

## Letter to the Editor

### Two Cystic Fibrosis Cases with Firstly Reported Compound Heterozygous Variants

Sinem Yalçıntepe<sup>1</sup>, Hakan Gürkan<sup>1</sup>, Engin Atlı<sup>1</sup>, Niyazi Cenk Sayın<sup>2</sup>,  
Ümit Nusret Başaran<sup>3</sup>

<sup>1</sup>Department of Medical Genetics, Trakya University School of Medicine, Edirne, Turkey

<sup>2</sup>Department of Perinatology, Trakya University School of Medicine, Edirne, Turkey

<sup>3</sup>Department of Child Surgery, Trakya University School of Medicine, Edirne, Turkey

**Address of Correspondence:** Sinem Yalçıntepe, Department of Medical Genetics, Trakya University School of Medicine, Edirne, Turkey

**Received:** 25 November 2019

**Accepted:** 24 February 2020

**DOI:** 10.4274/balkanmedj.galenos.2020.2019.11.128

**Cite this article as:** Yalçıntepe S, Gürkan H, Atlı E, Sayın NC, Başaran ÜN. Two Cystic Fibrosis Cases with Firstly Reported Compound Heterozygous Variants. *Balkan Med J*

#### To the Editor;

Cystic fibrosis (CF) is the most common and autosomal recessive genetic disease of the white race, it is known that its frequency is one in 2,500 live births. In Turkey, despite the limited number of studies reported, the incidence is 1/3000, it is believed that this rate is higher considering consanguineous marriages is very frequent. The cystic fibrosis gene is on the seventh chromosome, it is 230 kb long, encoding 1,480 amino acids and contains 27 exons. CF gene product protein, which is called protein regulating CF transmembrane regulatory (CFTR), basically acts as chlorine channel. Mutations reaching 1000 in the clinical and genetically heterogeneous CF have been reported to date (1). In this letter, we are introducing two CF cases with firstly determined compound heterozygous CFTR variants.

Case 1, one month old female patient was referred to us after neonatal cystic fibrosis (CF) screening result with a suspect of cystic fibrosis. She was the first liveborn child of the non-consanguineous couple. She had no problem after sectio birth at term. There is no pathologic history with the parents except Rh incompatibility and no cystic fibrosis history in the family. The birth weight was 4050 grams (>90 p), the birth length was 52 cm (75-90 p). On physical examination there was no anomaly with the patient. After the written informed consent form was taken, complete sequencing of the CFTR gene by next generation sequencing (NGS) revealed two different variants in trans, NM\_000492.4(CFTR):c.3909C>G (p.Asn1303Lys) inherited from mother, and NM\_000492.4(CFTR):c.2657+5G>A variant from father (Figure 1). These variations have been previously reported in patients with CF and/or carriers of CF, but not reported together as compound heterozygous in a patient. Our patient had CF diagnosis with this result and genetic counselling was given to the family. In our knowledge, this case is the first for this compound heterozygosity result.

Case 2, twenty-nine-year-old primigravida woman was referred for genetic counselling to our medical genetics clinic with foetal intestinal dilation and hyperechogenic intestine at 26 weeks' gestation from the gynecology and obstetrics clinic. The prenatal ultrasonography (US) revealed 26 weeks old, singleton foetus. Intestinal loops were dilated, thickened and concentric (snail sign) indicated intestinal volvulus. After prenatal genetic counselling, the family did not accept prenatal diagnosis. We analysed father and mother for cystic fibrosis. Mother had heterozygous NM\_000492.3(CFTR):c.1624G>T (p.Gly542Ter) variation, father had heterozygous NM\_000492.3(CFTR):c.489+1 G>T variation (Figure 3). Because of premature rupture of membranes and foetal distress, the foetus was delivered by caesarean section at 36 weeks' gestation. The measurements were 3190 gr/45 cm. She was operated immediately after birth due to meconium ileus (Figures 2 and 3). In the operation, the atretic segment that involved the proximal 6 cm of the ileum was resected, and, the surgeons performed end-to-end anastomosis. She was in intensive unit care for 45 days, then she was taken to gastroenterology clinic for insufficient weight gain. The written informed consent form was taken from the family.

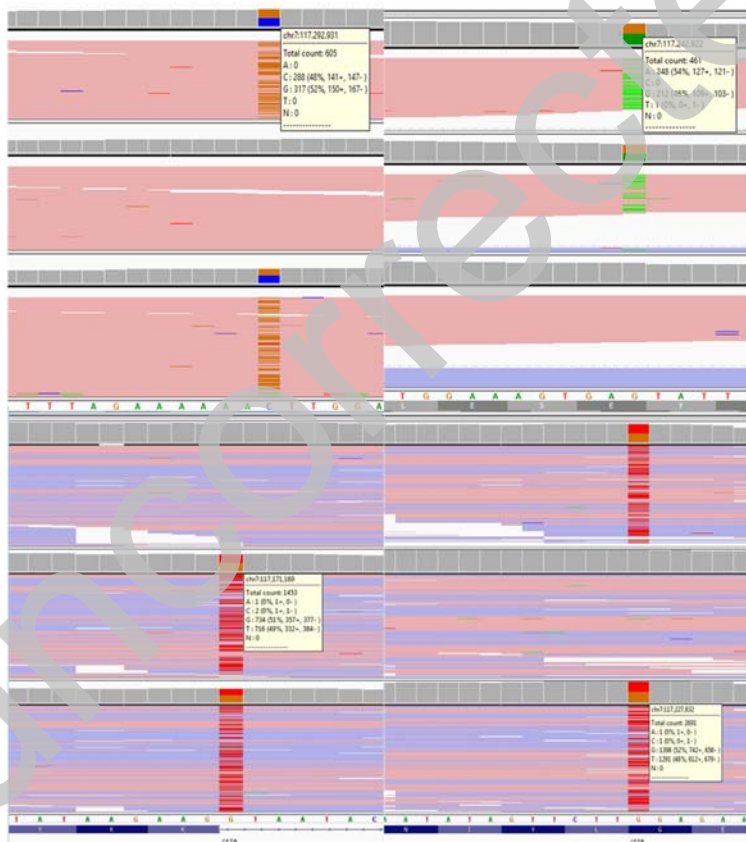
In our medical genetics clinic, the case were analysed for variations in the CFTR gene, compound heterozygosity for NM\_000492.3(CFTR):c.489+1 G>T and NM\_000492.3(CFTR):c.1624G>T (p.Gly542Ter) pathogenic variations were identified. Both mutations have previously been described separately in CF patients, but this infant is the first for the literature with this result. The informed consent form was taken from the family.

CFTR, is primarily located in the apical membranes of epithelial cells and acts as a chlorine channel in the cells. Thus, water and salt transport from the cell membrane is affected in CF and changes in the composition of the fluid secreted in the airways, pancreas, gastrointestinal tract, sweat glands and other exocrine tissues. These changes cause the infection agents to settle easily, with increased viscoelasticity of the mucus in the lungs and the epithelial gland fluid being more salty. Since cystic fibrosis is a disease involving more than one system, it manifests with many different clinical signs and symptoms (2).

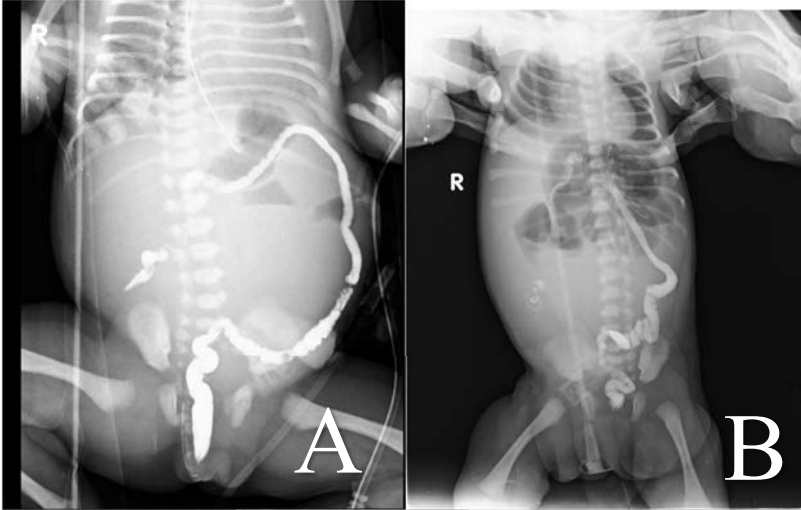
In our two cases, as a result of the genetic mutation analysis, we detected different compound heterozygous mutations in the *CFTR* gene. Due to autosomal recessive inheritance, compound heterozygosity is a diagnostic result. There have been innovations in the treatment of the disease in recent years. Studies on drugs that will activate the mutant *CFTR* gene are under investigation (3,4). As the genetic characteristics of the disease are illuminated, gene therapy will be possible in the future.

## REFERENCES

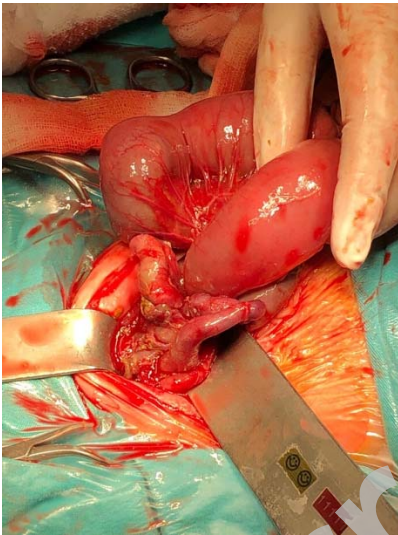
1. Sharma N, Cutting GR. The genetics and genomics of cystic fibrosis. *J Cyst Fibros*. 2019 Dec 23. pii: S1569-1993(19)30965-8. doi: 10.1016/j.jcf.2019.11.003.
2. Paranjapye A, Ruffin M, Harris A, Corvol H. Genetic variation in *CFTR* and modifier loci may modulate cystic fibrosis disease severity. *J Cyst Fibros*. 2019 Nov 13. pii: S1569-1993(19)30963-4. doi: 10.1016/j.jcf.2019.11.001.
3. Sugunaraj JP, Brosius HM, Murray MF, Manickam K, Stamm JA, Carey DJ, Mirshahi UL. Predictive value of genomic screening: cross-sectional study of cystic fibrosis in 50,788 electronic health records. *NPJ Genom Med*. 2019 Sep 4;4:21. doi: 10.1038/s41525-019-0095-6.
4. Hangül M, Pekcan S, Köse M, Acıcan D, Şahlar TE, Erdoğan M, Kendirci M, Güney D, Öznavruz H, Demir O, Ercan Ö, Göçlü F. The Incidence of Cystic Fibrosis in the Central Region of Anatolia in Turkey Between 2015 and 2016. *Balkan Med J*. 2019 May 10;36(3):179-183. doi:10.4274/balkanmedj.galenos.2018.2018.1332. Epub 2018 Dec 28.



**FIG. 1.** Molecular screenings of *CFTR* gene in the cases 1 and 2. The both cases are compound heterozygous for *CFTR* gene mutations, the parents are carrier for the variations.



**FIG. 2.** A. Pre-operative and B. Post-operative abdominal radiography of the case 2. Pre-operative screening shows the blockage of ileus due to meconium ileus, post-operative screening shows that there is no blockage after operation.



**FIG. 3.** Operation image of case 2 with meconium ileus. The figure shows enlargement of the bowel due to blockage of ileus with meconium.