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 may or may not be present. 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 was 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 ultrasound examination 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,23 multicystic kidney dysplasia,21 vesicoureteral reflux, 22 and ectopic kidney.22 Also, hydronephrosis and hydrocolpos 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.27 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), nephrological 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 nephropathy.

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 The wide spectrum of urological malformations encountered within a single pedigree of branchio-oto-renal syndrome further illustrates how 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 mediate a role in cranial neural crest migration or differentiation in the third and fourth pharyngeal pouches. However, the defects may 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 meta-nephric mesenchyme is 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 would therefore expected to show embryonic expression in the ureter bud.

Unstable mutation in incontinentia pigmenti?

I note with interest the report by Kirchman et al of possible gonadal mosaicism for incontinent pigment (IP) in a healthy male. The authors report two paternal half sisters who manifest incontinent pigmentation, 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 Vehring that IP may be associated with an unstable mutation.

(1) Two reports exist of mother–son transmission of IP.34 This observation is consistent with the half chromatid mutation model 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).28,34

(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. The existence of abnormal skin in a female without IP, however, skin manifestations are also expressed mosaically.47 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 similar distribution, rather than the patchy distribution that is always seen.

(3) In his review of IP, Carney7 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 (triplet repeat), this might explain not only the points already mentioned but also the case reported by Kirchman et al, 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.4 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 dystrophy). 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
in families with IP may, however, be fruitful in the search for the gene.

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The A-Z Reference Book of Syndromes and Inherited Disorders. 2nd ed. Patricia Gilbert. (Pp 378; £15.99 pb.) London: Chap-

The diagnosis of a rare condition in a child understandably raises many questions for that child’s parents and relatives. Such queries are 
usually posed to the paediatrician or GP 
caring for the child. However, there are a wide range of health professionals involved in the care of the child who need information about 
a condition, both for themselves, and 
to answer the questions inevitably also posed to these addresses. Overviews of “how did it happen?”, “can you treat it?”, “will it happen again?” and many more are well addressed in this reference book.

Dr Gilbert has produced an expanded sec-
ond edition of her book, designed to inform

health professionals and families after a 
syndrome diagnosis has been made. It has been 
specifically written in non-technical language, 
grounded in genetic expertise, who may not 
have a broad medical knowledge. Twenty new 
syndromes have been included at the request of 
readers, giving a total of 90 conditions, 
the majority of which are newly described. 
This is assisted by a clear appendix containing a good review 
of basic genetics by Peter Farnndon. A useful 
glossary is also included. There is an 
alphabetical listing of each syndrome, with 1000 words or more per entry 
describing the syndrome, causation, 
incidence, history, characteristics, 
management, and future developments. 
The descriptions show that Dr Gilbert has had 
extensive first hand experience in the care and 
management of children with rare disorders.

The inclusion of the addresses of support 
group associations, Contact-A-Family, and 
the UK clinical genetics centres also shows 
how understanding of parents’ needs. The 
language used for the most part is clear and 
simple to understand.

No such book could aim to cover all the 
rare syndromes. The author states that she 
can only cover a select number of syndromes. 
Her book is in fact an A-Z of syndromes, 
although she could have made it an A-Z by 
including Zellweger’s syndrome! There are also 
a few minor problems, such as the ab-
sence of any discussion of the additional 
problems, such as the appearance of Apol 
Alport’s syndrome, the omission of epilepsy 
as a complication of neurofibromatosis, and 
a rather unclear distinction between Finnish 
hypoplastic syndromes and the many other 
causes of hypoplastic syndromes. There is also 
no reference to the finding of an expanded 
triplet repeat causing fragile X syndrome, 
explaining the unusual inheritance. The index 
contains a list of signs and symptoms found 
in different syndromes, similar to that seen 
in Gorlin’s Syndromes of the Head and Neck, 
often as an aid to diagnosis. In fact, this 
volume is better used as a reference once a 
diagnosis has already been made. The lack 
of photographs also makes this volume more 
suited to the role of a lay reference work, 
rather than a diagnostic aid.

Overall, this is an excellent reference book 
for a wide range of health and educational 
professionals. It provides clear clinical 
information, and can give a quick snapshot 
of a condition for many people involved in 
the care of children with rare disorders.

ANDREW GREEN

Maternal Genetic Disease. Edited by N B 
Isada, A Drug, M P Johnson, M I Evans. 
(Pp 272; £65.95.) Stamford, Connecticut: 
Appleton and Lange. 1994. ISBN 0-8835-
1646-0.

People who advise pregnant women need to 
keep up with developments in genetics. 
Parents always want to know the risks of 
passing a condition to their children and 
whether anything can be done to reduce these. 
Often the first person they ask is their ob-
tetrician or midwife. This book, edited by a 
distinguished team from the United States 
and Israel, aims to provide the information 
required. It has some good features but these 
are outweighed by many faults.

The book opens with six chapters on gen-
eral aspects of genetic diseases, including 
specifically preconception counselling, chro-
mosomal problems, and mental retardation.

These deals with these problems in a similar 
way to most textbooks of genetics, albeit very 
briefly and with some important omissions. 
The problems changes character, and in the 
remaining 12 chapters a range of authors 
each tackle the genetic aspects of a specific 
maternal pregnancy problem, including 
the main medical problems that occur in preg-
nancy, renal, cardiac, haematological, neuro-
logical, and psychiatric disease, etc. This is 
a nice idea since, for generalists caring for 
pregnant women, these multifactorial con-
dacons are much more common than the 
single gene defects on which most traditional 
gene texts concentrate, and some chapters 
are very successful. However, for some dis-
ceses, once it has been stated that the 
hindrance is multifactorial, and the empirical 
recurrence risk given, there is little more to 
see. Unfortunately, this has not deterred con-
tributors from padding out their chapters with 
platitudes, irrelevances, and repetitions, and 
the whole book cries out for stronger editing.

The arrangement also leads to oddities. For 
example, cystic fibrosis (CF) appears only in 
chapters on anaesthesia and gastrointestinal 
problems. The reason for this appears to be that 
only written about malignant hyperpyrexia and 
succinylcholine sensitivity, the author needed a 
couple more pages to make a full chapter. The 
description of CF is quite inadequate to guide the 
day to day problems surmised by CF counselling 
and prenatal diagnosis for normal women with 
or without a family history.

There are many other omissions and im-
balance. Some are serious and others simply 
striking. For example, myotonic dys-
trophy gets only five lines in one of the in-
troductory chapters while multiple sclerosis 
gets 10 pages later on. It is unacceptable for 
a large genetics text in 1996 to omit any 
explanation of the whole area of triplet repeat 
sequences and genomic imprinting. Less ser-
ious, but still curious given the relative weight 
allocated to common multifactorial diseases, 
the omission from a three page description 
of pre-eclampsia any of mention of the fa-
miliar pattern of this disease. Readers will not 
learn that many experts even believe, albeit 
wrongly in my view, that this fascinating and 
common condition might be inherited in 
simple mendelian fashion, and that a number 
of groups are already doing gene linkage stud-
ies. They should be told.

This book bears all the hallmarks of being 
dashed off by busy authors and editors with 
more important calls on their time. I cannot recommend it.

J G THORNTON

The Molecular Biology and Pathology of 
Elastic Tissues. Ciba Foundation Sym-
posium 1992. (Pp 361; £49.95.) London: 

This book contains the published proceedings of an excellent Ciba Symposium on the 
Molecular biology and pathology of elastic tissues 
held in Kenya in 1994. As one expects of 
symposia proceedings, the book is beautifully 
produced and very portable. Fur-
thermore, it has been published within less 
than 12 months.

Non-American dominance in the field is 
very evident with 72% of the chapters and a
Unstable mutation in incontinentia pigmenti?

E Hatchwell

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