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

Derviendt et al. recently described in this journal a female fetus with Potter sequence caused by unilateral renal agenesis and contralateral multicystic renal dysplasia, 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 Derviendt 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 delay 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 and hydramnios. 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 components of a syndromic phenotype.
the Pitt-Rogers-Danks syndrome may be caused by a deletion in the same region.17

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

However, in their article "Translocations involving 4p16.3 in three families: deletion causing Pitt-Rogers-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) their idea that a triple dose of FGFR3 results in physical overgrowth.

First, we have reanalyzed the data from their table 2 to show that overgrowth is not really a prominent manifestation of duplication involving FGFR3 (table 1). For both height and head circumference, fewer than half of the patients have values ≥90th centile; only with respect to weight do slightly more than half of the patients have values ≥90th centile. On the other hand, a good proportion of patients have values ≤50th centile and even ≤25th centile. Combining all three parameters (n=76), at the extremes, 28% of patients have values ≥97th centile and 8% have values ≤3rd 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).

Secondly, the function of FGFR3 can be deduced from the Fgr(1-6) knockout mouse,1 which is overgrown with excessively long femora and elongated vertebrae, resulting in a long tail. Thus, the normal function of FGFR3 is to regulate endochondral ossification by "putting the brakes on".

Evidence is accumulating that the known mutations on FGFRs are of the gain of function type. For example, Neilson and Friesel18 made mutations in mRNA and expressed these in Xenopus oocytes where it is shown that wild-type 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. FGFR3 mutations for achondroplasia and thalassemic dysplasia have also been shown to have greatly increased levels of phosphotyrosine. 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 bond or hydrogen bonded FGFR dimers and (2) or involvement in the activation loop of the kinase domain.18

Thus, the mutations for short limb skeletal dysplasias on FGFR3 (hypochondroplasia, achondroplasia, and thalassemic dysplasia) are gain of function mutations that "put the brakes on even more" to various degrees. Fgr(1-6) heterozygous mice have been shown to be normal.

In conclusion, the idea put forth by Partington et al. that FGFR3 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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12 Webster MK, Donoghue DJ. Constitutive activation of fibroblast growth factor receptor 3 by the transmembrane point mutation found in achondroplasia. EMBO J 1996;15:520-7.


This letter was shown to Dr Partington et al, who reply as follows.

Thank you for the opportunity of seeing the comments of Cohen and Neri on our recent paper. We were mildly surprised at their confidence not only in dismissing the possibility of a dosage effect of FGFR3 on growth, but also in asserting that all the short stature syndromes associated with mutations in this gene are explained by loss of gain of function. We believe the jury is still out and all will be revealed in good time.

However, we must protest at Cohen and Neri's attempt to distinguish our overgrowth syndrome by the rather cavalier manipulation of the growth data presented in table 2 of our paper. They have chosen to ignore two explicit points stated clearly: first that II.12 in family 1 is a special case because of severe disease (enpyema), which probably limited growth in childhood and, second, that overgrowth "became more obvious in late adolescence and early adulthood".

What Cohen and Neri have done is to take our mixed longitudinal and cross sectional growth data, translate it all into cross sectional data and, neglecting age, treat these measurements in the same way. This does dilute the overgrowth patterns observed. However, if one omits the data on II.12 for the reasons stated and takes the measurements at the oldest age of the 10 remaining subjects (all over the age of 15 years), then all the heights are at or above the 75th centile and five of them are above the 90th centile. In the same way, the head circumferences are all at or above the 50th centile with five above the 97th centile. This tells quite a different story from table 1 presented in Cohen and Neri's letter.

Some confirmation of this late growth pattern emerges from the heights recorded on II.11 and II.12 from family 1. Thus, between the ages of 18 and 28 years 5 months, II.11 grew 15 cm and between 17 years 5 months and 28 years II.12 grew 26 cm. Such growth increments are commonplace between the ages of 12 and 16 years, but are quite abnormal after the age of 17 years.

Physical measurements do not convey the whole picture. Clinically, those with overgrowth appear to be big people with large body frames, prominent supraorbital ridges, heavy facial features, and big hands and feet. Some, but not all, of these features are shown in the illustrations in our article.

Lastly, your readers may be interested to know that since our paper was published we have managed to meet III.8 in family 1 again and, on this occasion, were able to make some measurements and take a blood sample. At the age of 33, III.8 is a big woman with a heavy body frame and rather coarse or heavy facial features of which she is self-conscious and which I, not allowing herself to be affected. Her height is 180 cm, head circumference 60 cm, and hand length is 20.5 cm. She has mild intellectual handicap and a duplication of 4p16.3.

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Robin syndrome

I would like to comment on the paper by Sabry et al. in the September issue of the Journal of Medical Genetics. In the two patients they diagnosed as having Robin syndrome in conjunction with a number of unusual abnormalities. When looking at the photographs of their patients, I doubt whether the diagnosis of Robin syndrome is correct, especially in the first patient. She has a number of facial characteristics that are indeed seen in Robin syndrome, such as hypertelorism and...