Letter to the Editor

Identification of the CFTR p.Phe508Del founder mutation in the absence of a polythymidine 9T allele in a Hispanic patient

To the Editor:

In the context of the comprehensive California cystic fibrosis (CF; OMIM #219700) newborn screening program, we recently identified a biparentally Hispanic male neonate to have heterozygous cystic fibrosis transmembrane conductance regulator (CFTR) mutations p.Phe508del (c.1521_1523delCTT) within legacy exon 10 (exon 11 by continuous numbering), and p.Phe1074Leu (c.3222T>A) in legacy exon number 17b (exon 20 by sequential numbering). Homozygous p.Met470 alleles were also identified, together with (TG)11-5T and (TG)11-7T alleles. p.Phe508del is the most common CFTR mutation across ethnicities and arose from a single mutational event in the Basque population more than 52,000 years ago (1). p.Phe508del is typically present on a (TG)10-9T-p.Met470 haplotype (Fig. 1a). Three different thymidine alleles (5T, 7T, and 9T) can be present in intron 8 with frequencies of 5%, 84%, and 11%, respectively. The number of thymidines determines the efficacy of exon 9 splicing; 5T results in a higher amount of exon 9 skipping (2). The TG repeat polymorphism is located immediately upstream of the polythymidine nucleotides; in general, the larger the number of dinucleotide repeats, the higher the chance of exon 9 skipping. p.Met470Val is considered benign and not included in diagnostic reports.

This newborn carried one severe (p.Phe508del) and one mild (p.Phe1074Leu) CF mutation. The cis/trans status of these two mutations as well as their relationship with the (TG)11-5T/(TG)11-7T alleles (Fig. 1b) would require parental DNA testing and/or the presence of the 9T allele. Unfortunately, the parents declined to participate. A previous report identified the p.Phe1074Leu mutation in three Spanish brothers to be in cis with the 5T allele (3), suggesting that the p.Phe508del allele may be in cis with the 7T allele. To date, sweat chloride levels for this child have been in the normal range.

p.Phe508del has always been reported with (TG)10-9T, except in Lebanese Maronites in whom 66.7% of p.Phe508del carriers have the 7T allele (4), and in one North Iranian individual who was homozygous for p.Phe508del and 7T (5). The unusual haplotype we report here is not known to occur in other populations, and because of the lack of parental involvement, we cannot rule out one of the parents having unreported Middle Eastern ancestry. The finding of p.Phe508del

![Fig. 1.](image-url)

(a) CFTR introns 7 through 10. The relative genomic positions (not to scale) of the TG dinucleotide repeat and the poly T tract in intron 8 as well as the sites of the p.Met470 polymorphism (M470) and p.Phe508del (ΔF508) in legacy exon 10 are depicted. The length of intron 9 is approximately 11 kb. (b) Sequence of IVS8 with (TG)11-5T/(TG)11-7T in forward and reverse directions. The IVS8 polymorphic (TG) m-nT repeat sequences are just upstream of legacy exon 9. In this case, both alleles carried (TG)11, while one such allele is combined with a 5T tract, and the other with a 7T tract. In the forward sequence tracing, the red peaks represent T and the black peaks represent G. In the reverse sequence, the corresponding nucleotides are A (green) and C (blue). (c) p.Phe508del (ΔF508) in legacy exon 10 is expected to occur with the p.Met470 variant and with a (TG)10-9T tract. However, in the newborn described in this case report, p.Phe508del is present definitively with (TG)11 and p.Met470 alleles, as they both were homozygous. The newborn also carried the 5T and 7T alleles, but the cis/trans relationship could not be determined without parent studies.
present either with the (TG)11-5T or (TG)11-7T allele (Fig. 1a) may have been created by a recombination event. Homozygous p.Met470 is compatible with such a recombination. p.Met470 is usually, if not always, associated with the (TG)10-9T-p.Phe508del haplotype (Fig. 1c). In the Maronites, the typical (TG) dinucleotide repeat number has not, to our knowledge, been characterized, but the 7T-p.Phe508del has been reported to occur in combination with p.Met470. Thus, we hypothesize that a recombination event between the parental (TG)11-5T/(TG)11-7T allele and a (TG)10-9T-p.Phe508del allele must have occurred. A second possible hypothesis is that of a point mutation occurring in the (TG)10-9T sequence, which could create an additional TG repeat and two fewer thymidines in the polythymidine sequence. Alternatively, albeit unlikely, a new p.Phe508del mutation could have occurred.

Overall, our patient has three significant CFTR alleles: the severe p.Phe508del mutation, the disease-modifying 5T allele, and the mild p.Phe1074Leu mutation. 5T has reduced penetrance, and when p.Phe508del and 5T are in trans, some females and males have symptoms in the CF spectrum, although these typically are very mild. In males with one CFTR mutation and (TG)11-5T, an increased risk of infertility due to CBAVD has been reported. Given the additional identification of p.Phe1074Leu, this patient is at risk for developing CF-related symptoms and will be clinically followed.

This patient is the first individual in the United States, and in the Hispanic population, to have p.Phe508del on a background of 5T and 7T alleles instead of the expected 9T. As a rule that is routinely used in clinical diagnostic interpretations, p.Phe508del is always present together with 9T. Although our patient is the first patient with p.Phe508del in this part of the world reported to not carry 9T, our case illustrates that the 9T assumption should not always be followed and raises the question whether other patients with a non-9T configuration may have been overlooked.

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References


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