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Commentary

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A hypothesis regarding the origin and spread of the cystic fibrosis mutation ΔF508

K.P. DAWSON and P.M. FROSSARD[1]

From the Departments of Paediatrics and [1]Pathology, Faculty of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates

Morral *et al.*[1] have presented strong evidence that the ΔF508 mutation arose in a population genetically distinct from the present European population. Further, data plotted on synthetic maps indicate a marked frequency gradient from south-east to north-west Europe, e.g. 100% presence of ΔF508 in CF mutations in the Faroe Islands compared with 27% of all mutations in the Turkish CF population.[2] The explanation offered for this phenomenon is that there has been a greater mixing and heterogeneity in the southern populations and relative isolation in the northern. The current view is that ΔF508 was not spread by the Indo-Europeans but by a group that preceded them and had originated in the 'Middle-East; or the East'.[1] Bertranpetit and Calafell[3] have summarized the basis of the estimates of the age of the ΔF508 mutation. The 1705 chromosomes studied carried 1477 microsatellite mutations (corresponding to a mean $\gamma = 0.866$). A mutation rate of 3.3×10^{-4} gave a total time of 2625 generations, which gives an estimate of 52 000 years. This is a mean estimate, and its standard error may be large.

We are thus considering a population based in the East, in which a mutation arising some 50 000 years ago provided some biological advantage to those who were carriers. Currently, some authors have hypothesized that this advantage could be considered as a protection from typhoid fever rather than cholera as had formerly been suggested.[4]

In attempts to determine where in Asia this mutation may have arisen, the study of the presence of ΔF508 in Asians living in Western countries has not been very rewarding. The lack of information from Asian countries has made this method necessary. In a large Asian population, the study of almost 900 chromosomes revealed the absence of carriers of the common Caucasian-related mutations (including ΔF508). However, an affected Pakistani child born to consanguineous parents was shown to be homozygous for mutation S549N (G→A).[5] Schwartz *et al.*[6] reported six affected Pakistani children, of whom three were homozygous for the ΔF508 mutation. It was not stated to which ethnic group within Pakistan the children belonged. Further study of Asians with CF was reported by Bowler *et al.*,[7] who outlined the clinical course in nine Pakistani Asians. Four of the nine were homozygous carriers for the ΔF508 mutation. A comparison was made with a group of 18 Caucasians, 17 of whom carried ΔF508, of which 12 were homozygous. A high degree of consanguinity was reported and a more severe clinical course, which it is suggested may have been influenced by genetic and environmental factors.

In a study from the USA of Asians with CF, 20 patients were identified in US CF clinics.[8] Seven patients carried the ΔF508 mutation, of whom four were homozygotes. Pakistanis represented 10 (probably 11) of these patients, Indians eight, and there was one Palestinian. Again, no information was given as to the ethnic subgroup of the families. The authors calculated that the incidence of CF in Asians was 1:40 750, but noted a figure of 1:10 000 proposed from the UK.[9] The only study which gives some information about ethnicity within the Indian subcontinent is that of Spencer *et al.*,[10] who reported on 13 CF patients. Seven patients were from Mirpur

Address correspondence to Professor K.P. Dawson, Chairman, Department of Paediatrics, Faculty of Medicine and Health Sciences, UAE University, Post Box 17666, Al Ain, United Arab Emirates. e-mail: KDawson@uaeu.ac.ae

(Kashmir) and one of them was homozygous for ΔF508. Four patients were Sikhs from the Punjab (India) and two of them carried the ΔF508 mutation. The remaining patients were mostly from Bangladesh, with one Moslem Punjabi, but their specific mutations were unknown. Overall, most reports about CF have focused upon Pakistanis and only rare reports come from others such as Sikhs and Bangladeshis. In about half of these, the ΔF508 mutation is implicated and is usually found in a homozygous pattern, which reflects the extensive consanguinity amongst these ethnicities.

If the founder ΔF508 mutation occurred in Asia some 52 000 years ago and bestowed some benefit on that early population, where are the descendants of these early people? It is highly unlikely that they all migrated to Europe, so there should be a remnant population which carries evidence of this genetic descent.

It is proposed that the most likely ethnic group who could provide evidence of this descent are the Baluchi people. They number about 5 million and are located in Iran (20%), Pakistan (Baluchistan Province 70%) and Afghanistan (10%). The original Baluchi homeland was said to be the Iranian Plateau and by the 10th century AD, they had migrated to their present location, as described in the Arabic Chronicles of that time, with migrations continuing into the 14th century AD.[11] Their eventual settlement area is an arid region surrounded by the daunting mountain regions of Bag-e Band and Bampusht. This region is regarded as one of the most isolated in the world.[11]

The Iranian Baluchi territory provided a land route to the Indus Valley and the Babylonian civilization. This route was exploited by Alexander the Great, who marched through Baluchistan in 326 BC. Thus the area was in a key position in relation to South-West Afghanistan, the Indus Valley, Iran, Iraq and the Levant. Later emigration occurred from Baluchistan into the Punjab of India, as well as to Oman and the present UAE.

The close geographical location of Baluchistan to the UAE makes it very likely that direct transfer of the ΔF508 mutation occurred by the well established sea links. The Baluchi people have remained an isolated group living in a large area (347 190 km^2) and have practised traditional arranged consanguineous marriages. It is not surprising, therefore, that all the patients we have seen of Baluch descent are homozygous for the mutation ΔF508.[12] Similarly, population screening has indicated that UAE nationals of Baluch descent and Pakistanis from Baluchistan living in the UAE were similar in their carrier state, i.e. ΔF508 only. Indirect supporting evidence for this hypothesis may be found in the study of Karjoo *et al.*[13] He investigated prospectively and retrospectively all suspected cases of CF in Southern Iran seen in the three University hospitals of Shiraz University. The people studied were living in Fars Province adjacent to the Baluchi areas of Iran, but are ethnically different. The investigators could find no previous reports of CF in a 20-year retrospective study nor a patient with a firm diagnosis of CF. In the prospective study of 125 suspected individuals, only three patients were considered to have the disease on clinical grounds. No genetic studies were undertaken. Thus in an area close to Baluchistan, CF appears to be a very rare disease, yet it is now found regularly in Baluchis.

Quaife *et al.* studied the spectrum of the disease beta thalassaemia in the UAE national population. They concluded that specific mutations were introduced into the UAE by immigrants from Baluchistan and matched those found in that region. One mutation in particular, the $\beta+$IVSI-5 (G→C), has rarely been found in Arab populations elsewhere and appears to have arisen in the Baluchi population.[14]

To gain genetic information about the relation of the early settlers in Europe and the present day residents in the UAE of Baluch descent and Pakistani Baluch people, a study of microsatellite markers on the respective alleles is necessary.

The hypothesis proposed here is that the original founder ΔF508 mutation giving rise to cystic fibrosis occurred in those inhabiting the Iranian Plateau and travelled from there eventually to Europe in the first wave of emigrants. Their descendants moved to the area of Baluchistan bringing the mutation with them. During the last 150 years, further migration has occurred into the Gulf Region and the ΔF508 mutation has joined the pool of CF mutations that are common in this region.[12]

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