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THE HOSPITAL FOR SICK CHILDREN

FAX MACHINE NUMBER: (416) 813-4931

HSC

LAP-CHEE TSUI, Ph.D.
DEPARTMENT OF GENETICS
PHONE: (416) 813-6015

DATE: September 29, 1992 (Newsletter #49)

TO: MEMBERS OF THE CYSTIC FIBROSIS GENETIC ANALYSIS CONSORTIUM

Amos, Boston U, USA
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Tümmler, Hannova, Germany
Verellen-Dumoulin,Bruxelles,Belgium
Willems, Univ Antwerp, Belgium
Williamson,St Mary'sLondon,England

FROM: LAP-CHEE TSUI TOTAL NUMBER OF PAGES: 1817

Operators: Please deliver this document to the member listed in your institute.

NEWSLETTER #49, September 29, 1992

1. Mutation reports:

Name	Amino acid change	Nucleotide change	Exon	Reference
1833delT	Frameshift	deletion of T at 1833	12	M. Schwartz, A.L. Palle, G.V. Christensen (Aug 20)
3293delA	Frameshift	deletion of A at 3293	17b	N. Ghanem, B. Costes, J. Martin, M. Goossens (Aug 24)
Q1071P	Gln→Pro at 1071	A→C at 3344	17b	N. Ghanem, B. Costes, J. Martin, M. Goossens (Aug 27)
R170G	Arg→Gly at 170	C→G at 640	5	M. Claustres, M. Laussel, G. Razakatsara (Sep 7)
S466X	Ser→Stop at 466	C→G at 1529	10	T. Meitinger, C. Aulehla-Scholz, I. Böhm, T. Deufel (Sep 14)
I566L	Ile→Leu at 566 (mutation?)	A→C at 1798	11	G. Ghanem, B. Costes, J. Martin, M. Goossens (Sep 18)
D1152H	Asp→His at 1152	G→C at 3586	18	W.E. Highsmith, L. Burch, K.J. Friedman, B.M. Wood, A. Spock, L.M. Silverman, M.R. Knowles (Sep 18)
W846X1 (see note)	Trp→Stop at 846	G→A at 2669	14a	J. Cheadle, L. Meredith (Sep 28)

Please note that the other mutation identified by Vidaud et al. (1990) is still W846X.

2. DNA sequence polymorphisms/variations in the coding region

3471 (T or C)	No change (Ala at 1113; T→C change accompanying Q1071P)	17b	N. Ghanem, B. Costes, J. Martin, M. Goossens (Aug 27)
2553 (A or G)	Ile→Met at 807	13	C. Ferec, I. Quere, M.P. Audrezet, C. Verlingue, H. Guillermit, B. Mercier (Sep 14)
1184 (C or G)	Thr→Ser at 351	7	W. Lissens, M. Bonduelle, I. Liebaers, C. Ferec, I. Quere, M.P. Audrezet, B. Mercier (Sep 14)

3. Correction: The putative splice mutation reported by Estivill et al. in NL#48 should be 3601-111G→C (not G→T).

4. The last general meeting for the consortium was held in Dublin during the International CF Conference on August 25, 1992. The synopsis of the meeting is as follows:

a. It is unanimously decided that the Consortium should continue to operate, primarily for the collection of new mutation information and updates of the list of mutations. Newsletter once a month is adequate.
b. The response to the request of data for the population screening table has not been overwhelming. It is also felt that we have already collected sufficient data for the

common mutations. Therefore, it is decided that collection population screening data will be reduced to at most once a year.

c. There was a short discussion on the Consortium guideline regarding citation of unpublished data. Members are reminded that the original reporting group should be consulted whenever the information is used for seminars or secondary reports are submitted for publication. Information regarding the general frequency of mutations across different geographic locations can be freely quoted for comparative purpose. To avoid unnecessary misunderstanding, members are asked to consult with the source group for citation of any specific information when in doubt.

5. Attached are some summary diagrams and tables that might be useful for general presentations. It was initially suggested that these materials would be provided to members in slides ready for presentation. The cost for large scale reproduction is prohibitive. Good copies may be obtained from a review article which will appear in the November issue of Trends in Genetics.

6. There will not be any formal CF Genetic Analysis Consortium meeting at the North American CF Conference.

7. For rapid publication of CF mutations, you may now also consider *Human Heredity*. Manuscripts should be addressed to Dr. Leo P. ten Kate, Department of Medical Genetics, University of Groningen, Antonius Deusinglaan 4, 9713 AW Groningen, The Netherlands. Tel: +31 50 63 29 25; FAX: +31 50 63 29 47.

Best regards,

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Dr. Lap-Chee Tsui
CF Genetic Analysis Consortium
Department of Genetics
555 University Avenue
Toronto Canada

Fax: 416 813 4931

Dear Consortium members,

We would like to report a new mutation in exon 12: 1833 delT. It has been found on one out of 68 non ΔF508 Danish CF chromosomes, associated with haplotype (KM18,XV2C) C and IVS8CA=7. It was found by SSCP analysis.
By screening for mutations by SSCP we found 11 chromosomes (out 68) with the previous published mutation 394 delTT (Claustres, NL#45). This mutation mighth be worth looking for. The mutation was associated with haplotype B (IVS8CA) 2 in 6 cases. The rest have not been determined yet.

Best regards,

Marianne Schwartz
Anne Lise Palle
Gitte Vedel Christensen
Pernille

CENTRE HOSPITALIER UNIVERSITAIRE HENRI MONDOR
UNIVERSITE PARIS XII- VAL DE MARNE

LABORATOIRE DE BIOCHIMIE - DEPARTEMENT DE GENETIQUE - INSERM U.91

Professeur Michel Goossens
Téléphone : (1) 49 81 28 61
Télécopie : (1) 49 81 28 42

FACSIMILE TRANSMISSION COVER SHEET

DATE: August 24, 1992

TO: Dr. Lap-Chee TSUI
C/O Consortium

FAX: **1-416-813-4931**

FROM: N.Ghanem / M. Goossens
FAX : 33.1.49.81.28.42

MESSAGE:
Dear Lap-Chee

We report to the Consortium a frameshift mutation in exon 17b of CFTR; it is a deletion of A at position 3293 (3293delA), detected via DGGE and direct sequencing.
The mutation was found in a 15-year French patient who bears ΔF508 on the other chromosome.

Best regards

N. Ghanem
B. Costes
J. Martin
M. Goossens

THIS TRANSMISSION CONSISTS OF 0 PAGE IN ADDITION TO THE COVER SHEET. IF THE TRANSMISSION IS INCOMPLETE OR ANY PORTION IS ILLEGIBLE PLEASE CONTACT US BY FAX AT 33.1.49.81.28.42 OR BY PHONE AT 33.1.49.81.28.61.

CENTRE HOSPITALIER UNIVERSITAIRE HENRI MONDOR
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Professeur Michel Goossens
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FACSIMILE TRANSMISSION COVER SHEET

DATE: August 27, 1992

TO: Dr. Lap-Chee TSUI
C/O Consortium

FAX: **1-416-813-4931**

MESSAGE:
Dear Lap-Chee

We report to the Consortium a mutation associated with a sequence change in exon 17b of CFTR; the double substitution was detected by DGGE and identified by direct sequencing; it is an A - C change at nt 3344 (Q1071P) and a T - C change at 3471 (A1113A).
The mutation was found in an adult French patient who bears ΔF508 on the other chromosome.

Best regards

N. Ghanem
B. Costes
J. Martin
M. Goossens

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Pr. Lap-Chee Tsui
The Hospital for Sick Children
555 University Avenue
Toronto. Ontario
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Fax N° 19 1 416 813 4931

from : Dr. Mireille Claustres
Laboratoire de Biochimie Génétique
Institut de Biologie
34060 Montpellier Cedex . France
Fax 33 67 52 15 59

Montpellier, September 7, 1992

Dear Lap-Chee,

We would like to report to the Consortium a new mutation in exon 5, that we found in one chromosome from a patient from Southern France : R170G (C-->G at 640).

This mutation was detected by SSCP. It does not alter a restriction site.
We do not know if this substitution is a rare variant or a mutant.

Best regards,

Mireille Claustres, Laussel M. , Razakatsara G.

Ludwig-Maximilians-Universität München

Abteilung für pädiatrische Genetik der Kinderpoliklinik

Abteilung für pädiatrische Genetik · Genetische Beratungsstelle
Goethestraße 29, 8000 München 2

Leiter: Prof. Dr. Jan Murken

CF-Consortium
c/o Dr. L-C. Tsui
The Hospital for Sick Children
Department.of Genetics
Toronto Ontario
Canada M5G 1X8

Fax: 001-416-813-4931

München, 14.9.92

Dear Lap-Chee,

by SSCP screening of non-dF CF chromosomes we have identified a new mutation in exon 10 in two unrelated CF patients. Sequenzing revealed:

C to G at nucleotide position 1529

This introduces a stop codon at an position 466 of the CFTR protein (Ser466stop).

In both cases, the second mutation is dF508 .

yours sincerely

Thomas

Thomas Meitinger, Christa Aulehla-Scholz, Ingolf Böhm, Thomas Deufel

CENTRE DE TRANSFUSION SANGUINE ET DE BIOGENETIQUE

Laboratoire agréé N° 29-39

Directeur Général : Docteur J.P. SALEUN

Centre Départemental de Transfusion Sanguine
Directeur : Docteur P. DEROFF

Centre de Biogénétique
Directeur : Docteur C. FEREC

N/Réf. : CF/ALM-0722/92

Brest le, 14 septembre 1992

Dr. L. C. TSUI
Hospital For Sick Children
Department Genetics
656 University Avenue
TORONTO
ONTARIO
CANADA M5G 1X8

Fax : 19 1 416 813 4931

Dear Lap Chee,

We would like to report to the Consortium an unpreviously described polymorphism we have identified in exon 7.

- The nucleotide change, C --> G, was observed at position 1184 leading to T351S. The change is very likely to be a polymorphism as it was observed on one chromosome of a healthy obligate carrier (the father of a CF child) bearing the R1162X mutation.

Best regards,

W. LISSENS
M. BONDUELLE
I. LIEBAERS

C. FEREC
I. QUERE
M.P. AUDREZET
B. MERCIER

48 Rue Félix Le Dantec - B.P. 454 - 29275 BREST Cédex
Téléphone : 98.44.49.39 - Télécopie : 98.43.06.66
Association (Loi de 1901) reconnue d'Utilité Publique

CENTRE DE TRANSFUSION SANGUINE ET DE BIOGENETIQUE

Laboratoire agréé N° 29-39
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Centre de Biogénétique
Directeur : Docteur C. FEREC

N/Réf. : CF/ALM-0723/91

Brest, le 14 septembre 1992

Dr. L.C. TSUI
Hospital for Sick Children
Department Genetics
555 University Avenue
TORONTO
ONTARIO
CANADA M5G 1X8

FAX 19 1 416 591 4931

Dear Lap Chee,

We would like to report to the Consortium a novel polymorphism we have identified in exon 13.

The nucleotide change A --> G was observed at position 2553 leading to I807M. This modification was observed on one normal French chromosome.

Best regards.

C. FEREC.
I. QUERE.
M.P. AUDREZET,
C. VERLINGUE,
H. GUILLERMIT,
B. MERCIER

46 Rue Félix Le Dantec - B.P. 454 - 29275 BREST Cédex
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CENTRE HOSPITALIER UNIVERSITAIRE HENRI MONDOR
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Professeur Michel Goossens
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FACSIMILE TRANSMISSION COVER SHEET

DATE: September 18, 1992

TO: Dr. Lap-Chee TSUI
C/O Consortium

FAX: 1-416-813-4931

MESSAGE:
Dear Lap-Chee

We report to the Consortium a possible mutation in exon 11 of CFTR detected by DGGE and identified by direct sequencing; it is a point mutation A-C at nucleotide 1798, leading to a change from Isoleucine to Leucine at position 556, a residue conserved between mouse and human CFTRs. The anomaly (I556L) was found once in an adult French patient with chronic bronchitis. No sequence variation has been found so far on his other chromosome.

Best regards

N. Ghanem
B. Costes
J. Martin
M. Goossens

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THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

The School of Medicine
Department of Pathology
Division of Molecular Pathology

The University of North Carolina at Chapel Hill
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Molecular Genetics
Research and Development
Molecular Neonatal Screening
Oligonucleotide Synthesis
Molecular Hematopathology

Surgical Pathology
Molecular Oncology
Molecular Cytogenetics
Molecular Microbiology

9/18/92

Cystic Fibrosis Gene Analysis Consortium
c/o Dr. Lap-Chee Tsui

Dear Lap-Chee,

We are reporting a new mutation in exon 18 of the CFTR gene to the Consortium. The mutation is D1152H, resulting from a G to C base substitution at base #3586. The mutation was identified by heteroduplex analysis on an MDE gel (AT Biochem, Malvern PA) and direct sequencing.

The family in whom this mutation was identified is of Ashkenazi Jewish/North European Protestant extraction and is remarkable for advanced age, mild pulmonary disease, pancreatic sufficiency, and normal sweat chloride values. The index patient was diagnosed with variant CF at age 57 on the basis of clinical phenotype and abnormal nasal epithelial bioelectric parameters. In an attempt to set phase for her XV.2c/KM-19 haplotype, linkage analyses were performed on her 8 living siblings. The index patient and two of her brothers were found to carry the BC haplotype. The diagnosis of variant CF was made in both brothers, ages 60 and 70. These individuals are among the oldest who have been newly diagnosed with CF. The other chromosome in these individuals carries G542X. The genotype D1152H/G542X was not found in the 6 unaffected siblings.

The mutation creates a new AflIII site; but may be more economically assayed for using a PSM mismatch primer:

5' tgg gct gta aac tcc agc tta 3'

with the reverse primer 18i-3 (Zielenski et al). Amplification of the normal allele yields a 225 bp product which is cut by DdeI to 207 + 18 bp. The mutant allele is not cut by DdeI. We have not found D1152H in 10 patients with pancreatic sufficiency or 3 additional patients with normal sweat chloride values.

Sincerely,

W. Edward Highsmith
Lauranell Burch
Kenneth J. Friedman
Beverly M. Wood
Al Spock
Lawerence M. Silverman
Michael R. Knowles

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Dr. P. S. Harper
Professor and Head of Department

Dr. D. J. Shaw
Senior Lecturer in Molecular Genetics

Dr. A. Clarke
Senior Lecturer in Clinical Genetics

Dr. M. Owen
Senior Lecturer in Neuropsychiatric Genetics (jointly with Psychological Medicine)

Lap-Chee Tsui, Ph.D.
c/o CF Consortium
Dept. of Genetics
Hospital for Sick Children
555 University Ave.
Toronto, Ontario
CANADA M5G 1X8

28/9/92

Dear Lap-Chee,

We would like to report to the consortium members a new mutation in exon 14a of the CFTR gene. This is a G to A substitution at position 2669, which introduces a stop codon at amino acid residue 846 (W846X). Vidaud et al. (1990), has previously reported a W846X mutation, but as a result of a G to A substitution at position 2670.

The G to A substitution at 2669 destroys an NlaIII restriction site, providing a suitable means of detection.

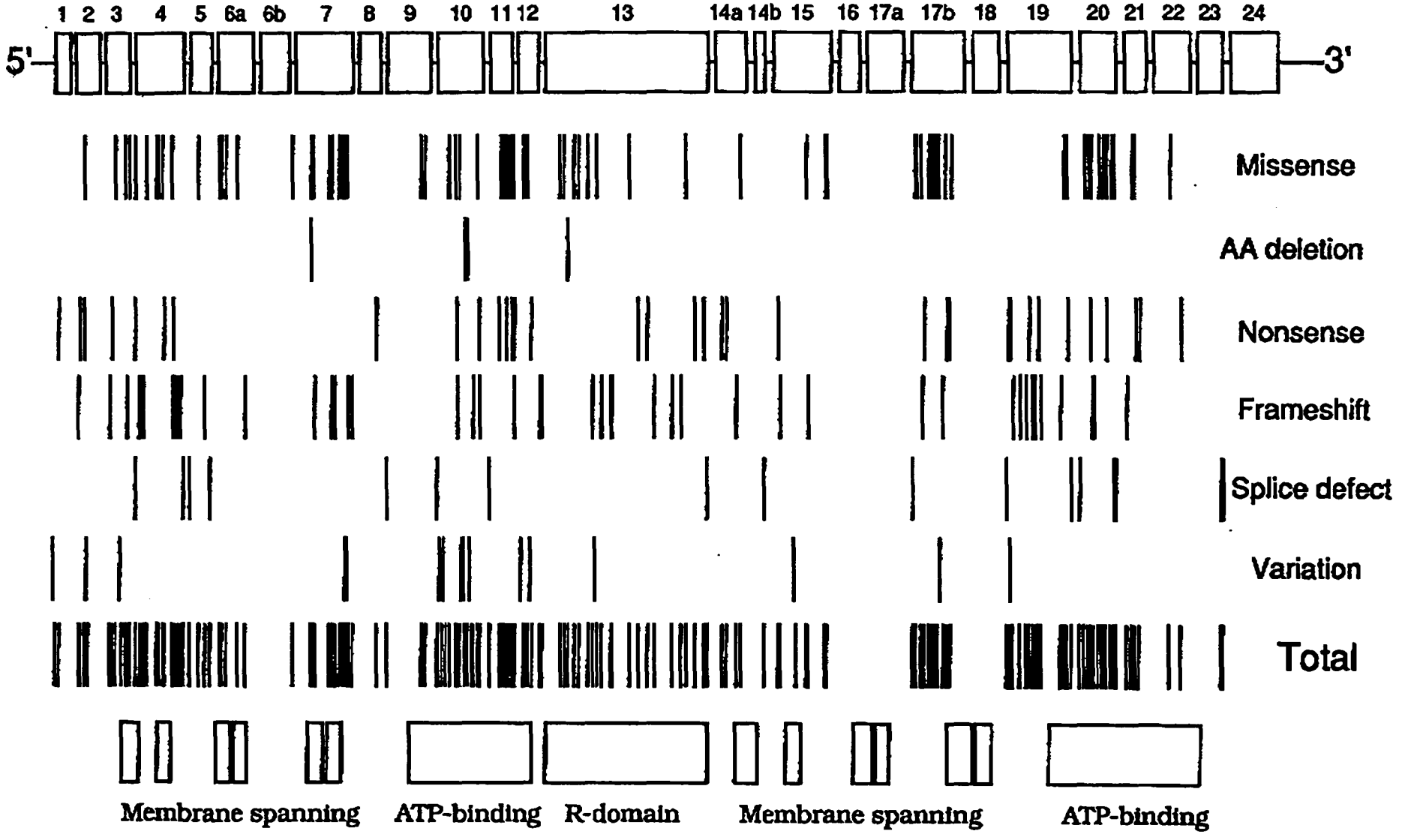
This mutation has only been identified in one individual, thus accounting for approximately 0.3% (1/369) of our total CF chromosomes.

Kind regards,

Jeremy Cheadle

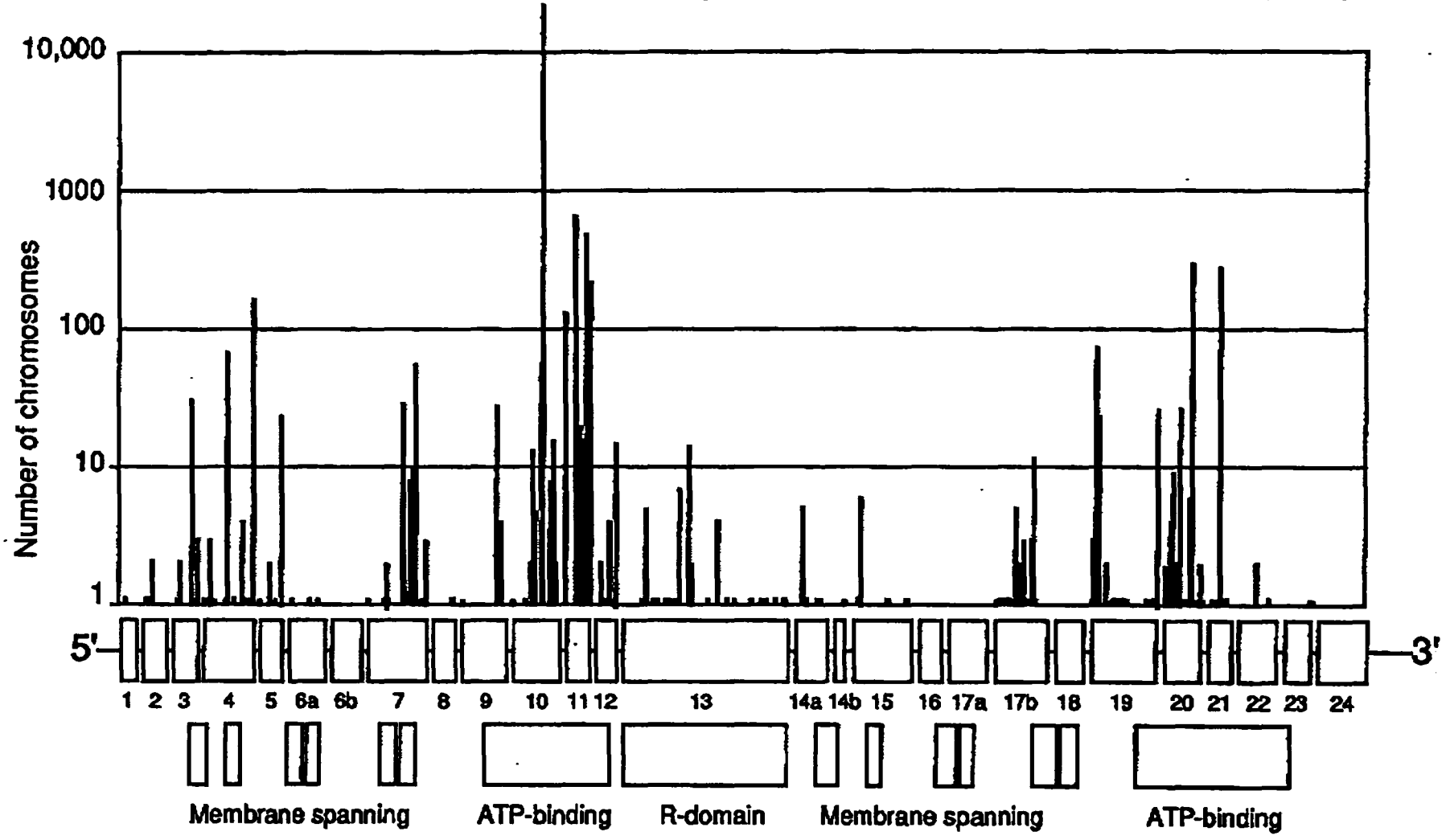
JEREMY CHEADLE
LINDA MEREDITH

Distribution of cystic fibrosis mutations (Data from the CF Genetic Analysis Consortium, May 1992)

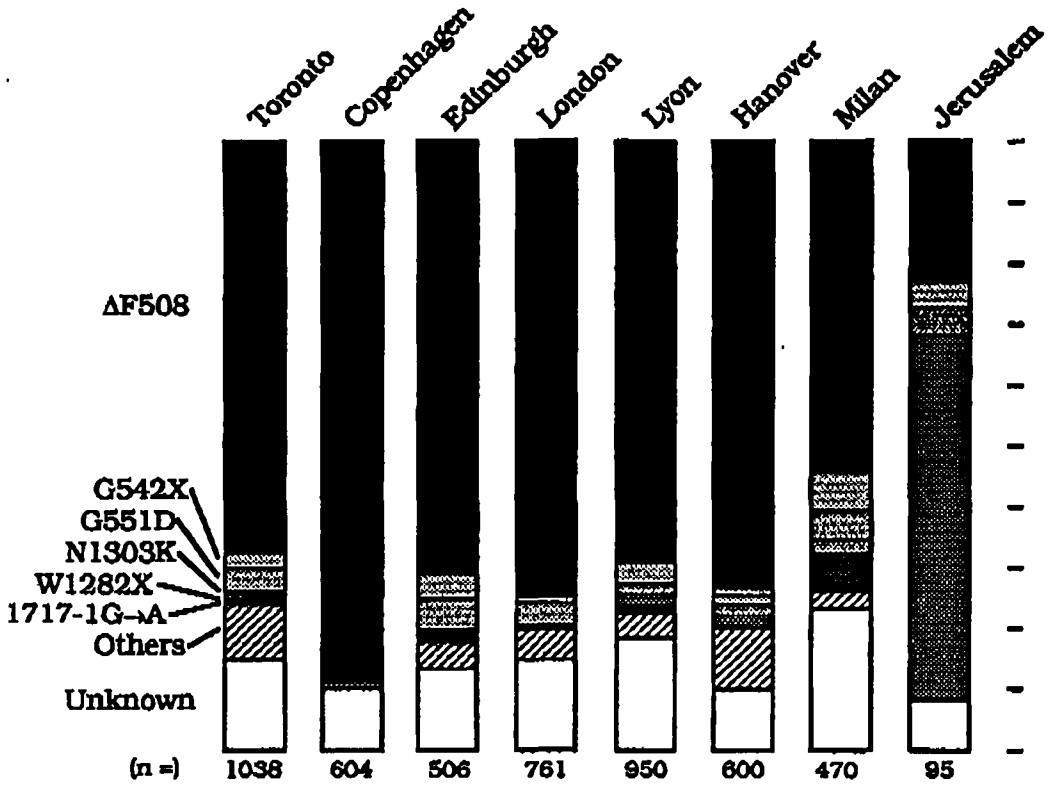


Locations and frequencies of cystic fibrosis mutations

(Data from the CF Genetic Analysis Consortium, May 1992)



Relative frequencies of common CF mutations in selected populations:



World frequency of CFTR mutations

(Data from CF Genetic Analysis Consortium, May 1992)

	Chromosomes Found	Chromosomes Screened			Chromosomes Found	Chromosomes Screened	
ΔF508	20,153	29,983	(67.2)	A455E	31	7,048	(0.4)
G542X	674	20,118	(3.4)	3659delC	29	3,634	(0.8)
G551D	492	20,827	(2.4)	3849+10kbC→T	28	1,955	(1.4)
N1303K	306	16,793	(1.8)	3905insT	27	1,313	(2.1)
W1282X	300	14,408	(2.1)	711+1G→T	25	2,860	(0.9)
R553X	248	19,600	(1.3)	S549N	21	12,516	(0.2)
621+1G→T	186	14,056	(1.3)	Y122X	19	6,535	(0.3)
1717-1G→A	151	13,715	(1.1)	2184delA	18	2,598	(0.7)
R117H	82	10,460	(0.8)	Y1092X	15	3,118	(0.5)
R1162X	74	8,699	(0.9)	S549R(T→C)	15	5,616	(0.3)
Δ1507	58	12,465	(0.5)	1898+1G→A	14	1,589	(0.9)
R347P	54	10,307	(0.5)	V520F	14	6,890	(0.2)
R560T	47	11,527	(0.4)	2789+5G→A	14	1,305	(1.1)
1078delT	34	3,192	(1.1)	Q493X	12	4,317	(0.3)
G85E	32	4,801	(0.7)	3849+4A→G	11	1,120	(1.0)
R334W	31	8,733	(0.4)	R347H	10	15,060	(0.1)

FILE

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THE HOSPITAL FOR SICK CHILDREN

FAX MACHINE NUMBER: (416) 813-4931

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LAP-CHEE TSUI, Ph.D.
DEPARTMENT OF GENETICS
PHONE: (416) 813-6015

DATE: December 15, 1992

TO: Dr. Arthur Beaudet
HHMI-Baylor College of
Medicine, Houston, Texas, USA

Dr. Francis Collins
HHMI-University of Michigan
Ann Arbor, Michigan, USA

Prof. Bob Williamson
St. Mary's Hospital Medical School
Norfolk Place, U.K.

Dr. Michel Goossens
SNSERM U.91, Hôpital Henri Mondor
Creteil, France

Number of pages (including this page): 31

Dear Art, Bob, Francis and Michel,

Here are some applications who would like to join the CF Genetic Analysis Consortium. As you will see, some of the applications are rather old because I have misplaced them earlier. I would make sure to let the applicants know that the delay was due to my fault and not the committee's.

As far as I am concerned, sending more newsletter out by fax is not a major problem. As we discussed at the last consortium meeting in Dublin, the purpose of the consortium now serves as an information repository for CFTR mutations. We will stop collection of population screening data until there is a need to do so again (please see below). The genotype-phenotype correlation study still remains to be the interest of Gary Cutting and Ada Hamosh. Therefore, please judge the applications by their merits.

Please put your comments on the attached sheets (2 pages) and return to me by FAX at your earliest convenience.

With regards to population screening data, I plan to submit a report on behalf of the consortium in a format very much like the one on ΔF508. The mutations to be included in the table will be the 12 most common ones according to the last data set (ie. ΔF508, G542X, G551D, N1303K, W1282X, R553X, 621+1G→T, R117H, ΔI507, R560T, R347P and 1717-1G→T). I would extract the data from the previous reports. The "author" will be the Consortium and a list of up to 3 individuals may be listed under each center/ethnic group. My suggestion of the format of the table would be as follows:

	Mutations (list names)										# of chrom.	
Study population (list city name or country name where samples were collected; list specific ethnic group where necessary)	1	2	3	4	5	6	7	8	9	...	screened	Contributing individuals up to 3 names per data entry (with affiliation)
Toronto, Canada	700	10	10	5	4	3	2	3	4	...	1000	J. Zielenski, D. Markiewicz & L.-C. Tsui The Hosp. for Sick Children
Hispanic Houston, USA	25	0	2	0	1	0	0	0	0		(60)*	A. Beaudet, ...

*Since it would be difficult for some groups to list the number of CF chromosomes screened, I would also ask for the closest approximation and the estimate would be listed in brackets.

Please let me your comments. If I do not hear any objections from you, I would make the announcement in the next newsletter and prepare the first draft of the table over the holidays. I would also ask the members to put down the name of a journal in which they would like to see the report printed. I expect the whole project would take 2-3 months.

Thank you again for your kind assistance.

Best regards,

UNIVERSITEIT VAN STELLENBOSCH
UNIVERSITY OF STELLENBOSCH

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Departement :
Department of :
Human Genetics

VERW. / REF. : JSH/mp

6 March 1992

Dr Lap-Chee Tsui
Cystic Fibrosis Consortium
Department of Genetics
Hospital for Sick Children
555 University Ave
Toronto, Ontario
CANADA MSG1X8

Dear dr Tsui

In responce to your letter to dr Michele Ramsay of the Department of Human Genetics, South African Institue for Medical Research, University of the Witwatersrand, Johannesburg, South Africa, I wish to register our laboratory as a member of the Cystic Fibrosis Consortium.

The genotypic data for the cystic fibrosis patients which have been generated in our laboratory will be submitted to the Consortium with dr Ramsay's data. To date we studied more than seventy South African CF patients to establish the frequency of the delta F508 mutation in the patient base that our laboratory serves. In this group of patients there is a group of 14 CF patients of mixed ancestory, the so-called Cape Coloured population. We are at present investigating non delta F508 CFTR genes to establish which mutations are present in these genes.

Yours faithfully

JEREMY HERBERT
SNR MEDICAL SCIENTIST

DR C J J OOSTHUIZEN
HEAD: DEPT OF HUMAN GENETICS

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

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Secrétariat (poste 3657)
Praticiens Hospitaliers :
Mme D. FELDMANN
M. G. MORGANT
Mme M. PRESSAC
Mme E. THIOULOUSE
Poste 3217 ou 3198

Lain, 23.03.92

Dear Dr Lap Chee Tsui,

I am very interested in joining the CF genetic analysis consortium - I hope that the steering committee members will agree my participation.

Best regards

D. Feldmann

CYSTIC FIBROSIS GENETIC ANALYSIS CONSORTIUM
MEMBER INFORMATION SHEET

Name of principal investigator: FELDMANN Delphine Title: PH

Name of contact person in the absence of P.I.: PRESSAC Monique

Location (site where research will be performed): Laboratoire de Biochimie
Hôpital TROUSSEAU
24-26 rue du Docteur A. Netter - 75571 PARIS Cédex 12
FRANCE

Mailing address (only if different from performance site):

Telephone number: (33)- (16)- ~~44 73 68 67 ou 44 73~~ 66 57
Country code- Area code

FAX number: (33)- (16)- ~~44 73 62 38~~

Patient origin (the geographic and ethnic background):
FRANCE (Paris area)

Level of involvement:
Identification of additional mutations? Yes ~~No~~
Collection of population data? Yes ~~No~~
Others:

Approximate number of CF chromosomes to be studied: 172

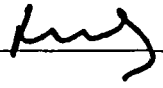
Other comments (please be brief):

	tested	Identified
DF 508	122	112
G 542 X	65	6
W 1282 X	65	4
621-1G	65	1

This information may be distributed among all members.

R 553 X	65	1
N 1303 K	65	1

I hereby acknowledge that I have read the Cystic Fibrosis Genetic Analysis Consortium Agreement and agree to join this Consortium under the guidelines stated.

Signature: 

Name (please print): FELDMANN

Location: PARIS Date: 20/03/92

D. HENTZEN, D. FELDMANN, A. PELLET, A. MUNNICH
"Mutations of CPG dinucleotides in ornithine transcarbamylase deficiency."
Symposium : "Proteins in the regulation of Hepatic Genes".
Basel liver week, 12-17 Octobre 1989

D. FELDMANN, A. PELLET, D. HENTZEN, P. AYMARD, A. MUNNICH
"Trois nouvelles mutations ponctuelles du gène de l'Ornithine Carbamoyl transferase, mises en évidence par amplification, clonage et séquençage."
Journées Franco-Belge de Biochimie et de Chimie Clinique
Pont-à-Mousson, 1-3 Octobre 1990

D. FELDMANN, M.A. SELVA, M. PRESSAC, A. SARDET, P. AYMARD
"Recherche de la mutation DF 508 chez le nouveau né dans des prélèvements de sang séché."
3è Assises Nationales de la recherche sur la mucoviscidose
Lyon, 16-17 Novembre 1990

D. HENTZEN, A. PELLET, D. FELDMANN, D. RABIER J. BERTHELOT, A. MUNNICH
"Fatal hyperammoniemia resulting from a C to T substitution at MSP 1 site in exon 7 of the Ornithine Transcarbamulase gene."
Hum. Gen. 1991, 88 : 153-156

E. GOURRIER, C. LAMOUR, D. FELDMANN, A. BENSMAN
Atteinte tubulaire précose dans l'intoxication par le plomb chez l'enfant
Arch; Fr. Pediatr.1991 ; 48 : 685-9

D. FELDMANN, J.M. ROZET, A. PELLET, D. HENTZEN, P. HUBERT, C. LARGILIERE, D. RABIER, J.P. FARRIAUX, A. MUNNICH
Site specific screening for point mutations in ornithine transcarbomylase deficiency
J. Med. Genet. (sous-presse)

D. FELDMANN, C. MAGNIER, C. CHAUVE, I. DORVAL, A. SARDET, P. AYMARD
Mutation screening in a french cystic fibrosis population using a simplified approach
European Respiratory Society annual congress (submitted)

A. SARDET, D. FELDMANN, P. AYMARD, G. TOURNIER, A. BACULARD
The association of genotype and phenotype in French patients with cystic fibrosis
European Respiratory Society annual congress (submitted)

D; FELDMANN, E. THIOULOUSE, A. GRIMFELD, P. MAJDALANI, P. AYMARD
Caracterisation of the W 1282X mutation in a french population
XIth International Cystic Fibrosis Congress (accepted)

D. FELDMANN, C. MAGNIER, C. CHAUVE, J. DORVAL, A. SARDET, A. BACULARD, G. TOURNIER, J.L. FONTAINE, P. AYMARD
Mutation screening in a french Cystic Fibrosis population
XIth International Cystic Fibrosis Congress (accepted)

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1992, Sept 17

Dr Lap-Chee Tsui
Deparment of Genetics
Research Institute
The Hospital for Sick Children
Toronto, Ontario, M5G1X8
Canada

Dear Dr Tsui,

At the CF centre in the Department of Paediatrics, Lund, Sweden we are at present trying to delineate the non-DF 508 mutations in our material of about 100 patients to improve our genetic counselling. It would be a great help if we can have access to the unpublished data in the files of the "CF-consortium". Our department is experienced in molecular biology techniques such as PCR, cloning and DNA-sequencing through the work on other inheritable diseases. We have had some co-operation with Dr Marianne Schwartz at the Dept of Clinical Genetics, Rigshospitalet, Copenhagen, Denmark, but since we are doing the laboratory work ourselves here in Lund, it is somewhat awkward to obtain the information through her. Of course, we are willing to comply with any rules of the consortium pertaining to reporting, confidentiality etc.

I enclose a recent reprint of ours. We also have some preliminary data about a candidate acceptor splice mutation, which, as far as I can tell, has not been published, but which needs further confirmation.

Sincerely, yours

Lars Holmberg, M.D., Ph.D.
Professor of Paediatrics

Acta Pædiatr 81: 262–3. 1992

RAPID COMMUNICATION

Cystic fibrosis mutations in southern Sweden: relationship to clinical severity

R Kornfält, B Andreasson[1] and L Holmberg

Department of Paediatrics, University Hospital, Lund, Sweden; Department of Paediatrics,[1] General Hospital, Malmö, Sweden

The frequency of the cystic fibrosis (CF) mutation, ΔF508 (1) on CF chromosomes was recently reported for most countries in Europe. It is less common in southern Europe than in the British Isles and northern Europe, the highest figure being that of 88% in Denmark (2). In contrast, it is fairly infrequent (45%) in Finland, which has a low incidence of CF. Data for Sweden have not yet been published. Here we report the frequency of ΔF508 and three other mutations, G542X, G551D and R553X in southern Sweden. Possible relationships were studied between occurrence of the genotypes and Shwachman score (3), weight and height in terms of SD from the normal mean, and lung function measured as vital capacity (VC) and forced expiratory volume in one second (FEV_1).

Sixty-six CF patients attending the CF centre in Lund were examined. The genotypes were determined using the polymerase chain reaction technique followed by restriction enzyme cleavage and electrophoresis or by dot blot with radiolabelled allele specific oligonucleotides (4). VC and FEV_1 were measured with a pneumotachograph or vitallograph and presented in percent of the predicted height-related normal value (5).

The prevalence of the ΔF508 mutation among CF patients in southern Sweden was 77% (102/132 chromosomes). Forty-one patients were homozygotes (group 1), 20 were heterozygotes (group 2), and five lacked the ΔF508 gene (group 3). One patient was a compound heterozygote (ΔF508/G542X). No G551D or R553X mutations were found.

Table 1 shows the values for lung function, Shwachman score, present age of the patients, weight and height in the three groups. There were no significant differences between the groups, although in group 3 (lacking the ΔF508 mutation) both mean and median age were somewhat higher. In group 1, all patients were dependent on pancreatic enzyme substitution as compared with 90% (18/20) in group 2 and 40% (2/5) in group 3. Twenty-two (54%) of the 41 patients in group 1 had recurrent infections with *Pseudomonas aeruginosa*, as

Table 1. Vital capacity (VC, % of predicted normal value), forced expiratory volume (FEV_1, % of predicted normal value), Shwachman (Shw) score, present age, weight and height in three groups of CF patients with different genotypes.

Genotype	No.	Median (%)	Mean (%)	SD
F508/F508				
VC%	37	89(27–130)[a]	88	19
FEV_1%	37	76(21–123)	77	23
Shw score	41	82(40–96)	80	13
Age	41	12(2–42)	14	19
Weight[b]	41	0(−2–1)	−0.29	0.87
Height[b]	41	0(−3–2)	−0.22	0.91
F508/C[c]				
VC%	18	92(40–122)	87	22
FEV_1%	18	76(31–155)	77	31
Shw score	20	86(55–98)	80	12
Age	20	15(1–36)	16	9
Weight	20	0(−2–1)	−0.45	0.82
Height	20	0(−2–1)	−0.40	1.05
C/C				
VC%	5	102(53–113)	91	25
FEV_1%	5	76(38–108)	73	25
Shw score	5	60(50–76)	64	11
Age	5	29(12–40)	27	11
Weight	5	0(−1–0)	−0.40	0.55
Height	5	0(−1–0)	−0.20	0.45

[a] Range; [b] weight and height are given as SD from the normal means; [c] unknown CF mutation.

Department of Genetics
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CANADA

October 22nd, 1992.

Dear Dr. Lap-Chee Tsui,

As I mentioned to you in Copenhagen at the 17th European CF Meeting in 1992 we would like to join to the CF Consortium. Returning from that meeting I FAX-ed over my letter to your office, but I have never got response for my FAX. Now I am sending this letter to you, again. Just recently, I have met Dr. Zielenski from your group at The North American CF meeting in Washington,D.C. and we discussed my request and he encouraged me to write to you, again.

In our Genetic Counseling Center in Budapest, Semmmelweis Univ.Med. School, I. Dept of Obstetrics and Gynaecology we have been counseling CF patients since 1985 and have been doing carrier testing and prenatal diagnosis based on DNA analysis.

Our Genetic Center is the only one in Hungary which has the clinical and molecular biology capability to provide this service.

The Hungarian CF population has never been tested for the mutations on CFTR gene. I have already completed the study of 47 Hungarian CF families including 140 family members so far. These studies include the analysis of the following mutations: ΔF508, G551D, R553X, G542X, R117H, 621+G-T, 1717-1G-A, W1282X and N1303K on this particular Hungarian population. Our results are summarised in the table.

The frequency of the Δ508 mutation in the Hungarian population is 65%, which is quite similar to the other middle European population.

Please find enclosed the list of our CF studies already published, and two papers of our CF studies, recently published.

Currently I am a Post. Doc. Fellow at Oakland Children's Hospital, Oakland ,CA, where I am continueing research on the Hungarian CF population to find unknown mutations. I am doing the SSCP study of the unknown CF patients, who are negative for 9 common mutations. I have already compleated the study of exons: 4, 7, 10, 11, 15, 19, 20, and 21. I have found abnormal SSCP band patterns in one patient in exon 7, and an another in exon 19. Now I am working to prove what kind of mutations are present.

As Hungary is not represented in the CF Consortium yet, we do hope you accept our application to be included in the Consortium and you are willing to share the latest results with us, too. Thank you very much.
Looking forward hearing from you.

Your sincerely,

Margit Nemeti

My address here:

Margit Nemeti Ph.D
Oakland Children's Hospital
Research Institute
747 52nd Street Oakland, CA 94609

Our address in Hungary:

Prof. Zoltan Papp
Semmelweis Medical School
I.Dept of Obst.& Gynaecol
H-1088 BUDAPEST
Baross u 27
Hungary
FAX: 36-1-1140231

SUMMARY OF THE SCREENING DATA OF CFTR GENE MUTATIONS IN HUNGARIAN CF FAMILIES

NAME OF MUTATION	NUMBER OF CHROMOSOMES SCREENED	NUMBER OF MUTANT CHROMOSOMES
ΔF508 (Exon10)	94	61 (64.89%)
G551D (Exon 11)	33	0 (0.00%)
R553X (Exon 11)	33	2 (2.12%)
G542X (Exon 11)	31	1 (1.06%)
R117H (exon 4)	30	0 (0.00%)
621+ 1G→T (Intron 4)	30	0 (0.00%)
1717-1G-A (Intron 10)	30	2 (2.12%)
W1282X (Exon 20)	28	1 (1.06%)
N1303K (exon 21)	27	2 (1.06%)

1. Németi M, Szabo M, Horvath K, Bolodar A, Papp Z.:
First trimester prenatal diagnosis of cystic fibrosis by DNA analysis.
Orvosi Hetilap (Hungarian Medical Journal), 128 (1987) 2577-2579.

2. Németi M, Papp Z.:
First trimester prenatal diagnosis of cystic fibrosis with linked DNA probes.
Acta Universitatis Carolinae Medica, 36 (1990) 135-138.

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4. Németi M, Louie E, Papp Z, Johnson JP.:
Study of the ΔF508 deletion in Hungarian cystic fibrosis families.
Miami Bio/Technology Winter Symposia: Advances in Gene
The Molecular Biology of
Human Genetic Disease.
Miami Short Reports 1: 96 (1991).

5. Preliminary study of CFTR mutations in the Hungarian population
17th European Cystic Fibrosis Conference, Copenhagen , Denmark, (July17-22, 1991) Programme: 7

6. Nemeti M, Louie E, Papp Z, .Johnson JP.:
Molecular analysis of cystic fibrosis in the Hungarian population.
Hum. Genet.:87 (1991) 511-512.

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The occurrence of various non-ΔF508 CFTR gene mutations among Hungarian
cystic fibrosis patients.
Hum. Genet.: 89 (1992) 245-246.

Hum Genet (1992) 89:245–246

Human Genetics

The occurrence of various non-ΔF508 CFTR gene mutations among Hungarian cystic fibrosis patients

Margit Nemeti[1], John P. Johnson[1], Zoltan Papp[2], and Elaine Louie[1]

[1] Division of Medical Genetics, Children's Hospital Oakland, 747 Fifty Second Street, Oakland, CA 94609, USA
[2] I. Department of Obstetrics and Gynaecology, Semmelweis University Medical School, Budapest, Hungary

Received November 27, 1991 / Revised January 20, 1992 / Revised February 6, 1992

Summary. Cystic fibrosis (CF) is an autosomal recessive disease caused by different mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The frequency of the major mutation (ΔF508) in the Hungarian population is 64%. To identify other common mutations in CF families from Hungary, 30 non-ΔF508 CF chromosomes were analyzed for selected mutations in exon 11 (G551D, R553X, G542X), intron 4 (621+1G→T), intron 10 (1717−1G→A), exon 20 (W1282X), and in exon 21 (N1303K) of the CFTR gene. In 6 of the 30 non-ΔF508 CF chromosomes the following mutations were detected: R553X, G542X, 1717−1G→A, W1282X, and N1303K. After analysis of the above eight mutations, 30% of CF chromosomes are as yet undefined and further analysis is planned.

Introduction

The genetic analysis of cystic fibrosis (CF) has improved considerably since the identification of the CFTR gene and the most common mutation (Riordan et al. 1989; Kerem et al. 1989). The average frequency of the major mutation (ΔF508) is about 70%, but it varies from 50%–80% in different ethnic populations (European Working Group on CF Genetics 1990).

Although more than 100 additional mutations have been reported to the CF Genetic Analysis Consortium, only a few have an incidence higher than 3%. Some mutations have a higher frequency among non-ΔF508 CF chromosomes in specific ethnic populations, such as the W1282X mutation in Ashkenazi Jews (77%; Shoshani et al. 1992), or the R1162X mutation among Italians (12%; Gasparini et al. 1991).

The frequency of CF chromosomes carrying the ΔF508 mutation in 33 Hungarian CF families was found to be 64% (Nemeti et al. 1991). In order to improve genetic diagnosis and to perform more accurate prenatal diagnoses of CF in Hungarian families, we further analyzed the non-ΔF508 CF chromosomes.

Offprint requests to: J.P. Johnson

Materials and methods

In the present report a total of 84 parental CF chromosomes from 42 CF families were screened. The families have one or more affected children and the diagnosis of CF was customarily made by measuring the concentration of chloride in sweat. We found 54 ΔF508 CF chromosomes. The 30 non-ΔF508 CF chromosomes were further analyzed for the following selected mutations.

As 13 different mutations have been reported within exon 11 alone (Cutting et al. 1990; Devoto et al. 1991; Dörk et al. 1991; Kerem et al. 1990; Sangiuolo et al. 1991; Strong et al. 1991), our first aim was to check the frequency of three of the more frequent mutations in this exon, namely G551D, R553X, and G542X. The following additional mutations were screened in different exons or introns of the CFTR gene: 621+1G→T in intron 4, 1717−1G→A in intron 10, W1282X in exon 20, and N1303K in exon 21. The mutations were analyzed by using the polymerase chain reaction (PCR; Saiki et al. 1985, 1988). After the necessary restriction enzyme digestion the PCR products were subjected to electrophoresis on vertical NuSieve agarose gels.

Primers 11i-3 (Cutting et al. 1990) and a modified primer, M11e-5 (Ng et al. 1991) flanking exon 11 were used to amplify its PCR product. Mutations G551D and R553X were detected by the method described previously (Cutting et al. 1990). The G542X mutation was detected using the modified primer and *Bst*NI digestion as described by Ng et al. (1991).

To detect the 1717−1G→A splice mutation in intron 10, we used flanking primers 11i-5 (Kerem et al. 1990) and a reverse primer containing a single base mismatch (T→G) that creates a novel *Ava*II restriction site in the amplified normal allele but not in the CF mutant allele (Cremonesi et al. 1991).

To analyze the N1303K mutation, primers 21i-5 (Kerem et al. 1990) and a modified internal primer, 21E-7 (5'-CTT GAT CAC TCC ACT GTT CAT AGG GAT CCT A-3') were used. The primer modification strategy was the same as mentioned above for detection of the G542X mutation and 1717−1G→A splice mutation (Haliassos et al. 1989). A restriction site for *Rma*I is created from the normal allele but not from the N1303K mutant allele.

To screen for the 621+1G→T splice mutation, primers, 4i-3 (Zielenski et al. 1991) and 4i-5A (5'-ATT TCT CTG TTT TTC CCC TTT TGT AG-3') flanking exon 4 were used to amplify this region. This CF mutation creates a new *Mse*I site, while the normal allele does not, thus enabling its detection by gel electrophoresis after restriction digestion with *Mse*I.

To detect the presence of W1282X mutation, primers flanking exon 20 (Kerem et al. 1990) were used to amplify this region. The CF mutation was detected using *Mnl*I digestion according to the method described previously (Shoshani et al. 1992).

Hum Genet (1991) 87:511–512

Human Genetics

Molecular analysis of cystic fibrosis in the Hungarian population

Margit Nemeti[1], Elaine Louie[1], Zoltan Papp[2], and John P. Johnson[1]

[1]Division of Medical Genetics, Children's Hospital Oakland, 747 Fifty Second Street, Oakland, CA 94609, USA
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Received January 8, 1991 / Revised February 27, 1991

Summary. Hungarian cystic fibrosis (CF) families (n = 33) including 114 family members have been analysed for the presence of the ΔF508 mutation within the cystic fibrosis transmembrane conductance regulator (CFTR) gene, and have been haplotyped with probes for restriction fragment length polymorphisms (RFLPs) known to be linked to the CFTR gene. The ΔF508 deletion was present in 64% of CF chromosomes. As in many other populations, linkage disequilibrium was found between the CF locus and the haplotype B (XV-2c: allele 1, KM-19: allele 2), which accounts for 95% of ΔF508 CF chromosomes in our families.

Introduction

One of the goals of current cystic fibrosis (CF) genetic studies is to determine the frequency of the ΔF508 mutation in different ethnic populations. ΔF508 is the most common defect found in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Mutations in the CFTR gene are known to cause CF (Riordan et al. 1989; Cutting et al. 1990). In the United States, the frequency of ΔF508 ranges from about 75% in carriers of Northern European extraction (Lemna et al. 1990) to about 37% among black CF carriers (Cutting et al. 1990). To add to the worldwide database (The Cystic Fibrosis Genetic Analysis Consortium 1990 and the European Working Group on CF Genetics, 1990), we recently analyzed 33 Hungarian CF families for the presence of the ΔF508. The frequency of ΔF508 in carriers (64%) is similar to that observed in Northern European populations (Kerem et al. 1989) and the haplotype associations on ΔF508 and non-ΔF508 CF chromosomes are likewise consistent with previous reports. Therefore, there is no compelling evidence for the presence of another predominant unique CFTR mutation in this particular Eastern European population.

Offprint requests to: J.P. Johnson

Materials and methods

Blood samples were collected from CF-affected families who sought predictive genetic testing either for their normal children or in a prenatal setting. The diagnosis of CF was customarily made by measuring the concentration of chloride in the sweat. DNA was isolated from leukocytes using standard methods as described (Kunkel et al. 1977). The ΔF508 mutation was analyzed by polymerase chain reaction (PCR) of exon 10. Two analyses were performed, allele-specific amplification (Ballabio et al. 1990) and heteroduplexing (Rommens et al. 1990). The primers utilized were essentially as previously described (Ballabio et al. 1990; Rommens et al. 1990). Haplotypes were determined on our families using the linked probes XV-2c and KM-19. These markers are in strong linkage disequilibrium with the CF locus (Estivill et al. 1987a, b). Those patients carrying the larger fragments (allele 1) and the smaller fragments (allele 2) of the RFLPs detected with XV-2c and KM-19, respectively, have the B haplotype. In the majority of CF affecteds the most common haplotype is the B haplotype as shown in our data (Table 1). The rarest haplotype among the CF affecteds is haplotype C (allele 2 of XV-2c and allele 1 of KM-19). The other two possible haplotypes have been identified as A (allele 1 of XV-2c and allele 1 of KM-19) and D (allele 2 of XV-2c and allele 2 of KM-19). Alleles at these loci were determined on CF and non-CF chromosomes (as defined by linkage with XV-2c and KM-19 or ΔF508 analysis) using Southern blots or PCR.

Results and discussion

Our families are grouped by the ΔF508 status of the CF child. Twelve families have CF probands who are homozygous for ΔF508, 18 families have CF probands who are heterozygous for the ΔF508, and 3 families have CF probands without ΔF508. The frequency of ΔF508 among carriers is 64%, based upon the number of CF chromosomes containing ΔF508 in our Hungarian population (42/66 CF chromosomes).

Haplotypes of ΔF508 CF, non-ΔF508 CF, and normal chromosomes in the Hungarian families are compared to the North American CF families (Lemna et al. 1990) as shown in Table 1. Both the ΔF508 mutation and non-ΔF508 mutation(s) showed strong association with the haplotype B (KM-19: allele 2; XV-2c: allele 1). Overall,

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A-8010 GRAZ, HARRACHGASSE 21/8, TEL. (0316) 380/4110

Fax: 0316-35 5 66

Dr. Lap-Chee Tsui Ph.D.
Department of Genetics
Hospital for Sick Children
555 University Avenue
Toronto, Ontario
CANADA M5G 1X8

Graz, 1992-10-01

Dear Dr.Tsui

In the last years we investigated the mutations of the CFTR gene in Austrian and Hungarian Cystic Fibrosis patients and in some of their families. Our hitherto results are shown in the enclosed table. The majority of Austrian patients are from the southern part of our country. The Hungarian patients are from the clinics of Pediatrics Universities Budapest and Pecs. We determined the allele frequencies for XV2c, KM19, Cs7 and D9 and diagnosed Delta F508 for all persons investigated. I presume the difference in the Delta F508 frequencies between Austrian and Hungarian patients is caused by differencies in clinical diagnosis. We will attend to them in the near future.

Now we analyse the "non Delta F508" mutations using GC-clamped DGGE and sequencing of the PCR products. The examination of exon 11 is completed and analysis of the other exons is in progress. I hope that our results are of interest for the Cystic Fibrosis Consortium and I am willing to communicate our results to the Consortium also in the future. I and my co-workers are very interested to collaborate with the Consortium. A reprint of our paper in Human Genetics is enclosed.

Of my knowledge Austria is not represented in the Cystic Fibrosis Genetic Analysis Consortium and so I may ask you if it is possible that I will get membership in the Consortium. Of course, I will accept the conditions for the membership in the Consortium.

I am looking forward to your answer. Please inform me as soon as possible.

Yours sincerely

Univ.-Prof.Dr.W.Rosenkranz

	Austria	Hungary
CF patients	146	62
F/F	65	37
F/N	52	15
N/N	29	10
ΔF508 frequency	62,3%	71,8%
Parents and sibs	160	145
NF	80	95
NN	80	50

Other mutations

1 x G542X/G541X	
4 x G542X/ΔF508	1 x G542X/ΔF508
2 x G551D/ΔF508	1 x G542X/ N
1 x G551D N	
2 x R553X/ΔF508	
1 x R347P/ΔF508	1 x R347P/ΔF508

Polymorphism

1540(A or G) } found
1525-61(A or G) } frequently

Hum Genet (1992) 89 : 437–438

Human Genetics

Frequency of ΔF508 and haplotype association in Austrian cystic fibrosis families

K. Wagner[1], M. Zach[2], and W. Rosenkranz[1]

[1]Institut für Medizinische Biologie und Humangenetik der Universität, Harrachgasse 21/8, and [2]Universitäts-Kinderklinik, Auenbruggerplatz 30, A-8010 Graz, Austria

Received August 5, 1991

Summary. The frequency of the major mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene was analyzed for 113 Austrian cystic fibrosis (CF) patients. An overall frequency of 55% for ΔF508 was found with values of 72% and 13% for patients with pancreatic insufficiency (CF-PI) and those with pancreatic sufficiency (CF-PS), respectively. Furthermore, the distribution of the alleles of the closely linked DNA markers XV2c/KM19/MP6d-9 in our families is described.

Introduction

Following the isolation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Rommens et al. 1989; Riordan et al. 1989; Kerem et al. 1989) the frequency of the 3-bp deletion leading to ΔF508 has been investigated in different populations. In a collaborative European study of cystic fibrosis (CF) chromosomes a South East-North West gradient for the deletion ΔF508 has been suggested, with gene frequencies for ΔF508 as high as 80% in Denmark in contrast to only 30% for the Turkish population. Moreover, patients suffering from pancreatic insufficiency (PI) should show less heterogeneity of mutations than patients with pancreatic sufficiency (PS) (European Working Group on CF Genetics 1990).

We investigated the frequency of the major mutation ΔF508 in 113 CF patients from Austria, predominantly Styria. Furthermore, a haplotype analysis of the association of the DNA markers XV2c/KM19/PM6-d with CF and normal chromosomes in our families was performed.

Materials and methods

Diagnosis of CF was confirmed by repeated positive sweat tests and by the evaluation of typical clinical features. The patients were divided into three subclasses according to their pancreatic function.

Correspondence to: W. Rosenkranz

DNA was isolated from peripheral blood lymphocytes according to Miller et al. (1988). Polymerase chain reaction (PCR) amplifications and detection of the deletion ΔF508 were performed as described by Rommens et al. (1990). Protocols for amplification and restriction fragment length polymorphism (RFLP) detection of XV2c (Rosenbloom et al. 1989), KM19 (Feldman et al. 1988) and MP6d-9 (Huth et al. 1989) have been published. *Taq* DNA polymerase was obtained from Promega and a PHC-2 Dri-Block thermocycler from Techne was used for PCR.

Results and discussion

The distribution of the major mutation in the CFTR gene in different clinical subgroups of Austrian CF patients is shown in Table 1. An overall frequency of 55% for ΔF508 was determined; this value is lower than that described for Germany and higher than that found in Italy (The Cystic Fibrosis Genetic Analysis Consortium 1990). CF patients with PI showed this specific mutation on 72% of their chromosomes whereas the frequency for chromosomes of CF-PS patients was only 13%. In our population approximately 25% of the patients were classified as CF-PS.

The association of XV2c/KM19/MP6d-9 haplotypes with normal and CF chromosomes in the families analyzed is listed in Table 2. The majority of ΔF508 chromosomes is associated with the haplotype 1/2/2 (92%), whereas the distribution on non ΔF508 CF chromosomes is more heterogeneous. We are now investigating these

Table 1. Frequency of ΔF508 in Austrian cystic fibrosis (CF) patients with pancreas insufficiency (CF-PI), pancreas sufficiency (CF-PS) and for unclassified patients

	No. of chromosomes	
	ΔF508 (%)	Non ΔF508 (%)
CF-PI	102 (72)	40 (28)
CF-PS	7 (13)	45 (87)
Unclassified	15 (47)	17 (53)
Total	124 (55)	102 (45)

October 28, 1992

GeneScreen
3500 Stemmons Fwy
Suite 131
Dallas, Texas 75247
214 631-4152
800 752-2772

Dr. Lap-Chee Tsui
Department of Genetics
Hospital for Sick Children
Toronto, Ontario M5G 1X8
CANADA
FAX: 416-813-4931

Dear Lap-Chee:

On November 1, 1992 I will be leaving GeneScreen and moving to Baylor College of Medicine in Houston. I would like to continue to be a member of the Consortium and to receive the newsletter. My new address, telephone and fax are as follows:

Institute Molecular Genetics
Baylor College of Medicine
One Baylor Plaza, T536
Houston, TX 77030
TEL: (713) 798-6528
FAX: (713) 798-6584

The individual who is taking my place at GeneScreen is Bob Giles, and he will want to be a member of the Consortium and receive the newsletter at GeneScreen.

Please let me know as soon as possible if you have any problems with this request.

Sincerely,

Sue Richards

Sue Richards, Ph.D.
Director of Genetics

United Nations Industrial Development Organization

International Centre
for Genetic Engineering
and Biotechnology

Padriciano 99
I-34012 Trieste

Tel. (40) 37571
Telex 460396 ICGEBT I
Telefax (40) 226555

Prof. F.E. Baralle PhD. MD. - Director ICGEB Trieste Tel. 3757337

Dr. L.C. Tsui
Department of Genetics,
The Hospital for Sick Children,
Toronto, ON M5G 1X8
Canada

Trieste, November 11th, 1992

OUR REF: FB/ms-376/92

Dear Dr. Tsui,

Please find attached herwith our completed Consortium application form, in the hope that it will be submitted to and subsequently approved by the Steering Committee.

So far, we've analyzed a cohort of 49 CF families which are follwed by the CF Centre of the Hospital for sick children in Trieste.

Among these patients (98 CF chromosems) we found that:

(1)	ΔF508	=	54.4% (53 chromosomes)
(2)	ΔF508 homozygotes	=	31.1%
(3)	ΔF508 hoterozygotes	=	46.6%
(4)	non-ΔF508	=	22.2%

During our screening we found a patient with ΔF508/Δ1677, which is the only case in this area.

Our current interest is focused on sequencing the CFTR genes in non-ΔF508 patients with very mild C.F. symptons.

We hope to correlate their clinical situation to their genotype.

Looking forward to hearing from you,

Best regards,

F.E. BARALLE

CYSTIC FIBROSIS GENETIC ANALYSIS CONSORTIUM
MEMBER INFORMATION SHEET

Name of principal investigator: Prof. FRANCISCO BARALLE Title: HEAD OF COMPONENT OF I.C.G

Name of contact person in the absence of P.I.: CRISTINA SERRA

Location (site where research will be performed):
I. C. G. E. B. 99, PADRICIANO

Mailing address (only if different from performance site):

Telephone number: (011)- (40)- 3757342
Country code- Area code
FAX number: (011)- (40)- 226555

Patient origin (the geographic and ethnic background):
NORTH-EAST OF ITALY

Level of involvement:
Identification of additional mutations? Yes No
Collection of population data? Yes No
Others: GENOTYPE-PHENOTYPE CORRELATION

Approximate number of CF chromosomes to be studied: 288

Other comments (please be brief):

This information may be distributed among all members.

Vanderbilt University Medical Center

Vanderbilt University School of Medicine
Department of Pediatrics
Division of Genetics

DD 2205 Medical Center North
Nashville, TN 37232-2578
Phone: 615-322-7601
FAX: 615 343-9151

NOVEMBER 30,1992.

TO LAP-CHEE-TSUI
DEPARTMENT OF GENETICS
THE HOSPITAL FOR SICK CHILDREN
TORONTO,ONTARIO M5G 1X8
CANADA FAX (416)5914931
943

Dear Lap-Chee;
How are you doing?

I am writing you this letter to make the following requests;

a) I would like to have a duplicate of all your slides on Molecular Genetics of CF. I am going to defend my thesis (Molecular Analysis of CF in Brazil) next March in Brazil, and I would apreciate if you could send me these duplicates (for example, slides of the pictures of your recent reviow in Human Mutation). Please enclose the bill, so that I can pay you for the duplicates.

b) Next February I am returning to Brazil after three years of training in America with John Phillips, and I will get a position as the head of the DNA Lab in the University where I graduated and did my residence training in Pediatrics (Curitiba, State of Parana, Brazil). I will keep working with CF DNA analysis, this should be the Cf reference center in Brazil (I hope...) and the long term goal will be to identify the mutations in the "remuining" 40% of Brazilian CF alleles (250 alleles...).

I am already part of the Genotype/Phenotype Consortium, and I have contributed to the work done by Lucy Osborne (N1303) and Ada Amosh (G542X). We will have the CF Latin American Congress next April in Recife , Brazil, and we are already working to estabilish a Latin American CF Genetics Consortium during the Congress. We would like our Consortium to be part of your Consortium, and therefore I would like to apply once again for the CF Consortium, so that we could receive up-to-date information in the near future in Brazil. How should I proceed?

c) I would like to have as soon as possible the Consortium KM-19/ XV-2C haplotype data of the CF mutations,so that I can compare with the ones I found in our population.

d) And last (but not least..), I have a young friend in Brazil (Pediatrician working with Genetics in the last three years) that is very interested in applying for a Research Fellowship (one or two years) in your service, working with the not-yet characterised Brazilian CF alleles. It would be great for him and also for our plans if you could find a place for him in your Lab. Do you think this should be possible?

I look forward to hear from you!!

Yours sincerely, Salmo Raskin

SALMO RASKIN , M.D.

INSTITUT DE RECERCA ONCOLOGICA
INSTITUTO DE INVESTIGACION ONCOLOGICA
CANCER RESEARCH INSTITUTE

Generalitat de Catalunya
Hospital Duran i Reynals

Lap-Chee Tsui, PhD.
Department of Genetics
555 University Avenue
Toronto, Ontario
Canada M5G 1X8

Barcelona 12 February 1992

Dear Lap-Chee,

Please enclosed find the letters from the different Spanish groups that want to join the CF analysis consortium. These are the groups with whom we will create the "Spanish microconsortium". We know very well all these groups, all of them have been trained by us and we are confident about their work. As you remember we talked about this matter when you were here in Barcelona last November. We want to organize this miniconsortium in order to get as much information as possible about CF in Spain and our first point will be to do a genotype-phenotype correlation. If you agree with this we will pass them the "newsletters" from the consortium.

The groups are:

Dr. Guillermo Antiñolo.	Unidad de Genética Humana. Sevilla
Dr. Guillermo Glover.	Unidad de Genética. Murcia
Prof. A. Gullón.	Dto. Genética. Universidad de Navarra
Dr. Javier Benítez Esther Fernández	Dto. Genética. Fundación Jiménez Díaz Madrid.
Dra. Ana Palacio	Dto. Microbiología. Fac. Medicina Zaragoza.

Best regards,

X. Estivill and V. Nunes

UNIDAD DE GENETICA HUMANA.
Hospital U."Virgen del Rocio".
Avda. Manuel Siurot S/N.
41013 Sevilla.
Spain
Tlf. 4558009
E-mail: antinolo@cica.es

Dr.Lap-Chee Tsui
Department of Genetics
Hospital for Sick Children

Sevilla 06/02/92

Dear Dr.Tsui:

We would like to join the Spanish Consortium for the study of Cystic Fibrosis.

We have studied fifty five families for ΔF508,G542X,N1303K and R1162X mutations of CFTR gene.

We would appreciate the conditions to be included in this consortium.

Thank you for your time and consideration.

We look forward to hearing from you.

Dr.G.Antiñolo

Región de Murcia
Consejería de Sanidad

CENTRO DE BIOQUIMICA Y GENETICA CLINICA
CONJUNTO RESIDENCIAL
Apartado 61
Telfs. (968) 83 01 04 - 83 02 62 - Fax. 968 30 50 05
30100 ESPINARDO - MURCIA (ESPAÑA)

6-02-92

Dr. Lap-Chee Tsui

Appreciate Dr. Tsui

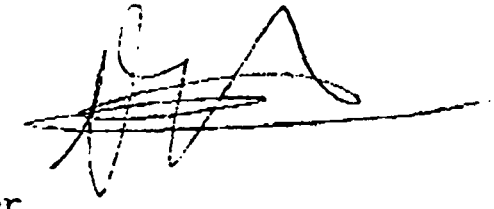
I'd like to be included in the proyect of a Spanish miniconsortium to estudy the C.F.

We have analyzed near 30 families affected in the last two years with F508, G542X, N1303X and R1162X.

We'l be agree with special conditions that could be requested.

Looking forward to your reply

Your most sincerely



Dr. G. Glover
Unidad de Genética
Centro de Bioquímica y Genética Clínica
apartado 61 Espinardo
Espinardo 30100 (Murcia) Spain

Fax Int + (68) 30.50.05
Phone Int + (68) 83.02.62

UNIVERSIDAD DE NAVARRA
DEPARTAMENTO DE GENETICA

14th Januar 1992

Dr Lap-Chee Tsui
Department of Genetics
The Hospital for Sick Children
Toronto, Ontario M5G 1X8
Canada

Dear Dr Tsui:

In order to participate in the spanish mini-consortium promoted by Dr Estivill I am pleased to give you the following data as requested by you in your meeting with Dr Estivill in Barcelona:

1. Number of studied families: 12

2. Mutations we have already searched for: F508 and all known mutations of exons n. 4 and n. 19 with DGGE and sequencing.

We are now studying systematically also with DGGE exons n. 21, 22 and 23.

3. We know and accept the promulgated rules of your consortium.

4. As a complementary information I inform you that we participate in a collaborative study with Dr De Arce, Dublin, in which we have already analyzed about 200 irish patients and some of their families.

Sincerely yours

Prof. A. Gullón

Address: 31080 Pamplona (Spain) POB 273 Telephone: 34 48 252150 Fax: 34 48 175500
Dirección: 31080 Pamplona (España) Apartado 273 Teléfono: 9 48 252150 Fax: 9 48 175500

FUNDACIÓN JIMÉNEZ DÍAZ
CLINICA DE NUESTRA SEÑORA DE LA CONCEPCION
Avda. Reyes Católicos, 2 (Ciudad Universitaria)
28040-MADRID

TELEFONOS:
544 15 00 - 544 17 00
544 11 00 - 549 10 07
549 11 00
Fax 549 47 54

8 January, 1992.

Dear Dr. Lap-Chee Tsui:

I have been working in Cystic Fibrosis since 1987, in Jiménez Díaz Foundation, Madrid, Spain.

During these years, we have been studied Spanish Cystic Fibrosis families (Fernández E. et al (1990), Hum Genet; 84:379-380; Fernández E. et al (1990), Hum Genet; 86:102). We have colaborated with other Spanish and Italian groups (Estivill X. et al (1989), Lancet; 2:1404; Novelli G. et al (1990), Prenatal Diagnosis; 10:413-416; Gasparini P. et al (1990), N Engl J Med; 323:62-63; Chillón M. et al (1990), Hum Genet; 85:396-397).

Now we are studing the new mutations: G542X, G551D, R553X, N1303K, W1282, D110H, R117H, and we would be very interested to recive all information about the advance of Cystic Fibrosis Genetic Analysis. I have the commitment to respect the rules of C.F. Genetic Analysis Consortium and I wolud be very pleased if you send to me this infromation.

Sincerely Yours.

Esther Fernández
Fundación Jiménez Díaz
Department of Genetics

Dr. Lap-Chee Tsui
Department of Genetics
Hospital for Sick Children
Toronto, Ontario M5G 1X8

Ana Mª Palacio de Parada.
Dto. Microbiologia.
Facultad de Medicina
ZARAGOZA. SPAIN.

30 th Jan. 1992.

Dear Lap-Chee:

I am sending you both the objectives and the porcess of my present research.

The objectives of my study are first of all to analyse the most frequent mutations in those families FQ affected from a well-defined aragonese origin.

Secondly to differenciate FQ chromosomes and normal ones by means of their different haplotype in order to establish eventual prenatal diagnosis.

Thirdly to associate genotype and phenotype in the FQ affected patients.

Finally to search for new mutations.

I am carrying out a study on FQ. in ARagón, a region in Northern Spain with a population of approximately 1.3 millon. The study includes 45 families who have at least one affected child. All patients had typical symptoms of FQ and at least two positive sweat tests.

Out of these families, 72 chromosomes are aragonese in origin.

There you have a list of the resulting analysed mutations.

Mutations	chromosomes	%
ΔF508	30	41'6
G542X	3	4'16
N1303K	1	1'38
R1162X	0	0
1609-CA	1	1'38
Unknown	37	51'38
Total	72	100

In order to establish the underlying haplotype associated with the above-mentioned mutations the following analysis have been carried out, so that Fq chromosomes and normal ones can be differenciated. These analysis have been done through the PCR (Polymerase chain reaction technique).

Microsatellites IVS8-1; AT 17b and AC 17b.

Extragenic polymorphisms XV-2C/Taq I; KM19/ScrfI; KM19/Pst I; MP6d-9/MspI, J3-11/MspI , in the all patients.

Extragenic polymorphisms J3-11/Pst I; CS-7/Cfo I; Met h/Msp I. in those patients in those patients who did not give positive information with the adoue-mentiones probes.

Intragenic polymorphisms 1898+152 (T-A), Exon 12.

At the moment I am still searching for new mutations by means of SSCPs (Single Strand Conformation Polymorphism).

It was during this search carried out in X. Estivill's departement that M. Chillón and I came across the 1609-CR mutation in Exon 10.

I also want to let you know that I accept all rules set on by the Consortion and thank you beforehand for everything you can do in order to facilitate my future research.

Yours sincerely

Ana M. Palacio

THE AUSTRALIAN NATIONAL UNIVERSITY

DIVISION OF BIOCHEMISTRY & MOLECULAR BIOLOGY
JOHN CURTIN SCHOOL OF MEDICAL RESEARCH

GPO Box 334
Canberra ACT 2601
Australia

Graeme B. Cox, PhD
Acting Head of Division

Telephone 06 249 2032
International +616 249 2032
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International +616 249 0415

23 November 1992

Dr Lap-Chee Tsui
Hospital for Sick Children
555 University Avenue
Department of Genetics
Toronto, Ontario
CANADA M5G 1X8

Dear Dr Lap-Chee Tsui

I wrote to Dr Francis Collins requesting details of mutations affecting the cystic fibrosis transmembrane conductance regulator and have been referred to you as Director of the Cystic Fibrosis Genetic Analysis Consortium..

I have been working on the molecular mechanism of the E.coli phosphate transporter - a member of the Traffic ATPase or ABC superfamily. We have used a modelling - mutational analysis approach and have reached some understanding of the mechanism (publication in December J.B.C.). I would appreciate very much a current list of CFTR mutations to compare with those mutations that eliminate activity of the phosphate transporter.

I, of course, would undertake not to breach any confidentiality restrictions and hope that you will be kind enough to allow me to have the information.

Yours sincerely

Graeme Cox

CENTRE HOSPITALIER UNIVERSITAIRE HENRI MONDOR
UNIVERSITÉ PARIS 12 - VAL DE MARNE

LABORATOIRE DE BIOCHIMIE - DÉPARTEMENT DE GÉNÉTIQUE - INSERM U.91
Hôpital Henri Mondor - 94010 Créteil Cedex

Professeur Michel Goossens
Téléphone : (1) 49 81 28 61
Télécopie : (1) 49 81 28 42

Créteil, December 30, 1992

Lap-Chee Tsui, Ph. D.
c/o Consortium
Dpt. of Genetics
Hospital for Sick Children
555 University Ave.
Toronto, Ontario
CANADA M5G 1X8

TÉLÉCOPIE
De : M. Goossens
A : Francis Collins
Date : 30/12/92 Nb de pages : 1
1-313-936 9353
3M Post-it™

Dear Lap-Chee,

Thank you for your recent letter about the new consortium members. I fully agree with Bob's answer, and also with your idea that the steering committee should continue to play its role in accepting membership applications.

Happy new year,

With very best wishes

cc. Art Beaudet, Francis Collins, Bob Williamson

555 UNIVERSITY AVENUE
TORONTO, ONTARIO
CANADA M5G 1X8

THE HOSPITAL FOR SICK CHILDREN

FAX MACHINE NUMBER: (416) 813-4931

HSC

LAP-CHEE TSUI, Ph.D.
DEPARTMENT OF GENETICS
PHONE: (416) 813-6015

DATE: December 23, 1992 (code: B,C,P,18)

TO: 011-44-71-706-3272
Prof. Bob Williamson
St. Mary's Hospital Medical School
Norfolk Place, U.K.

1-713-797-6718
Dr. Arthur Beaudet
HHMI-Baylor College of Medicine
Houston, Texas, USA

1-313-936-9353
Dr. Francis Collins
HHMI-University of Michigan
Ann Arbor, Michigan, USA

011-33-1-42.07.07.04
Dr. Michel Goossens
SNSERM U.91, Hôpital Henri Mondor
Creteil, France

Number of pages (including this page): 1

Dear Bob,

Thank you for your letter which I received by fax this morning. I cannot agree with you more about the current mission of the consortium, ie. to serve as an information repository for CFTR mutations. The data in turn provide the basis for genetic testing and genotype/phenotype studies. It would not be a major problem for me to send out additional newsletters by fax but I hope you would agree that acceptance of membership application will remain to be the function of the steering committee. I would like to hear any comments from the other members of this committee. I do not think CFF would object to our change of philosophy.

Have a happy holiday season and a prosperous new year.

Best regards,

Lap

cc. Art Beaudet, Francis Collins, Michel Goossens

DEPARTMENT OF BIOCHEMISTRY & MOLECULAR GENETICS
ST. MARY'S HOSPITAL MEDICAL SCHOOL
NORFOLK PLACE, LONDON W2 1PG

Professor R. Williamson PhD FRCPath
Hon MRCP Hon MD (Turku)

Tel: 071 723 1252 Ext: 5485
Fax: 071 706 3272

23rd December 1992

Dr Lap-Chee Tsui,
Genetics, Hospital for Sick Children, Toronto

FAX 0101-416-813-4931

Dear Lap-Chee,

Thanks for the forms of those requesting membership of the CF Genetic Analysis Consortium. I think that times have changed, and they should all be accepted. When the Consortium started, it was primarily a way of distributing unpublished data rapidly and in a way which (to some extent) protected the interests both of those submitting the data and of the CF community as a whole. It is worth remembering that at the time most people thought there would only be a limited number of mutations, and therefore one concern was to ensure that there were no "unseemly" races between groups to publish a significant mutation. Clearly this is not the case.

The Consortium now plays quite a different role - it represents an up-to-date collection of data on mutations from throughout the world, is regarded as an appropriate place to "store" private and rare mutations which might or might not be published eventually, and perhaps most important, is the best place to seek out an overview of the frequency of mutations worldwide and by country. Therefore, it is now of great value not to the research scientist interested in CF pathophysiology or genetics, but to the clinician who wishes to establish a screening programme (whether amongst patients or in the community) or to use phenotype/genotype correlations. If you agree, I do not think it is correct any longer to sort applicants into categories as we did at the beginning, since the relevance of those categories to the Consortium data base has become blurred.

The key question is how much work it represents for you. If it is truly little, and is paid for the by C.F.F., I vote to include all legitimate CF groups when they ask, though I particularly like the structure proposed by Xavi, which seems the most economical and integrated.

With best wishes,

BSb

cc. Art Beaudet, Francis Collins, Michel Goossens.