journal of Pediatrics and Adolescent Medicine*, *4*(1), 41-46.
2. Brugnon, F., Bilan, F., Heraud, M. C., Grizard, G., Janny, L., & Creveaux, I. (2008). Outcome of intracytoplasmic sperm injection for a couple in which the man is carrier of CFTR p.[R74W; V201M; D1270N] and p. P841R mutations and his spouse a heterozygous carrier of p. F508del mutation of the cystic fibrosis transmembrane conductance regulator gene. *Fertility and sterility*, *90*(5), 2004.
3. Banjar, H., Kambouris, M., Meyer, B. F., Al-Mehaidib, A., & Mogarri, I. (1999). Geographic distribution of cystic fibrosis transmembrane regulator gene mutations in Saudi Arabia. *Annals of tropical paediatrics*, *19*(1), 69-73.
4. Savov, A., Angelicheva, D., Balassopoulou, A., Jordanova, A., Noussia-Arvanltakis, S., & Kalaydjieva, L. (1995). Double mutant alleles: are they rare?. *Human molecular genetics*, *4*(7), 1169-1171.
5. Banjar, H., Alkassas, W., Ghomraoui, F., Ghomraoui, R., & Moghrabi, N. (2020). Double homozygous Cystic Fibrosis Transmembrane Regulator gene (CFTR) mutation: A case series and review of the literature. *Global Journal of Rare Diseases*, *5*(1), 015-021.

This could be a place for your sources.