EDMOND CHIU

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This letter was shown to Dr Penman Splitt, who replies as follows.

We entirely agree with Marino *et al* that the conotruncal anomalies seen in patients with heterotaxy are likely to be secondary to distortion of cardiac looping and thus the mechanism is different from that seen in cases of 22q11 deletion. Their observations confirm our impression that 22q11 deletions are rare in patients with heterotaxy. While the two cases that we referred to are exceptional, they show the extreme phenotypic diversity associated with deletions of 22q11.

Heterotaxia syndromes and 22q11 deletion

In a recent issue of your journal we read with interest the very accurate review by Penman Splitt *et al*¹ on defects of left-right asymmetry. The authors correctly reported that in patients with heterotaxia (asplenia and polysplenia syndromes), conotruncal defects are one of the more frequent heart malformations. It is well known that 22q11 deletion has been described in a subgroup of patients with conotruncal anomalies in the setting of DiGeorge²⁻⁴ and velocardiofacial syndromes. In the paper of Penman Splitt *et al*¹ it was reported (personal communication to the authors) that the same microdeletion has been found in two patients, one with dextrocardia and one with left isomerism (polysplenia syndrome).

Since 1993 we have performed clinical and molecular evaluation of all patients with conotruncal anomalies observed at our hospital,⁵⁻⁷ including 20 cases with heterotaxia. Fifteen had asplenia syndrome and five polysplenia. All patients underwent phenotypic and cardiac examinations. Fluorescent *in situ* hybridisation was used for detecting 22q11 deletion.

No patients had phenotypic features of DiGeorge or velocardiofacial syndromes, and the genetic study did not show 22q11 deletion in any case. Our experience suggests that the conotruncal anomalies in the setting of heterotaxy syndromes are not related to 22q11 deletion, and are probably secondary to distortion of cardiac looping or to the anomaly of the situs itself. Different gene(s) and different developmental mechanisms may be involved in the pathogenesis of conotruncal anomalies in patients with situs solitus and in those with laterality defects.

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First report of three cystic fibrosis patients homozygous for the 1717-1G→A mutation

We report the identification for the first time of three cystic fibrosis (CF) patients homozygous for the 1717-1G→A¹ mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The clinical presentation of CF varies widely, the most common characteristics being chronic obstructive lung disease, raised electrolyte content of sweat, and pancreatic insufficiency (PI).² About 15% of patients display pancreatic sufficiency (PS).³

The isolation of the CFTR gene⁴⁻⁶ has made it possible to identify the main disease causing mutation, ΔF508, accounting for about 70% of molecular defects in the world population,⁴ and over 600 rarer presumptive mutations (CF Genetic Analysis Consortium). Among these, the 1717-1G→A mutation is a splice site alteration causing a G→A base change at the 3' end of the consensus sequence of intron 10. It was first reported in a patient of Celtic origin¹ and since then it has been detected in other populations, having an overall frequency of 1.1%.⁷

To date, a clinical correlation for this mutation has been defined only in patients who are compound heterozygotes for ΔF508, who display a similar pancreatic and pulmonary phenotype to that of homozygotes for ΔF508.⁸

In this report we describe the first three patients found to be homozygous for the 1717-1G→A mutation. They showed early pancreatic insufficiency (one meconium ileus) and two of them had early onset of respiratory symptoms, but with subsequent minimal lung involvement progression. These findings suggest that this mutation might predispose to a milder respiratory course.

Two patients (cases A and B) regularly attend the Milan CF Centre at the Department of Pediatrics, University of Milan; the third patient (case C) is followed at the Naples CF Centre, Pediatrics Department, II University of Naples.

The three 1717-1G→A homozygous patients include: case A, a female, born at term (birth weight 3550 g) to healthy, non-consanguineous parents. At birth, she presented with meconium ileus, which was sur-

gically treated with a 10 cm ileal resection. She had a high immune reactive trypsinogen (IRT) value at 5 days of life (173 ng/ml, normal value <40 ng/ml) and CF was confirmed by a positive pilocarpine iontophoresis sweat test (112 mmol/l chloride).⁹ Global treatment for CF was started at 2 months with pancreatic enzyme supplementation (Pancrease^R) and chest physiotherapy (positive expiratory pressure technique). At the latest clinical visit, aged 2 years 4 months, she was normal on examination, weight was 14 kg (75th centile), height 94 cm (97th centile). Good nutritional status was obtained with a low dose of pancreatic enzyme (1785 U/kg/day of pancrelipase) associated with a high fat content diet. A chest x ray showed only minimal thickening of the bronchial walls in the lower lobes. *Staphylococcus aureus* was intermittently isolated from bronchial secretions. She needed only one therapeutic antibiotic course for upper respiratory tract infection, and had had no admission to hospital since the diagnosis. No alterations in hepatic or nutritional indices were ever noted. Liver ultrasound was in the normal range.

The second patient, case B, a male, was born at term (birth weight 2850 g) to healthy, non-consanguineous parents. CF presented with malabsorption and bronchiolitis, requiring four hospital admissions in the first months of life. CF was confirmed by a positive pilocarpine iontophoresis sweat test (80, 105 mmol/l chloride). Regular follow up at our specialised CF Centre and adequate treatment were started at 6 months, with pancreatic enzymes (Pancrease^R), mucolytic and bronchodilator aerosol, and physiotherapy. He grew impressively after the start of therapy, body weight reaching the 50th centile at 2 years, and developing along the 97th centile from 5 years. At the last clinical visit, he was asymptomatic, not clubbed, his weight was 38 kg and height 139 cm. Steatorrhoea was absent and fat absorption coefficient was 93%, with 1061 U/kg/day of pancrelipase and a high fat content diet. A chest x ray showed only basal bronchial wall thickening. *Staphylococcus aureus* was chronically isolated from sputum samples. He needed only one therapeutic antibiotic course per year for upper respiratory tract infection and the clinical course was mild, with no further hospital admission, after starting treatment at our Centre following diagnosis. Lung function tests were always in the normal range. As compliance with chest physiotherapy was poor, daily sporting activities were encouraged. No alterations in nutritional indices were ever noted. Liver function tests were normal until July 1995, when serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), and glutamyltransferase (GT) were slightly increased (42 U/l, 47 U/l, and 53 U/l, with normal values less than 37 U/l, 41 U/l, and 49 U/l). Ultrasound liver examination showed early signs of liver disease, so ursodeoxycholic acid therapy was prescribed.

The third patient, case C, a female, was born to healthy, non-consanguineous parents. Both paternal and maternal ancestors came from the same small city near Naples. Cystic fibrosis presented early with failure to thrive, malabsorption, and bronchiolitis, and she had atelectasis in the upper left lobe, leading to hospital admissions at 1 and 3 months of age. CF was confirmed by a positive pilocarpine iontophoresis sweat test (93 mmol/l chloride). Regular follow up at the CF Centre and treatment was started with pancreatic enzyme

Table 1 Anamnestic, clinical, and laboratory data for the three 1717-1G→A homozygous patients

	Case A	Case B	Case C
Sex	F	M	F
Onset of symptoms	Birth	1 mth	1 mth
Meconium ileus	Yes	No	No
Data at diagnosis			
Age at diagnosis	Birth	6 mth	3 mth
Sweat chloride (mmol/l)	112	105	93
Pancreatic insufficiency	Yes	Yes	Yes
Failure to thrive	Yes	Yes	Yes
Pulmonary symptoms	No	Yes	Yes
Data at latest visit			
Age	2 y 4 mth	9 y	7 y
Weight/weight centiles	75/97	97/90	25/25
Cole's index*	95%	128%	108%
Chest x ray score†	5/38	9/38	10/38
Steatorrhoea‡	No	No	No
<i>Pseudomonas</i> colonisation	No	No	Intermittent
FEV ₁ (% of predicted)	ND§	93	ND§
FVC (% of predicted)	ND§	96	ND§

* Weight expressed as a percentage of the ideal weight for height.

† Chrispin-Norman score.

‡ With enzyme supplementation.

§ Not determined (patients were not able to perform reproducible tests).

Table 2 Clinical data of patients according to genotype

Variable*	Genotype		p value	
	ΔF508/ΔF508	ΔF508/1717-1G→A		
No of patients (male)	21 (62%)	21 (62%)		
Age (y)	15 ± 7.9	14.9 ± 7.3		
Age at diagnosis (y)	1.3 ± 2.6	2.4 ± 3.2	0.478	NS
Sweat chloride (mmol/l)	106 ± 12.4	115 ± 36.6	0.271	NS
Weight (kg)	39 ± 15.7	39.5 ± 13.2	0.904	NS
Height (cm)	145.2 ± 25.2	146.3 ± 19.7	0.884	NS
Chest x ray score	7.8	8.8	0.926	NS
(Range)	(5–31)	(5–33)		
FEV ₁ % of predicted	67.8 ± 26.2	80.7 ± 26.7	0.158	NS
(Range)	(26–113)	(30–128)		
FVC % of predicted	79 ± 29.3	90.2 ± 18.9	0.158	NS
(Range)	(36–127)	(53–122)		
No positive (%)				
Pancreatic insufficiency	21 (100)	19 (90.5)	0.468	NS
<i>Pseudomonas</i> colonisation	17 (80.9)	19 (90.5)	0.65	NS
Meconium ileus	2 (9.5)	4 (15.4)	0.5	NS
Nasal polyps	1 (4.8)	2 (9.5)	1	NS
DIOS	2 (9.5)	0	0.46	NS
Pancreatitis	0	0		
Liver disease	5 (23.8)	8 (38.1)	0.5	NS
Diabetes mellitus	3 (14.3)	3 (14.3)	1	NS
ABPA	4 (19.0)	5 (23.8)	1	NS

FEV₁ = forced expiratory volume in one second. FVC = forced vital capacity. DIOS = distal intestinal obstruction syndrome. ABPA = allergic bronchopulmonary aspergillosis. NS = not significant.

supplementation, mucolytic and bronchodilator aerosol, antibiotics, oral aminophylline, and intensive chest physiotherapy. Growth increased after the start of therapy. During the first years of life she had episodic attacks of dyspnoea and recurrent wheezing, then gastro-oesophageal reflux (GER) was identified as the cause of the symptoms and appropriate therapy was started. She needed several therapeutic antibiotic courses per year for lower respiratory airway infections. *Staphylococcus aureus* was chronically isolated from sputum samples and she harboured *Pseudomonas aeruginosa* intermittently. At the latest clinical visit, aged 7 years, she presented with daily cough; her weight was 19.3 kg (<25th centile) and height 112 cm (<25th centile). No alterations in nutritional or hepatic indices were ever noted. Table 1 shows anamnestic data and clinical characteristics of the three 1717-1G→A homozygotes.

None of the three patients showed any additional CF related complications (nasal polyposis, allergic bronchopulmonary aspergillosis, etc), maybe owing to their young age.

It is interesting to note that in northern Italy the frequency of the 1717-1G→A mutation is higher than in other northern European populations, being present in about 4.0% of CF chromosomes (41/1018). Also noteworthy, of the 32/41 chromosomes carrying the 1717-1G→A mutation identified in our

patients for which the origin was known, most were of northern Italian ancestry, originating from Lombardy.

In order to evaluate whether chromosomes bearing the 1717-1G→A mutation shared a common genetic background, we determined the haplotypes of the three highly polymorphic intragenic clusters of dinucleotide repeats (IVS8CA, IVS17BTA, and IVS17BCA)^{10,11} identified in the CFTR gene. Microsatellite mapping showed that all 26 chromosomes tested shared the same 16/7/17 haplotype. The genetic homogeneity underlying the 1717-1G→A mutation in Italy may suggest a common origin for this mutation, the relatively high incidence of which could be ascribed to a possible founder effect in our population.

Correlation between genotype and phenotype for the 1717-1G→A mutation had previously been defined only in an international collaborative survey, including our centre, of CF patients who were compound heterozygotes for this mutation and ΔF508, since at that time no patient homozygous for 1717-1G→A had been detected. This study showed that the clinical features, including pulmonary status, of compound heterozygotes for ΔF508 and 1717-1G→A did not differ significantly from that of homozygotes for ΔF508.⁸

The same findings were obtained for a group of 21 1717-1G→A/ΔF508 compound

heterozygous patients (13 males, 62%) compared with 21 ΔF508 homozygotes of the same age and sex, all patients being followed in the Milan Centre with the same diagnostic and therapeutic approaches. In all patients, CF diagnosis was confirmed by two positive sweat tests (>60 mmol/l chloride). Pancreatic status was assessed by the steatocrit method¹² and, in patients aged over 3 years, by stool fat content, analysed according to the method of van der Kamer *et al*.¹³; fat absorption was expressed as percentage of fat intake. Pulmonary function tests (forced vital capacity or FVC, and forced expiratory volume in one second or FEV₁) were expressed as a percentage of predicted values for sex and height.¹⁴ Growth and nutritional status were assessed by anthropometric measures. Pulmonary radiographs were evaluated using the Chrispin and Norman score, ranging from 0 (no damage) to 38 (the worst score).¹⁵

In our group, the severity of pulmonary disease associated with the 1717-1G→A mutation is highly variable in compound heterozygous patients, but although their mean FVC and FEV₁ values are higher than those in ΔF508 homozygotes, the differences are not statistically significant (table 2).

The clinical courses of the two CF patients (cases A and B) homozygous for the 1717-1G→A mutation showed that both had early pancreatic involvement and the second an early onset of respiratory symptoms. Conversely, the progression of lung involvement was minimal in both patients, who only require a small amount of therapy. The clinical course is different from that observed in 1717-1G→A/ΔF508 compound heterozygotes and ΔF508 homozygotes, even if ΔF508 homozygotes may exist who display clinical features similar to those of our patients, taking into account their young age.

The general clinical pattern for patient C was slightly more severe than for the other two patients, but the association between GER and acute and chronic respiratory disease in infants and children is well known. In addition, GER has been reported increasingly often in CF and it is known that pulmonary function may be worse in CF patients presenting with GER.¹⁶ Thus, we cannot exclude that in the absence of GER this patient homozygous for the 1717-1G→A mutation might also have developed only a mild lung phenotype.

The data reported here for three 1717-1G→A homozygous patients show an association of early onset of pulmonary symptoms (two patients) and pancreatic involvement (three patients) with a surprisingly slow progression of pulmonary disease (evident in two patients). Our data suggest that the 1717-1G→A mutation in the homozygous state may be associated with mild to minimal lung disease, even if prediction of slow, mild, progressive pulmonary deterioration in such young CF patients needs further confirmation both in a larger survey and over time when longitudinal data will be available.

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BOOK REVIEWS

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Look Back to the Future. The Cells of the Body: A History of Somatic Cell Genetics. Henry Harris. (Pp 263; \$59.00.) New York: Cold Spring Harbor Laboratory Press. 1995. ISBN 0-87969-460-2.

As the Editor will attest, it has taken me far too long to find the time to read this book and write the review. In large part, this is because life is far too fraught and hectic for scientists these days to sit back and reflect on the origins and evolution of their subject and the ideas that have shaped it. Yet, ultimately, it was a most rewarding experience to be guided by the deliberately erudite Henry Harris through this fertile terrain which con-

stitutes the still evolving history of somatic cell genetics. After all, I myself had been a participant in some of the crowd scenes, and had met or heard lectures delivered by many of the eminent scientists whose photographs grace the second half of the book, if not their predecessors in the first half.

Before somatic cells could be used to explore biology, their credentials had to be painstakingly established. The still continuing elucidation of the role of chromosomes and their constituent DNA in directing cell division and function was begun in the 19th century. Harris cites not only the well known greats like Boveri, but also many less well known figures whose ideas and experiments influenced the star players. The development of cell culture techniques, the inevitable but fateful use of malignant and embryonal cells, improved cytogenetic methodology for visualising chromosomes, the enabling technology of selectable mutant lines which made possible the use of classical complementation techniques, all led eventually to the idea of using these potential tools in more controlled cell fusion experiments. The discovery of interspecific somatic cell hybrids in which species specific chromosome loss (still unexplained) occurs led to the development of the more narrowly defined concept of somatic cell genetics, where parasexual chromosome segregation can be harnessed for the beginnings of gene assignment and mapping. This proved to be a particular bonus for human genetics which had lagged so far behind other organisms where breeding experiments were permissible. Many refinements were introduced, for example, the fragmentation of chromosomes by x irradiation to allow gene order determination (by Steven Goss in Henry Harris's laboratory in the mid 1970s). This approach has recently been revived on a grand scale when development of a combination of automated molecular microtechniques and statistical analysis have made possible the mapping to a very high density of DNA markers, as a prelude to the final human genome sequencing effort which is now in progress.

Gene mapping is only one area revolutionised through the use of somatic cell genetics. Initially, before DNA level analysis by "molecular biology" was made possible through the development of restriction enzymes, Southern blotting, and eventually the polymerase chain reaction (PCR) - each step carefully traced by Harris - all gene mapping was through analysis of express functions. Of course, many functions expressed in tissues in vivo are not expressed in cell culture. Even when obvious differentiated functions, such as melanin production or serum albumin synthesis, are seen in culture, early fusions between cells from different lineages showed that differentiated functions were frequently extinguished after fusion but subsequently re-expressed as more chromosome loss took place, removing genes which presumably mediate extinction. Cell culture methods have been improving gradually as new growth factors are defined; cells from different tissues can now be grown under conditions where control of expression of a wide spectrum of differentiated functions can be studied. The development of monoclonal antibody technology in Cambridge in the late 1970s heralded a major step in harnessing the ability of appropriately chosen somatic cell partners to express specific products of differentiation.

Another area in which Harris and co-workers make some seminal contributions is in our

understanding of the mechanisms of tumorigenesis. Many aspects of current ideas in this field were developed using somatic cells: from the examination of specific chromosomal rearrangements in cells derived directly from patients, to the finding, perhaps surprising at first glance, that malignant and normal cells fused together initially produce normal hybrids, although malignancy may be re-expressed as certain specific chromosomes are lost. This, together with some other observations, led to the concept of tumour suppressor genes. DNA transfection studies to define oncogenes were also done in somatic cells.

The use of embryonal stem cells to make mouse chimaeras is another area that has been elaborated into the great industry of making transgenic mice and specific gene knockouts which are providing so much insight into developmental control and gene interaction.

Somatic cells continue to provide new approaches to unravelling biological function. Reading this scholarly account of their history is well worth the effort, not only to provide hindsight, but quite likely foresight and new ideas.

VERONICA VAN HEYNINGEN

Transcription Factors. Editor J Locker. (Pp 150; £12.99.) Chichester: John Wiley & Sons. 1996. ISBN 0-471-95339-3.

Fundamental to cell differentiation and development is the regulation of gene expression in a spatial and temporal specific manner. This is brought about by unique combinations of specific binding sites and transcription factors in conjunction with RNA polymerase II. This little book is, in essence, a catalogue of the eukaryotic transcription machinery components. It is one of a series entitled "Essential Data", of which most are concerned with laboratory equipment and methods.

Chapter 1 consists of a brief account of the various polypeptide subunits of the RNA polymerase II enzyme complex. It then lists the subunits and defined interacting transcription factors in yeast and other organisms, along with molecular weight, brief comments, and references.

Chapter 2 consists of a very brief introduction to transcription factors and a 40 page long comprehensive list of DNA binding sites, factors which bind to them, the family or families to which the factor belongs, and a very brief comment on each, including references.

Chapter 3 provides a detailed and informative account of RNA polymerase I and III transcription factors. The tables in this chapter include GenBank accession numbers, which are absent in the previous two chapters.

Chapter 4 consists of charts of the major transcription factor families, indicating the relative frequency and importance of specific amino acids at each position. Migraine sufferers would do well to avoid looking at these charts.

The book is full of jargon, much of which is not explained. For example, despite a section of text on UBF, I failed to find out what UBF was an abbreviation of.

It is clear then that this book is intended for transcription factor aficionados with a desire to have a little information on all transcription factors and the references for finding the details they require. For those wishing to know more about transcription factor molecular biology, this book is not for you. The Royal Society philosophical transactions issue on transcription factors would be a better bet.

ROSS HAWKINS