Occasional Review
The S549R (T→G) Cystic Fibrosis Gene Mutation

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Cystic fibrosis (CF) is due to variations in DNA that result in modifications in the sequence, structure, function and/or expression of the cystic fibrosis transmembrane conductance regulator (CFTR) gene situated on chromosome 7.1 Over 895 CF-causing mutations have been identified worldwide in the CFTR gene.2 While the ΔF508 mutation accounts for over 60 per cent of these alterations there are a number of important mutations being recognized among differing ethnic groups.2,3 Within the context of the Gulf States, CF has been reported from all countries and descriptions suggest that the disease is usually severe clinically. In the past it had been regarded as a rare disease in Arabs, but the rapid development of health services in the Gulf over the last 30 years has probably helped in focusing attention on the disorder, which in the past had resulted in the premature deaths of many children.

Among the several mutations that have been described in exon 11 of the CFTR is S549R (T→G). This mutation is a missense mutation (i.e., results in an abnormal protein being produced) occurring at nucleotide position 1779 that is the result of a G (glycine) to T (threonine) transversion. The consequence of this mutation, in codon 549, is the replacement of a serine by an arginine in the first nucleotide binding domain of the CFTR gene. Serine is a highly conserved amino acid in this important binding domain and its replacement by an arginine residue is expected to result in a severe chloride dysfunction and hence severe clinical disease.4 S549R is defined as a Class II mutation.5–8 These are associated with defective protein processing. The abnormally processed protein fails to progress through the biosynthetic pathway and is degraded. The protein is thus either missing or present in reduced amounts in the apical membrane. It is thought that the mutation prevents the protein from being properly posttranslationally glycosylated. This results in incorrect folding, so that the protein is recognized as abnormal and degraded.5–8 These events appear to be similar to those seen with the ΔF508 mutation in that the misfolded protein is trapped in the endoplasmic reticulum prior to its degradation.7,8 This, more simply put, means that the mutation results in the placing of an incorrect amino acid into the CFTR protein. The resulting protein is recognized by the cell as being ‘faulty’ and is removed before being placed in the correct position in the cell membrane. The consequence is a marked reduction in chloride channels in the tissues in which chloride channels are normally located.

The existence of the mutation S549R (T→G), was first reported to the Cystic Fibrosis Genetic Analysis Consortium on 9th February 1990 by Kerem and Tsui.2 The individual who carried the CF chromosome was a non-Ashkenazi Jewish patient from Morocco who also carried the ΔF508 mutation on the other allele.4 Further reference to this and one other Moroccan patient was made by Kerem, et al.9 who studied cystic fibrosis mutations in Jewish communities. It was reported that CF mutations vary within each Jewish ethnic group, each one having its own repertoire of mutations. S549R was found only in these two patients from Morocco and it thus accounted for 6 per cent of the identified Jewish CF patients from that country.

There have been four separate mutations described in codon 549, namely S549R (A→C), S549I, S549R (T→G), and S549N2 (codons = triplet codes for each amino acid). A study of 27 177 CF chromosomes from 29 European and three north African countries showed that of the 272 mutations examined, S549R occurred on 12 occasions (0.04 per cent) and the S549N on 16 occasions (0.059 per cent). Interestingly, despite its general rarity, the S549R mutation accounted for 2.6 per cent of all mutations in Algeria.1 However, a recent detailed study of 10 Algerian CF families revealed no patients with a mutation on exon 11.9

Another important report in the literature regarding the S549R mutation is from Saudi Arabia. Banjar, et al.11,12 described a single individual who was homozygous for the mutation. The patient was a Saudi native who came from the eastern province of Saudi Arabia. The affected individual had pancreatic insufficiency and mild chest disease. However, El-Harith, et al.13 investigated 15 Arab children from 12...
families who had CF. No examples of S549R were detected and it is of significance that the families studied were all from the eastern region from where the one previous Saudi patient with S549R had been identified.

While studying patients with CF in the United Arab Emirates (UAE), it became apparent that the otherwise common CF mutation, ΔF508, was mostly found in those belonging to the minority Baluch ethnic group, while it was absent in the majority Bedouin population. Overall in the UAE, those who are homozygous for the mutation S549R (T→G) account for over 90 per cent of all patients with CF. Only one example of a heterozygote has been encountered and this patient had a mild phenotype and a genotype R1158X/S549R (T→G). Sporadic examples of other mutations occur, such as homozygous examples of N1303K. The study of 15 Bedouin families with CF revealed that they were all homozygous for the S549R (T→G) mutation.

In a genotype–phenotype correlation with assessment based upon 20 outcome variables, it was apparent that in the homozygous state this mutation leads to a severe disease presentation with pancreatic insufficiency, early severe lung disease, and early colonization with *Pseudomonas aeruginosa*. Further radiological assessment of this group confirmed the association of extreme lung disease and rapid pulmonary decline in those patients homozygous for S549R (T→G). The founding mutation may have originated in eastern Arabia. However, there is considerable ethnic variation between the UAE and Oman, and there is little evidence of the mutation in Bedouin Saudis. The reports of sporadic alleles from Israel, north Africa and France confuse the issue further. Current evidence suggests the origins lie in Bedouins of eastern Arabia.

Romey, *et al.* reported three nucleotide alterations in the CFTR minimal promoter, defined as a 250-bp fragment upstream of the ATG translation short codon. These mutations are: 33G→A, −94G→T and −102T→A. The latter was detected in two unrelated CF patients from southern France. The −102T→A mutation was found on the same allele with the mutation S549R (T→G) in a compound heterozygote situation with ΔF508 in one female patient. A male patient had a compound heterozygote S549R (T→G)/S945L with −102T→A promoter mutation. The patients having these CFTR mutations were described as having mild disease, pancreatic sufficiency, and mild pulmonary disease. This contrasted with the prior report that S549R was associated with severe disease. The French patients were not, however, homozygous for S549R, but one had a severe mutation, ΔF508, in a compound heterozygote situation.

A comparative study of the main clinical features of six patients with cystic fibrosis carrying the complex allele [−102T→A+S549R(T→G)] was made with that of 16 CF patients from the UAE with S549R(T→G) alone. Those patients with the complex alleles had higher ages at diagnosis, lung colonization was delayed in comparison with those with unique mutations, sweat chlorides were lower, and they had better clinical scores overall. All the homozygous patients had pancreatic insufficiency, as compared with only half of the patients with the complex alleles. These observations strongly suggested that the addition of the sequence change (−102T→A) in the CFTR minimal promoter might attenuate the severe clinical phenotype of the S549R(T→G) mutation. This hypothesis has been further confirmed by Romey, *et al.* who subsequently showed that the −102T→A mutation creates a Yin Yang 1 core element that increases CFTR expression significantly.

Further study of what appeared at first to be a rare or private mutation is contributing to our understanding of genotype–phenotype correlations. To date the distribution of the mutation does not fit patterns of historical population migration, such as that associated with the ΔF508 mutation, but it is found mainly in the Bedouin Arab people of Oman and the UAE. Disease severity in the homozygous patient appears to be very severe. It can be postulated that this severity, in itself, probably accounts for the early demise of those with the disease in the early times. With the introduction of the medical services in the Gulf region, recognition has occurred
and the high fertility and consanguinity have prevented the resultant disorder from being eliminated from society.

References


