A mother with VCFs and unilateral dysplastic kidney and her fetus with multicystic dysplastic kidneys: additional evidence to support the association of renal malformations and VCFS

Dreviendt et al. recently described in this journal a female fetus with Potter sequence caused by unilateral renal agenesis and contralateral multicystic dysplasia renal, who was retrospectively found to have a deletion in chromosome 22q11 following identification of the deletion in the father. The father presented with typical VCFs features but no urological anomalies. We describe a patient with a clinical diagnosis of VCFs and a unilateral dysplastic kidney but with negative high resolution cytogenetic and FISH studies, who had a female fetus with bilateral multicystic kidneys. This provides additional evidence to support the conclusion of Dreviendt et al. that in VCFs the renal malformation can dominate the clinical phenotype.

Our patient is a 24 year old female initially referred because of facial dysmorphism and developmental delay. She had a long nose and a long, thin face, a small chin, prominent incisors, a deep philtrum (fig 1), a high palate which had the appearance of a cleft, velopharyngeal insufficiency, and long, thin fingers and toes. She also had a repaired ASD, developmental and speech delay, depression, chemical dependency, and seizures. A renal ultrasound showed a unilateral multicystic dysplastic kidney. Karyotype analysis and FISH using a digoxigenin labelled probe localised to 22q11.2 (Oncor Inc, Gaithersburg, MD) were negative. Her first pregnancy was uncomplicated and she delivered a healthy male with no dysmorphic features. He had a normal renal ultrasound and at the age of 2 years is developmentally appropriate. During her second pregnancy, ultrasound examination of her female fetus at 19 weeks 4 days identified bilateral multicystic kidneys and anhydramnios. The pregnancy was terminated and necropsy confirmed the presence of multicystic dysplastic kidneys, hypoplastic bladder, and low set ears. No other abnormalities were noted. Karyotype analysis was normal.

Of patients diagnosed clinically with VCFs, only 68% to 81% have a deletion of 22q11.2. Several recent articles have noted the presence of nephropathological malformations as a component of VCFs syndrome.1 The 39 patients reported by Dreviendt et al. with 22q11 deletions, four had nephropathological malformations. Another patient with unilateral renal agenesis and dysmorphic features suggestive of DiGeorge sequence had a normal G band karyotype. Dreviendt et al. reported a patient with a multicystic kidney and a normal karyotype; however, molecular studies showed the absence of a paternal 22q11 allele. Of 11 patients with DiGeorge syndrome reported by Palacios et al., one had a dysplastic right kidney and left ureterohydrenephrosis and one had a right megaureter; karyotype analysis was not performed on these two patients.

We concur with Dreviendt et al. that renal malformations associated with VCFs can lead to the Potter sequence and can dominate the clinical phenotype. These authors retrospectively investigated 10 additional cases of Potter sequence and no other patient with a del(22q11) was found. They concluded that performing FISH for 22q11.2 on all fetuses with Potter sequence, along with a thorough evaluation of both parents for physical features of VCFs, needs to be examined further.

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the Pitt-Roger-Danks syndrome may be caused by a deletion in the same region.\(^1\)

In a recent issue of the *Journal of Medical Genetics*, Partington et al reported on a number of patients with deletions or duplications of 4p16.3; adding new information potentially useful for characterising this segment of the human genome.

However, in reading their article "Translation involving 4p16.3 in three families: deletion causing Pitt-Roger-Danks syndrome and duplication resulting in a new overgrowth syndrome", we have serious concerns about (1) their definition of a new overgrowth syndrome and (2) the idea that a triple dose of FGF3 results in physical overgrowth.

First, we have re-examined the data from their table 2 to show that overgrowth is not really a prominent manifestation of duplication involving FGF3 (table 1). For both height and head circumference, fewer than half of the patients have values \(\geq 90\)th centile; only with respect to weight do slightly more than half of the patients have values \(\geq 90\)th centile. On the other hand, a good proportion of patients have values \(\leq 50\)th centile and even \(\leq 25\)th centile. Combining all three parameters (n=76), at the extremes, 28% of patients have values \(\geq 97\)th centile and 8% have values \(\leq 3\)rd centile. Although some values for all three growth parameters are large and the trend appears to be in that direction, so many patients have middle and lower range values that overgrowth per se does not seem to us to be a particularly prominent manifestation of dup(4p16.3). In fact, when thinking of classical overgrowth syndromes, such as Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome, or Bannayan-Riley-Ruvalcaba syndrome with overgrowth frequently present at birth,\(^9\) it is difficult to think of dup(4p16.3) as an overgrowth syndrome at all.

Secondly, the function of FGF3 can be deduced from the Fgf3-/-knockout mouse,\(^11\) which is overgrown with excessively long femora and elongated vertebrae, resulting in a long tail. Thus, the normal function of FGF3 is to regulate endochondral ossification by "putting the brakes on growth.

Evidence is accumulating that the known mutations on FGF3Rs are of the gain of function type. For example, Neison and Friesel\(^1\) made mutations in mRNA and expressed these in Xenopus laevis to correspond to human mutations on FGFR1 and FGFR2. Analysis of mutant receptor proteins expressed in Xenopus oocytes indicated that all but one had increased tyrosine kinase activity compared to their wild type counterparts. FGF3 mutations for achondroplasia and thanatophoric dysplasia have also been shown to have greatly increased levels of phosphotyrosine and ligand independent constitutive signalling produced by these mutations results in premature maturation of bones of the skeleton and cranium. This type of activation depends on the particular mutation and its location on the receptor and appears to result from (1) aberrant disulphide bonded orhydrogen bonded FGF3 dimers

Table 1 Rearranged data

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<thead>
<tr>
<th>Height</th>
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<td>31</td>
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<td>26</td>
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or (2) involvement in the activation loop of the kinase domain.\(^13\)

Thus, the mutations for short limb skeletal dysplasias on FGF3R (hypochondroplasia, achondroplasia, and thanatophoric dysplasia) are gain of function mutations that "put the brakes on even more" to various degrees. Fgf3-/- heterozygous mice have been shown to be normal.

In conclusion, the idea put forth by Partington et al that FGF3 in single dose leads to growth failure and in triple dose to physical overgrowth is not tenable in view of current clinical and experimental evidence.

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8 Partington MW, Fagan K, Soubijski V, Turner G. Translocations involving 4p16.3 in three families: deletion of a constitutively known human mutations on FGFR1 and FGFR2. Analysis of mutant receptor proteins expressed in *Xenopus* oocytes indicated that all but one had increased tyrosine kinase activity compared to their wild type counterparts. FGF3 mutations for achondroplasia and thanatophoric dysplasia have also been shown to have greatly increased levels of phosphotyrosine and ligand independent constitutive signalling produced by these mutations results in premature maturation of bones of the skeleton and cranium. This type of activation depends on the particular mutation and its location on the receptor and appears to result from (1) aberrant disulphide bonded orhydrogen bonded FGF3 dimers

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Robinov syndrome

I would like to comment on the paper by Saby et al. In the September issue of the *Journal of Medical Genetics*, Saby et al. describe three patients they diagnosed as having Robinow syndrome in conjunction with a number of unusual abnormalities.

When looking at the photographs of their patients, I doubt whether the diagnosis of Robinow syndrome is correct, especially in the first patient. She has a number of facial characteristics that are indeed seen in Robinow syndrome, such as hypertelorism and

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New overgrowth syndrome and FGFR3 dosage effect.

M M Cohen, Jr and G Neri

J Med Genet 1998 35: 348-349
doi: 10.1136/jmg.35.4.348-a