LETTERS TO THE EDITOR

Prevalence of 22q11 microdeletion

Since its first description in DiGeorge syndrome, microdeletion of chromosome 22 within the q11 region has been reported in association with various clinical pictures. The true prevalence of this submicroscopic rearrangement is unknown. In 1994, Wilson *et al*¹ reported a minimum prevalence of 1/4000 live births. Their estimation was based on the fact that chromosome 22q11 deletions were the cause of at least 5% of congenital heart defects.

The present data were extracted from the Birth Defects Registry of the Bouches-du-Rhône area in southern France. Since 1984, this Registry has covered all births to mothers resident in the department. The registration is based on voluntary notification from the maternity units. Controls are found by active case searching in the departments of paediatrics and genetics and laboratories of pathology and cytogenetics. All registered cases are reviewed by a geneticist. The total number of births is extracted from the vital statistics given by the National Institute of Statistics. In the present study, the cases recorded were those born from January 1989 to December 1993. During this five year period, the registry monitored 116 452 births and identified 12 cases of chromosome 22q11 deletions, giving a prevalence of 1/9700 livebirths. In one case, a visible microdeletion was identified on R banded chromosomes. In another one, born in 1992, the microdeletion was shown by dosage Southern blotting. In the 10 others, the diagnosis was made by FISH analysis. This prevalence varied from 1/4500 in 1993 (five cases out of 22 624 births) to 1/23 975 in 1989 (one case out of 23 975 births). Table 1 shows the annual distribution

of cases and the exact 95% confidence intervals (Poisson distribution) for the total cases.² We have used a chi-square for linear trend to compare the number of annual cases. The observed differences are not statistically significant and variations could be the result of chance. However, since FISH analyses have been available in our centre since 1993, the real prevalence is probably closer to the 1993 one. The children born before 1993 were diagnosed much later (mean age at diagnosis 34 months) when compared with those born in the last year (mean 2 months). There is a significant difference ($p < 0.02$).

Of course, this prevalence is probably underestimated and only accounts for symptomatic cases. Most of the children included in these data exhibited prominent features of the CATCH 22 phenotype. Table 2 summarises the clinical features of the 12 patients. Of interest is the presence of a heart defect in 10 out of the 12 patients. This high percentage of CHD was confirmed in a larger series including children born in other French departments or before or after the study period (56/74). It is obvious that now most paediatricians, paediatric cardiologists, and geneticists are aware of the high percentage of 22q11 deletion in typical cases of DGS, VCFS, and more generally in any child born with a CHD and a typical face. However, an increasing number of atypical cases without any cardiac involvement have been reported recently.³⁻⁵ A significant number of familial cases have been described. Most of the carrier parents are almost asymptomatic or exhibit late onset disorders.⁵ Therefore, it seems likely that most of these mild cases are not diagnosed during infancy or childhood. Thus, we estimate that this prevalence of 1/9700 is significant for 22q11 deletion associated with a typical clinical picture. The true prevalence accounting for milder or atypical cases is probably higher. Systematic screening for 22q11 deletion in all newborns would be the best way to determine the exact frequency of this rearrangement. However, in the light of our partial knowledge about the long term prognosis in this condition, such screening would have important ethical implications.

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Should the 3C (craniocerebellocardiac) syndrome be included in the spectrum of velocardiofacial syndrome and DiGeorge sequence?

We read with interest the report by Lynch *et al*¹ of a 34 year old man presenting with cerebellar atrophy, neonatal hypocalcaemia, an atrial septal defect, a corrected cleft palate, and a dysmorphic face characteristic of velocardiofacial syndrome. Molecular cytogenetic studies showed a deletion of 22q11.2. The authors proposed that this man was the first reported patient with neurodegeneration, a 22q11.2 deletion, and velocardiofacial syndrome. They stated that neurological abnormalities, apart from developmental delay (present in this patient) and hypotonia, have not been commonly reported in association with either velocardiofacial syndrome or DiGeorge sequence. However, structural brain abnormalities such as a small cerebellar vermis, a small posterior fossa, and cysts have been detected by magnetic resonance imaging. Interestingly, an MRI of the head from this patient showed vermian and hemispheric cerebellar atrophy, basal ganglia calcification, a small brain stem without focal loss of volume, and white matter lucencies.

In reading their report we were impressed by the similarity between this patient and the eight published cases of patients with the 3C (craniocerebellocardiac) syndrome.² The 3C syndrome is rare and is characterised by hindbrain malformations, including cerebellar vermis hypoplasia, congenital heart defects, including tetralogy of Fallot, atrioventricular septal defect, and atrioventricular canal, along with several additional anomalies (cleft palate, micrognathia, ear and nose malformations, prominent forehead, and hypertelorism).²⁻⁷ Phenotypic variability exists for the 3C syndrome, and possibly the frequency of this syndrome is underestimated. In addition, the most recently reported patient with this syndrome² was originally suspected to have CHARGE association, a phenotypically similar condi-

Table 1 Annual distribution of prevalences of 22q11 microdeletions

	Cases		Prevalence		Total births
	No	95% CI	Per 100 000	95% CI	
89	1	0-5.6	4.2	0.1-23.2	23 975
90	2	0.2-7.2	8.6	1.0-30.9	23 341
91	3	0.6-8.8	12.7	2.6-37.2	23 559
92	1	0-5.6	4.4	0.1-24.3	22 953
93	5	1.6-11.7	22.1	7.2-51.6	22 624
Total	12	6.2-26	10.3	5.3-22.3	116 452

Table 2 Phenotype of the 12 deleted cases

	CHD	Hypocalcaemia	Hypo/aplasia of the thymus	Dysmorphism	Velopharyngeal insufficiency/cleft palate
1	-	-	?	+	+
2	+	+	+	+	+
3	+	?	+	?	?
4	+	-	+	+	?
5	+	?	?	+	-
6	+	?	+	+	?
7	+	-	?	+	+
8	+	-	+	+	?
9	+	+	+	+	+
10	*	+	+	+	?
11	+	-	?	-	-
12	+	+	+	+	-

*Aberrant subclavian artery.

tion to velocardiofacial syndrome and DiGeorge sequence.

Therefore, we propose that the 34 year old male reported by Lynch *et al*¹ with velocardiofacial syndrome, cerebellar atrophy, and a 22q11.2 deletion may have the 3C syndrome. Molecular cytogenetic testing of patients with the 3C syndrome using chromosome 22q11.2 probes could support whether the 3C syndrome is an extension of the spectrum of features resulting from a deletion of 22q11.2 or a contiguous gene syndrome. These molecular cytogenetic studies have been initiated.

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BOOK REVIEWS

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Non-Isotopic Methods in Molecular Biology. A Practical Approach. Editors E R Levy, C S Herrington. (Pp 221; £27.50.) Oxford: IRL Press. 1995. ISBN 0 19 9634556.

Safety and environmental considerations have recently encouraged the replacement of radioisotopic methods with the more recently developed methods that obviate the need for radioactivity. This slim volume assists this transition by providing both a general overview of some non-isotopic approaches as well as specific protocols to perform some common molecular biology procedures non-isotopically.

This book has a marked bias towards cytogenetic and histological techniques involving *in situ* hybridisation which is no bad

thing given the dominance of such techniques in hospital laboratories. In this regard, there should be a ready readership for this book.

However, as a volume purporting to cover non-isotopic methods in molecular biology, entire swathes of the field appear to be either lightly covered or omitted altogether. While the omission of protein blotting may perhaps be excusable, the omission of non-isotopic sequencing (both manual and automated variants) and reporter gene assays leaves a huge gap in coverage that should be rectified. Similarly, the large range of non-isotopic mutation detection techniques used in the burgeoning field of molecular epidemiology was restricted to a single chapter devoted to DNA analysis using PCR. If anything, there must be a ready market for a similarly sized volume addressing mutation detection techniques together with, say, non-isotopic sequencing.

In summary, this volume admirably covers non-isotopic hybridisation techniques but falls well short of its ambitious claim made for itself in its title. Dare we expect its omissions to be made good in another volume shortly?

DAVID HUEN

Human Molecular Genetics. Tom Strachan, Andrew Read. (Pp 606; £29.95.) UK: Bios Scientific. 1996. ISBN 1-872748-69-4.

At last! A textbook of human molecular genetics. One volume which considers not just meiosis and pedigrees, but molecular genetics in its many applications to the human genome. This is a beautifully crafted book in which a great deal of thought and effort must have been used to present a wealth of information in a very clear and readable format. The chapters of the book are organised logically and little previous knowledge is assumed. As the book progresses the material becomes more advanced, preceding chapters providing the information required to be able to understand the next topic. For readers with little background knowledge of DNA/human genetics the first three chapters of the book provide an introduction to DNA, chromosomes, and pedigree structures. In these chapters, and throughout the book, the authors are careful to point out when definitions or theories remain the subject of debate. Students will not be lulled into a false sense that all the information presented is absolute fact. The next three chapters describe the principles and applications of cloning and nucleic acid hybridisation. The authors then highlight chapters 7 to 10 (which consider the structure, function, evolution, and mutational instability of the human genome and human genes), as those which differentiate it from other volumes. These are followed by a section on mapping the human genome that describes the methods used in physical and genetic mapping and then discusses The Human Genome Project. Next there are chapters in which disease gene identification and molecular pathology are considered. Mutation testing in individual people and populations is discussed, for example, see table 16.7: "A test which performs well in the laboratory may be useless for population screening". Somatic mutations and cancer are reviewed, as are the theory and methodology for the study of complex disorders. The penultimate chapter considers studying human gene structure and function in cell cultures and the generation of

transgenic animal models of disease. And finally? Gene therapy, *ex vivo*, *in vivo*, and using genetically engineered hammerhead ribozymes, among others.

Why is this such a good textbook? It provides a comprehensive overview of the area. It is easy to read and understand. The index works. It conveys the enthusiasm of the authors for their subject matter. There are relevant references. It is concise, explaining principles with well chosen examples. The excitement of working in such a rapidly expanding area of science is tangible. Succinct summaries of the main points of each chapter are highlighted in coloured boxes, a real gift if you need to cram for an exam or plan lecture material for the examinees.

In Box 13.2, "A guide to the Internet", the hard core computer nomenclature is brief and a warning is issued about information on the Web. It is not peer reviewed and therefore "It may be good, poor, bad or even maliciously misleading." A quick poll of reviewers in the laboratory (one or two have already purchased personal copies) puts this publication firmly in the excellent category. We all agree that it will appeal to a very wide readership including undergraduate and postgraduate life science and medical students, and professional molecular and medical geneticists. It will probably become a standard text for an undergraduate human molecular genetics course.

JO WHITTAKER

NOTICES

Seventh Annual Medical Device Technology Conference

The Seventh Annual Medical Device Technology Conference and Table-Top Exhibition will take place on 18-19 November 1996 at the Swissôtel, Düsseldorf/Neuss. An essential briefing for all medical device manufacturers operating in the European market, this conference will provide delegates with a comprehensive update on the implementation of the medical devices Directives, focusing on current concerns such as technical standards, product liability, and environmental considerations. For further details contact Sonja Lloyd, Associate Conference Manager, fax: + 44 (0)1244 370 011.

UICC Symposium on Familial Cancer and Prevention Molecular Epidemiology: A New Strategy Toward Cancer Control

This symposium will take place on 14-16 May 1997 in Kobe, Japan. As part of a worldwide project of the International Union Against Cancer, this major international symposium will be the forum for examining controllable causative factors in familial cancer, evaluating markers of possible use in epidemiological studies and management, disseminating recent advances, and discussing ethical, legal, and social aspects. For details, contact the Organising Office (The Simul International Inc, Kansai Office, Kogin Building, Annexe 8F, 4-2-7 Koraibashi, Chuo-ku, Osaka 541, Japan. Tel: 81-6-231-2444; fax: 81-6-231-2447; Email: KYM04075@niftyserve.or.jp). Organising Committee: W Weber (Chair and European node), T Kitagawa (Molecular Epidemiology), and J J Mulvihill (North American node).