

LETTERS TO THE EDITOR

Renal and urological tract malformations caused by a 22q11 deletion

Deletions in the chromosomal region 22q11 cause a variable spectrum of congenital malformations recognised as either velocardiofacial syndrome (VCFS, Shprintzen syndrome) or DiGeorge syndrome. Typically these defects involve the heart (conotruncus and aortic arch), palate, thymus, parathyroid glands, and mesenchymal structures of the face. In addition, a large number of associated features have been reported.^{1,2}

Among the 39 patients with a 22q11 deletion followed at our centre, four have a well documented congenital nephrourological malformation. The first patient has bilateral obstructive megaureter discovered after he presented with acute pyelonephritis at the age of 1 month. The second patient has unilateral renal agenesis, which was detected during a cardiac catheterisation. The third patient had a right multicystic kidney, presenting as an abdominal mass and surgically removed at the age of 6 weeks. In the fourth patient, unilateral renal agenesis was detected during routine abdominal ultrasound in the neonatal period. Interestingly, in two patients, the urological malformation was discovered during routine screening. In our series, as not all patients with VCFS have so far been systematically screened for the presence of a nephrourological malformation, the incidence of urological malformations is probably higher than 10%.

Nephrourological malformations have been reported before in DiGeorge syndrome and VCFS and include renal agenesis,^{2,3} multicystic kidney dysplasia,^{4,5} vesicoureteral reflux,¹ and ectopic kidney.⁶ Also, hydronephrosis and hydronephrosis have been described in several patients with DiGeorge syndrome, but the data available do not allow the distinction between vesicoureteral reflux, obstructive megaureter, or pelviureteral junction obstruction.^{2,7} The frequent occurrence of nephrourological malformations in these syndromes strongly suggests that this is not coincidental, but rather a variable manifestation of the underlying genetic defect.

In the evaluation of children with a del(22q11), nephrourological investigation should therefore be mandatory. In the absence of overt disease, renal ultrasound would be the preferred method. Many patients with a 22q11 deletion have a congenital heart defect, and will undergo cardiac catheterisation. During this procedure, contrast medium is injected into the circulation and, therefore, renography and pyelography can easily be performed simultaneously. As shown by the second patient in this series, this can lead to the detection of a nephrouropathy.

These different urological malformations found in association with a 22q11 deletion can be regarded as the variable expression of the same embryological defect, that is, an abnormal development of the lower or upper

ureteral bud.^{8,9} The wide spectrum of urological malformations encountered within a single pedigree of branchio-oto-renal syndrome further illustrates that these urological malformations are pathogenetically related and can be caused by the same genetic defect.¹⁰

It is generally thought that the critical gene(s) in 22q11 must have a role in cranial neural crest migration or differentiation in the third and fourth pharyngeal pouches. However, the defects affect many other tissues. The present observation suggests that one or more gene(s) in 22q11 also have a role in ureter bud development. This is not unprecedented, since the Ret proto-oncogene has a critical role in both neural crest and ureter bud development. In mice, this gene is expressed in both the nervous system and in the ureter bud, and a homozygous disruption of the Ret gene in mice leads to renal dysplasia or agenesis and enteric aganglionosis.¹¹ Several genes have already been isolated from the critical deletion region on 22q11, and most of them show widespread expression, including in the kidney. However, it appears that gene expression in the metanephric mesenchyme or kidney alone probably cannot explain the spectrum of kidney malformations observed in 22q11 deletions. Rather, based upon the presented clinical evidence, candidate genes for DiGeorge or Shprintzen syndrome are therefore expected to show embryonic expression in the ureter bud.

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Unstable mutation in incontinentia pigmenti?

I note with interest the report by Kirchman *et al*¹ of possible gonadal mosaicism for incontinentia pigmenti (IP) in a healthy male. The authors report two paternal half sisters who manifest incontinentia pigmenti, and in whom the paternal X is preferentially inactivated. The authors' arguments and conclusions are, however, predicated on the assumption that the relevant mutation (that is, that resulting in IP) is stable. A number of observations in IP, however, have led to the hypothesis, first suggested by Traupe and Vehring² that IP may be associated with an unstable mutation.

(1) Two reports exist of mother-son transmission of IP.^{3,4} This observation is inconsistent with the half chromatid mutation model⁵ put forward to explain the occurrence of IP in males who are cytogenetically normal (the majority of males with IP are cytogenetically normal, contrary to the authors' assertion that most have been found to have a 47,XXY karyotype^{2,6}).

(2) Mosaic phenotypic expression of skin abnormalities in females with IP follows Blaschko's lines and is thought to reflect the existence of two functionally distinct populations of cells as a result of (random) X inactivation. In cytogenetically normal males with IP, however, skin manifestations are also expressed mosaically.^{2,4,7} While this may be expected in sporadic (new mutation) males, and those with a 47,XXY karyotype, this would not be expected in the two cases of mother-son transmission, where the affected males are described as having features similar to females with IP. It might have been expected that males inheriting a maternal mutation might have diffuse disease affecting their entire skin. It might also have been expected that the occasional male with IP, who has a de novo mutation, might have diffuse involvement of skin in a segmental distribution, rather than the patchy distribution that is always seen.

(3) In his review of IP, Carney⁸ found a statistically significant tendency for daughters inheriting IP to have more severe manifestations than their mother, an indication of possible anticipation in IP.

If IP were found to be associated with an unstable mutation (?triple repeat), this might explain not only the points already mentioned but also the case reported by Kirchman *et al*,¹ interpreted as gonadal mosaicism. In this case, the father might have a premutation which expanded on transmission to his daughters; this would be analogous to the normal transmitting male in fragile X.⁹ In addition, a recent report of three families with new mutations in IP, all originating in a male progenitor, would also be consistent with the NTM hypothesis, although a high rate of new mutations is to be expected in X linked conditions with reduced male fitness (for example, Duchenne muscular dystrophy¹⁰). The question of an unstable mutation in IP will only be resolved with the cloning of the gene and elucidation of causative mutations. A careful search for triplet expansions in Xq28