the Pitt-Rogers-Danks syndrome may be caused by a deletion in the same region.[5 7]

In a recent issue of the *Journal of Medical Genetics*, Partington *et al*[8] 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 "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, more importantly, (2) their idea that a triple dose of FGFR3 results in physical overgrowth.

First, we have rearranged 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). 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 FGFR3 can be deduced from the *Fgfr3* -/- knockout mouse,[10] 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 growth".

Evidence is accumulating that the known mutations on FGFRs are of the gain of function type. For example, Neilson and Friesel[11] made mutations in mRNA and expressed them in *Xenopus* that corresponded to 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. FGFR3 mutations for achondroplasia and thanatophoric dysplasia have also been shown to have greatly increased levels of phosphotyrosine.[12 13] 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 or hydrogen bonded FGFR dimers or (2) involvement in the activation loop of the kinase domain.[14]

Table 1 Rearranged data

		Centiles (%)		
	No	*≥90*	*≤50*	*≤25*
Height	31	32	29	26
Weight	23	52	35	22
Head circumference	22	41	32	9

Thus, the mutations for short limb skeletal dysplasias on FGFR3 (hypochondroplasia, achondroplasia, and thanatophoric dysplasia) are gain of function mutations that "put the brakes on even more" to various degrees. *Fgfr3* +/- heterozygous mice have been shown to be normal.[10]

In conclusion, the idea put forth by Partington *et al*[8] 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.

M MICHAEL COHEN JR
Department of Oral and Maxillofacial Pathology, Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada

GIOVANNI NERI
Istituto di Genetica Medica, Università Cattolica, Rome, Italy

1 Estabrooks LI, Breg WR, Hayden MR, *et al.* Summary of the 1993 ASHG ancillary meeting "Recent research on chromosome 4p syndromes and genes." *Am J Med Genet* 1995;55:453-8.
2 John RM, Robbins CA, Myers RM. Identification of genes within CpG-enriched DNA from human chromosome 4p16.3. *Hum Mol Genet* 1994;3:1611-16.
3 Thompson LM, Plummer S, Schalling M, *et al.* A gene encoding a fibroblast growth factor receptor isolated from the Huntington disease gene region of human chromosome 4. *Genomics* 1991;11:1133-42.
4 Wright TJ, Ricke DO, Denison K, *et al.* A transcript map of the newly defined 165 kb Wolf-Hirschhorn syndrome initial region. *Hum Mol Genet* 1987;6:317-24.
5 Clemens M, Martsolf JT, Rogers JG, Mowery-Rushton P, Surti U, McPherson E. Pitt-Rogers-Danks syndrome: the result of a 4p microdeletion. *Am J Med Genet* 1996;66:95-100.
6 Donnai D. Editorial comment. Pitt-Rogers-Danks syndrome and Wolf-Hirschhorn syndrome. *Am J Med Genet* 1996;66:101-3.
7 Zollino M, Bova R, Neri G. From Pitt-Rogers-Danks syndrome to Wolf-Hirschhorn syndrome. And back? *Am J Med Genet* 1996;66:113-15.
8 Partington MW, Fagan K, Soubjaki V, Turner G. Translocations involving 4p16.3 in three families: deletion causing the Pitt-Rogers-Danks syndrome and duplication resulting in a new overgrowth syndrome. *J Med Genet* 1997;34:719-28.
9 Cohen MM Jr. A comprehensive and critical assessment of overgrowth and overgrowth syndromes. In: Harris H, Hirschhorn K, eds. *Advances in human genetics*. Vol 18. Chap 4. New York: Plenum Press, 1989:181-303. Addendum, pp 373-6.
10 Deng C, Wynshaw-Boris A, Zhou F, Kuo A, Leder P. Fibroblast growth factor receptor 3 is a negative regulator of bone growth. *Cell* 1996;84:911-21.
11 Neilson KM, Friesel R. Ligand-independent activation of fibroblast growth factor receptors by point mutations in the extracellular, transmembrane, and kinase domains. *J Biol Chem* 1996;271:25049-57.
12 Naski MC, Wang Q, Xu J, Ornitz DM. Graded activation of fibroblast growth factor receptor 3 by mutations causing achondroplasia and thanatophoric dysplasia. *Nat Genet* 1996;13:233-7.
13 Webster MK, Donoghue DJ. Constitutive activation of fibroblast growth factor receptor 3 by the transmembrane domain point mutation found in achondroplasia. *EMBO J* 1996;15:520-7.
14 Webster MK, Donoghue D. FGFR activation in skeletal disorders: too much of a good thing. *Trends Genet* 1997;13:178-82.

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 extinguish 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 in the text: first that II.12 in family 1 is a special case because of severe disease (empyema), which probably limited growth in childhood and, second, that overgrowth "became more obvious in late adolescence and early adult life".

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 will not allow herself to be photographed. 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.

MICHAEL PARTINGTON
GILLIAN TURNER
Hunter Genetics, PO Box 84, Waratah, New South Wales 2298, Australia

Robinow syndrome

I would like to comment on the paper by Sabry *et al*[1] in the September issue of the *Journal of Medical Genetics*. In it, they 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

flat nasal bridge with a small snub nose, but the overall pattern of the face does not seem to fit Robinow syndrome as I have seen it in a total of seven cases.

First, the frontal bossing is not impressive and actually looks more like a metopic ridge. Infants with Robinow syndrome usually have pronounced frontal bossing and more obvious macrocephaly than case 1 of Sabry *et al.* Her head also may seem large as a result of the obvious dystrophic condition she is in.

Second, the lower face is too fine and the chin too pointed for Robinow syndrome. The mouth does not look like the typical thin lipped "carp mouth". The overall facial structure seems too finely sculpted to me. The face in Robinow syndrome tends to be rather coarse, Greig hypertelorism-like, in contrast, with a rounded lower half. The coarseness can be so pronounced that sometimes metabolic investigations are initiated because a mucopolysaccharidosis is suspected (own observation).

Third, eyelid hypoplasia giving the impression of exophthalmos seems to be quite a constant feature. I do not see it in this patient.

Fourth, the mesomelia in case 1 is certainly not impressive. It is a highly variable feature and actually not of much use in the diagnosis (see, for instance, Bain *et al*[2]), but if present it is an extra argument for the diagnosis, so some measurements of bone length would have been helpful here.

Finally, stating that the labia minora and clitoris were "slightly hypoplastic" seems a bit vague. What is "slightly"? A photograph would have been helpful.

The photograph of subject 2 in fig 7 poses some difficulties. Though it is true that the facial abnormalities tend to become somewhat less obvious with age, some anomalies remain quite obvious: the snub nose, the hypertelorism, and the thick alveolar ridges. The face also remains rather square and coarse. Subject 2 has a large nose compared to some of my patients of the same age and his hypertelorism is rather modest. His face seems too fine, much like his sister's. His alveolar ridges can, of course, not be judged from the picture. In my opinion, a diagnosis of Robinow syndrome is not certain in his case either.

As far as case 2 is concerned, her photograph (fig 8) is more convincing. Particularly when comparing the lower half of her face with that of case 1, it will be seen that there is a clear difference between the two. In my opinion the face of case 2 is definitely more "Greig-like". Though there is no mesomelia in this patient, this feature can be variable, as stated. I feel that in this case the diagnosis of Robinow syndrome is probably correct. This patient is not related to the other patients and, considering this, I think it is possible that the authors have in fact encountered, in case 1 and subject 2, a new recessive malformation syndrome with some resemblance to Robinow syndrome.

MAURICE VAN STEENSEL
Department of Human Genetics, Clinical Genetics Section, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands

1 Sabry MA, Ismail EAR, Al-Naggar RL, *et al.* Unusual traits associated with Robinow syndrome. *J Med Genet* 1997;**34**:736-40.
2 Bain MD, Winter EM, Burn J. Robinow syndrome without mesomelic "brachymelia": a report of five cases. *J Med Genet* 1986;**23**:350-4.

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

We read the comments of Dr van Steensel concerning our report of unusual traits associated with Robinow syndrome. In family 1 of our report, we described a female patient with many of the constant traits of Robinow syndrome, who showed other unusual traits in addition. We also observed variable expression of some of the traits of Robinow syndrome in healthy sibs/cousins of the proband in this consanguineous family. Like many syndromes for which no molecular/biochemical/cytogenetic markers have been identified, the diagnosis of Robinow syndrome remains solely dependent on the clinical phenotype of the patients. Naturally, this gives wide scope for different subjective views to argue for or against a given diagnosis. This is particularly true for Robinow syndrome with its wide spectrum of inter/intrafamilial phenotypic heterogeneity that would be expected to reflect a corresponding degree of molecular variability. Of course the profile in the proband of family 1 does not show a straightforward Robinow phenotype, or it would have been of little interest to the genetics community. Although we bear in mind the possibility of a new Robinow-like malformation syndrome in family 1 of the report, we are reluctant to designate it a new syndrome until all available possibilities are exhausted. Incidentally, we have recently received a letter from Dr H G Brunner from the Department of Genetics, University Hospital, Nijmegen, expressing interest in our Robinow syndrome cases and requesting our collaboration in their ongoing molecular study to map and clone the gene(s) responsible, which we are now considering.

M A SABRY
E A R ISMAIL
N AL-TORKI
S FARAH
Kuwait Medical Genetics Centre, Farwania and IbnSina Hospitals, Kuwait

BOOK REVIEW

If you wish to order or require further information regarding the titles reviewed here, please write to or telephone the BMJ Bookshop, PO Box 295, London WC1H 9JR. Tel 0171 383 6244. Fax 0171 383 6662. Books are supplied post free in the UK and for BFPO addresses. Overseas customers should add 15% for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank or by credit card (Mastercard, Visa, or American Express) stating card number, expiry date, and full name. (The price and availability are occasionally subject to revision by the Publishers.)

Human Cytogenetic Cancer Markers. Editors Sandra R Wolman, Stewart Sell. ($125.00.) New Jersey, USA: Humana Press. 1997. ISBN 0-896-03357-0.

This book reviews the genetic changes observed in solid tumours with particular emphasis on the practical issues of diagnosis, prognosis, and monitoring therapy. The book provides comprehensive coverage of the impact of the new genetic technology in furthering the understanding of the mechanisms underlying tumour development. The opening chapter illustrates the increasing relevance of genetic markers in tumour diagnosis and prognosis and provides a good introduction to the subject. Part 1 of the book, consisting of several chapters, covers the application of the major techniques, including flow cytometry, in situ hybridisation, CGH, and nucleic acid amplification. The relevance and applications of these techniques are well described. Part 2 of the book comprises comprehensive reviews of the current knowledge of the cytogenetic and molecular genetic changes observed in organ specific tumour types/subtypes. Each of these chapters is contributed by acknowledged experts in the field.

There is, almost inevitably, some variability in the apparent quality of the reviews and as advances in this field are taking place continually a book of this nature is always going to be a little behind hand. With the exception of an excellent chapter on the morphological, antibody, and chromosomal classification of haematological malignancies, this book does not cover leukaemias and lymphomas. One chapter at the very end of the book describes special techniques in cytogenetics, with emphasis on microdissection, which would perhaps have been better placed earlier in the volume along with the other methodologies. Although the colour plates are replicated as black and white photographs within the chapters, their placement within the centre of the book is disappointing. This necessitates frequent page turning, as the colour is fundamental to the illustration in some instances! However, this book provides excellent background information and an overview from which it would be possible to delve deeper using the cited references, although a quick scan for the new publications would also be wise in some instances.

A certain level of knowledge of solid tumours, cytogenetics, and molecular biology is assumed. This should be a useful book for the interested pathologist and clinician as well as students in these areas. Those in research will find the book an easy introduction to a topic and useful in the process of formulating ideas and methodological approaches before embarking on conducting their own investigations. Selected areas of cancer cytogenetics represented in this book are also areas of expanding interest for cytogeneticists and genetic technologists who, working in league with pathologists, may ultimately be able to provide more information of practical use for patients.

LIONEL WILLATT
JANET SHIPLEY

NOTICE

Call for patients with familial pancreatic disease: the EUROPAC Register

We are establishing a European register (EUROPAC) of families with hereditary pancreatitis, familial pancreatic cancer, and where pancreatic cancer has occurred as part of a familial cancer syndrome. This collabo-