LETTERS TO THE EDITOR

Kuwait type faciodigitogenital syndrome

In 1988 we reported a newly recognised autosomal recessive malformation syndrome with some resemblance to Aarskog type faciodigitogenital syndrome, including short stature, hypertelorism, short, stubby nose with anteverted nostrils, long philtrum, ear anomalies, long neck with sloping shoulders, small, broad hands with mild interdigital webbing, fifth finger clinodactyly, hyperextensible hand joints, and shawl scrotum. However, the face was somewhat triangular or elongated, the eyes did not slant downwards, and there was no ptosis. In addition, the hair was coarse, dry, and hypopigmented in four of the five affected sibs (three male and two female).

In the large Kuwaiti Bedouin tribe (approximately 10,000) from which this family comes, after the publication of our paper, we observed another sibship with two affected males who are double first cousins to the reported cases (figure). Moreover, we also observed three other distinctly related sibships with nine affected subjects who all can be traced to a common ancestor. This raises the total number of cases encountered so far to 16, including nine males and seven females, with ages ranging from 6 months to 10 years. This reflects a very high prevalence for a monogenic malformation syndrome in this tribe (at least 1 in 625) and if age specific minimum prevalence is considered it would be even higher. It is also noteworthy that these cases all live in Farwania district with a population of 400,000 only 15% of which is Bedouin. If the minimum prevalence is estimated among the Bedouin community in that district it would be 1 in 3750 (16:60,000) which is four times the frequency of Bardet-Biedl syndrome among the Bedouin.2

The consistent manifestations are the triangular or elongated face, telecanthus or mild hypertelorism, wide palpebral fissures without ptosis, short, stubby nose with anteverted nostrils, high arched and narrow palate, long, deep philtrum, wide mouth with protruding lower lip, posteriorly rotated ears with minor ear anomalies, long neck with sloping shoulders, small, broad hands with mild interdigital webbing and fifth finger clinodactyly, hyperextensible hand joints, and shawl scrotum. Short stature was confirmed in 10 cases while the heights of the other six were between the 10th and 25th centile for age. Hair changes were present only in the four originally reported sibs, which might suggest that they are segregating as an independent trait in that branch of the family. None of the 16 cases showed physical disability or mental retardation. Their parents were all phenotypically normal and were either first or second cousins.

This study further characterises the phenotype and confirms the previously suggested autosomal recessive inheritance in this type of faciodigitogenital syndrome. It also highlights the importance of diagnosing such a disorder for proper counselling, particularly in Arab countries with large Bedouin communities such as Kuwait, Saudi Arabia, Qatar, and the United Arab Emirates. It is possible that the gene founder effect originating in this tribe might spread through intermarriage to other Bedouin tribes and probably to the whole population, especially after the recent trend of breaking the traditional practice of consanguineous marriage.

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Pericentromeric heterochromatin of chromosome 3

Pericentromeric heterochromatin of human chromosome 3 is usually identified as an intensity variation by the QFQ technique. We show that the Alul-Giemsa technique is a much more informative approach.
Immediately after the inception of the QFQ banding technique, it was recognised that certain regions of the human genome stain with variable fluorescent intensity, termed variants, polymorphisms, or heteromorphisms. The intensity of quinacrine fluorescence varies depending on the amount and type of chromatin fraction present. With a few exceptions, most of these regions are pericentromeric heterochromatin. One of these regions is the centromere of chromosome 3 whose intensity using QFQ banding has been well evaluated. Inversion of the fluorescent segment of chromosome 3 has also been noted and determined to be simply a polymorphic trait. But what happens if this inverted segment is non-fluorescent? We feel that this is exactly the case in Petrovic’s observation entitled ‘A new variant of chromosome 3 with unusual staining properties’. Our conclusion is based on CBG banding as this area stains positively by this procedure and is also present in the mother whose reproductive history is normal. Therefore, we would like to clarify the point for cytogenetists who may encounter heterochromatic variants of non-fluorescent regions on other chromosomes as well. These so-called new or rare variants are not really new; one only has to analyse them more thoroughly using multiple banding techniques. There is no direct relationship between polymorphic markers identified by one technique and those identified by another, as the mechanisms of various banding techniques are different.

In an attempt to explore the extent of expression of pericentromeric heteromorphism of the centromere of chromosome 3, we used restriction enzyme AluI digestion on fixed chromosomes along with QFQ and CBG banding techniques. It has been accepted that only a small portion of pericentromeric heterochromatin is resistant when chromosomes are treated with restriction endonucleases. Observations on chromosome 3 clearly suggested that heterochromatin is far more variable than originally described. We have found that there are subjects in whom C band positive regions are smaller using the CBG technique as compared to AluI digests (figure). Heterochromatin observed using the AluI-Giemsa method ranged from completely negative to various gradations of positive bands within the pericentromeric region. The increase in the amount of DNA is not always homogeneous but is caused by independent, cytochemically distinct fractions; this would also explain the lack of a definite relation between the size of the C band and various banding techniques. Furthermore, if one wishes to investigate the ‘size’ heteromorphisms of the pericentromeric region of chromosome 3, AluI-Giemsa staining may prove to be more effective than CBG and QFQ techniques. This approach is very useful, especially during prenatal diagnosis, allowing one to rule out maternal cell contamination. We think that fluorescent polymorphisms of pericentromeric regions of chromosome 3 are observed
better with the AluI-Giemsa technique.

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Cystic fibrosis in Bulgaria

In an article published in the journal, Cuppens et al described a cystic fibrosis patient who was homozygous for the G542X mutation yet presented with a relatively mild clinical picture.

This mutation, although rarer than Δ F508, seems to occur in all European populations. In the Bulgarian CF patients we are testing it is found at a frequency of 5% of CF alleles. So far we have detected six patients with G542X including one homozygote (table). The clinical course of the disease is invariably severe in our patients. Symptoms of CF had been present from the first months of life and in all cases the diagnosis had been established during the first year. Taking into account the fact that CF is often diagnosed late in this country, early diagnosis suggests a severe course of the disease. At present only one of the six patients with G542X is still living. Early infant death occurred in four of the families (in two of them a previous affected child had also died at a very early age). Two patients had meconium ileus (MI); this has been recorded in about 10% of our CF patients and thus seems to be over-represented in the G542X subgroup (seven MI out of a total of 78 CF patients and two MI out of six with G542X).

Our findings are thus in agreement with the assumption that a stop codon at position 542 results in the synthesis of a functionally inactive protein. On the other hand an increasing number of publications, as well as our own observations, suggest that in a number of patients the actual clinical findings conflict with the molecular evidence. Heterogeneity within groups with the same molecular defect could suggest the existence of additional, perhaps genetic, factors which modify the clinical course of cystic fibrosis.

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Floating Harbor and the good ship Shprintzen

I would like to take issue with the authors of the ‘Syndrome of the month’ concerning the Floating Harbor syndrome, particularly their penultimate patient number 1.

This looks to me very much like a case of velocardiofacial (Shprintzen) syndrome on the basis of facial phenotype, especially speech delay, immobile palate, malocclusion, and pulmonary stenosis. Pulmonary stenosis can be associated with the Shprintzen syndrome.2 The facial dysmorphism appears typical in this photograph: deficient alae, high nasal bridge, almond shaped palpebral fissures, myopathic facies, and mandibular hypoplasia. This patient does not have a large mouth. Immobile palate is of particular interest and I would suggest that this patient be reviewed as regards submucous cleft of the palate. Even if it is not obviously present, it may well be at operation. Videofluoroscopy of the palate would be of some assistance in this regard. These patients are uniformly unresponsive to speech therapy and respond only to palate lengthening or pharyngoplasty or both.

It is clear that if there is some considerable doubt about the first patient the other reported patients need to be reviewed. The details supplied were not adequate enough to determine if other syndromes or small, odd-looking children have been lumped together under this enticing name. In particular, actual height centiles would be of interest. Patients with the velocardiofacial (Shprintzen) syndrome are small, but not several standard deviations below the mean.

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Bulgaric cystic fibrosis patients with G542X

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Mutations</th>
<th>Family and clinical data</th>
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<tr>
<td>33</td>
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<td>3</td>
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<td>66</td>
<td>G542X/N1303K</td>
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