UMC Utrecht

Nasal Potential Difference and Follow-up in suspected CF patients with 5T polymorphism

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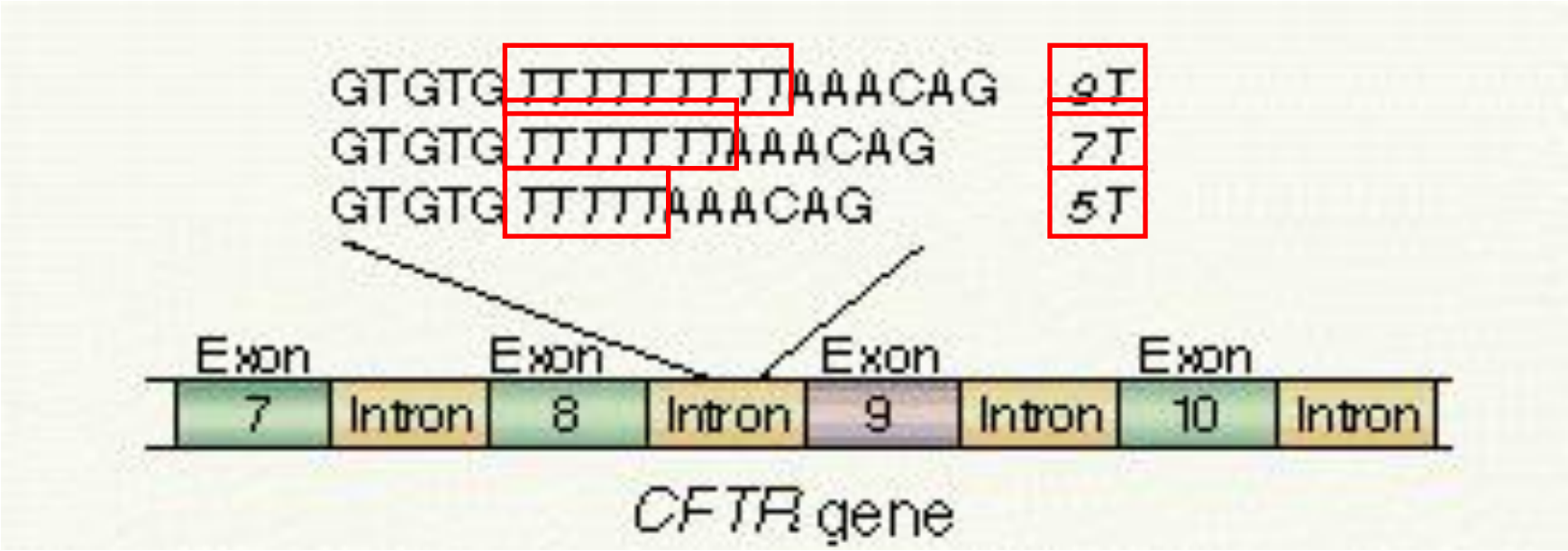
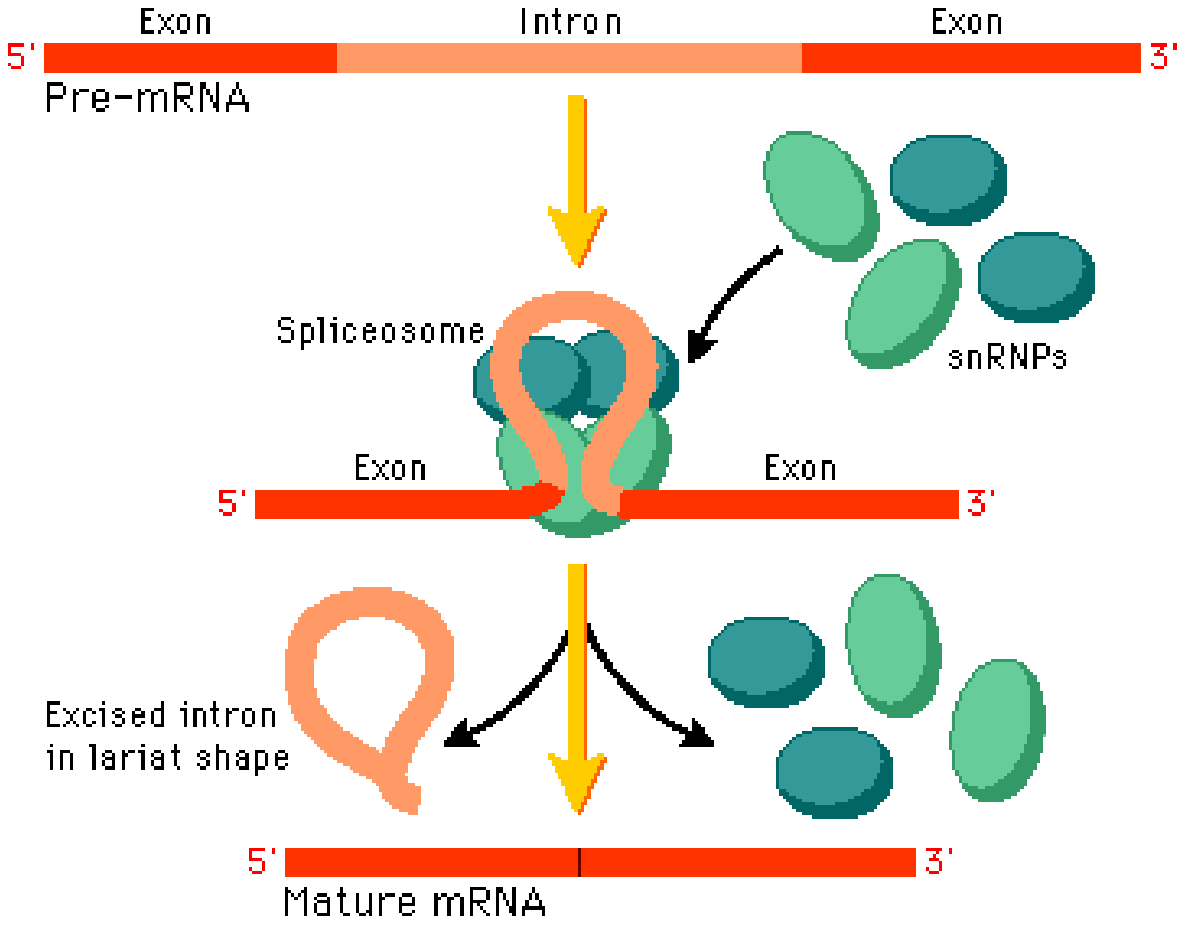
Where is 5T?

In intron 8 of the CFTR gene



Normal splicing

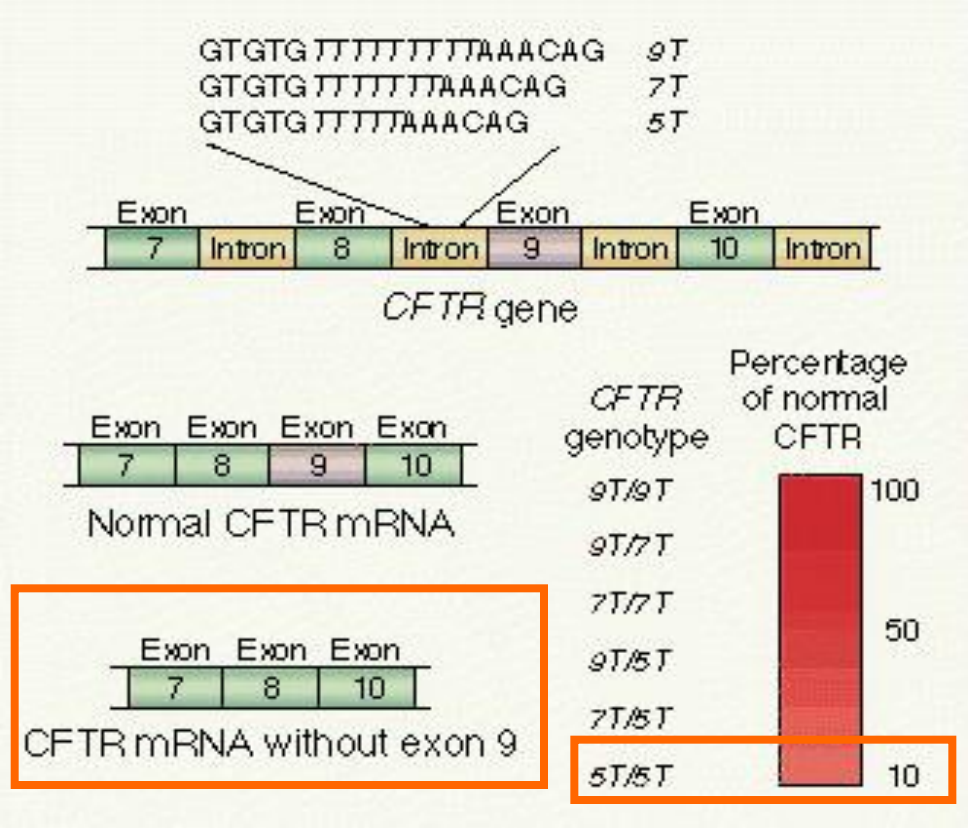


PolyT tract in intron 8

- **In 5T**, exon 9 is spliced out in 70-95% of mRNA strands: CFTR protein is too short to function

- In 7T/7T 50-100% normal length, in 9T/9T >95% normal length

- Effect on protein level:
  normal protein, low quantity



Background 5T

- 'Mutation with variable consequences'
- Symptoms:
  - no complaints
  - single organ disease
  - CFTR-related disease
  - CF or atypical CF
- Influences: R117H, TG repeats, etc.

Influences……

R117H*:

CF-causing mutation/R117H and 5T

CF-causing mutation/R117H and 7T

CF-causing mutation/R117H and 9T

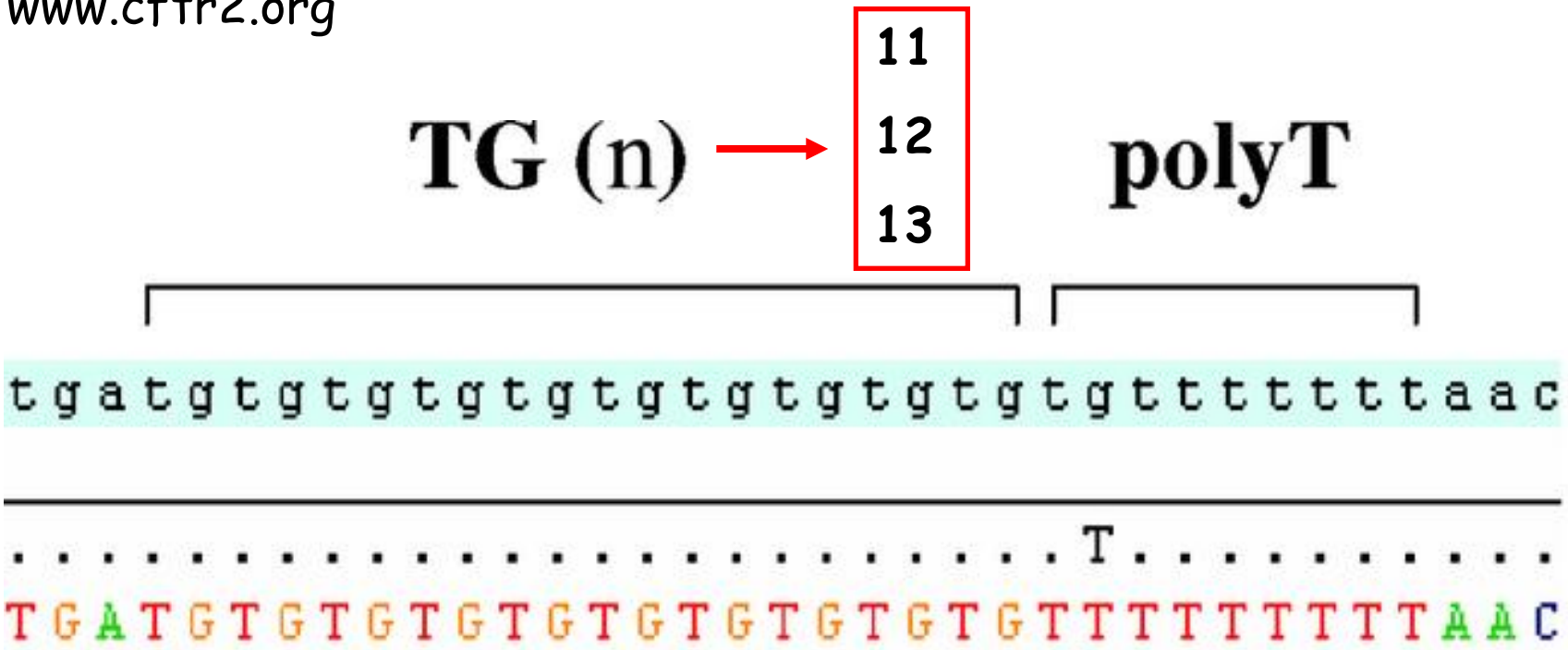
* www.cftr2.org

TG repeats*:

CF-causing mutation/5T and 11TG

CF-causing mutation/5T and 12TG or 13TG

* www.cftr2.org



Sun W et al. Genet Med 2006;8:339-345.

Aim

Assessment of CFTR function in 5T patients and correlation with long term symptoms / influencing factors

Methods

- 42 patients with 5T polymorphism underwent NPD (1996-now)
- Follow up using a questionnaire: change in symptoms, new CFTR-RD, sweat test repeated, (male infertility), CF diagnosis, change in treatment
- Comparing groups divided according to mutations and NPD results

Patient characteristics

- 42 patients
- Mean age 24±16 (range 5.5-65) years
- 13 (31%) female, 29 (69%) male
- Mutations:
  - 21 (50%) compound heterozygous (5T/other mutation)
  - 4 (10%) homozygous (5T/5T)
  - 17 (40%) no second mutation found (5T/-)
- NPD :
  - 17 (40%) abnormal (exp index ≥0.7)
  - 24 (57%) normal (exp index <0.7)
  - 1 (3%) test was not completed

Results – Follow up characteristics

- Follow up completed: 34 patients
- Symptoms:
  - Resolved/improved/stayed away/ limited to CBAVD in 11 (32%)
  - Remained/worsened in 23 (68%)
- Male infertility: present in 9 (out of 22 males)
- Diagnosis of atypical CF: in 18 (53%)

Follow up results – divided by mutations

Division according to mutations	Compound heterozygous, N= 15	Homozygous 5T N=3	5T 'carrier' N=16
Mean age in years (range)	32 (12-63)	33 (27-36)	32 (10-54)
Gender, M=male, F=female	11 M, 4 F	1 M, 2 F	11 M, 4 F
Sweat test (mean±SD)	45±20	62±32	51±23
FEV1 % predicted (mean±SD)	92±13	85±12	85±28
Abnormal NPD	80%	33%	25%
Improved symptoms in follow up	13%	0%	56%
Diagnosis – atypical CF	80%	33%	31%

Follow up results – divided by NPD

Division according to NPD	**Abnormal NPD, N= 17 (exp index ≥0.7)**	**Normal NPD, N=17 (exp index <0.7)**
Mean age in years (range)	30 (10-52)	35 (10-68)
Gender, M=male, F=female	12 M, 5 F	11 M, 6 F
Sweat test (mean±SD)	51±18	48±26
FEV1 % predicted (mean±SD)	88±17	88±25
Mutations		
Compound heterozygous	80%	20%
Homozygous 5T	33%	67%
5T 'carrier'	25%	75%
Improved symptoms in follow up	18%	47%
Diagnosis – atypical CF	94%	18%

Conclusions

- Large variation in symptoms and clinical parameters in every mutation group

- Abnormal NPD correlated with compound heterozygous for 5T and less improvement of symptoms

Future plan - 5T project

- Increasing sample size, including international collaboration
- TG repeats analysis

Acknowledgements

- Prof. Michael Wilschanski and Dr. Michael Cohen

- Physicians from CF centers in Israel:

  D. Atar, M.Aviram M, A. Augartan, L. Bentur, H. Bibi, H. Blau, O. Efrati, A. Hevroni, E. Kerem, M. Kramer, M. Lavy , M. Mei-Zahav, H. Mutzaffi E. Picard, J. Rivlin, Y. Yahav, A. Tal

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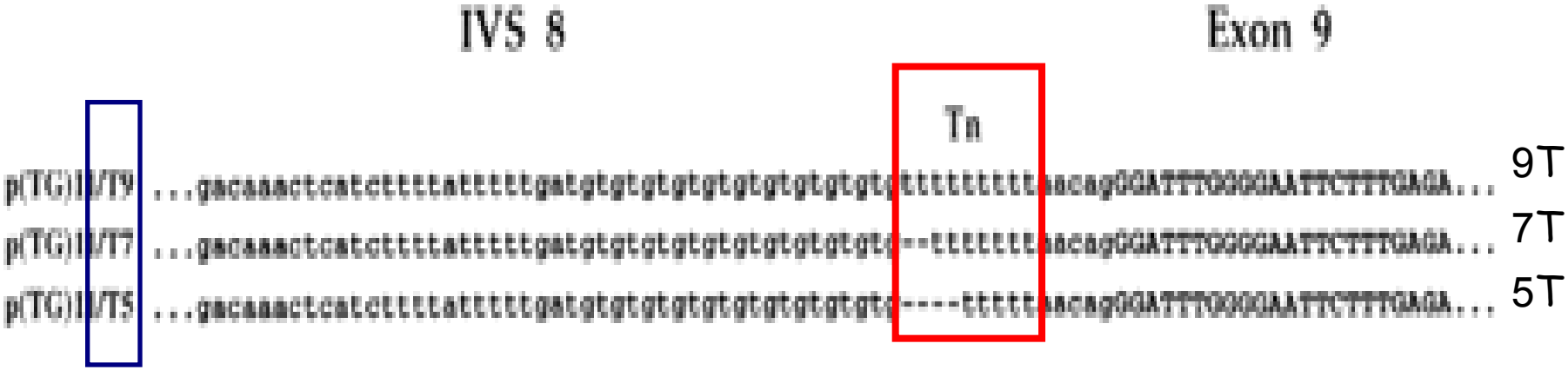


Results – follow up

- Follow up completed in 34 out of 42 patients (8 excluded)
- Mean age 23±15 (range 5.5-65) years
- 12 (35%) female, 22 (65%) male
- Mutations:
  - 15 (44%) compound heterozygous (5T/other mutation)
  - 3 (9%) homozygous(5T/5T)
  - 16 (47%) no second mutation found (5T/-)
- NPD: 14 (41%) abnormal, 20 (59%) normal

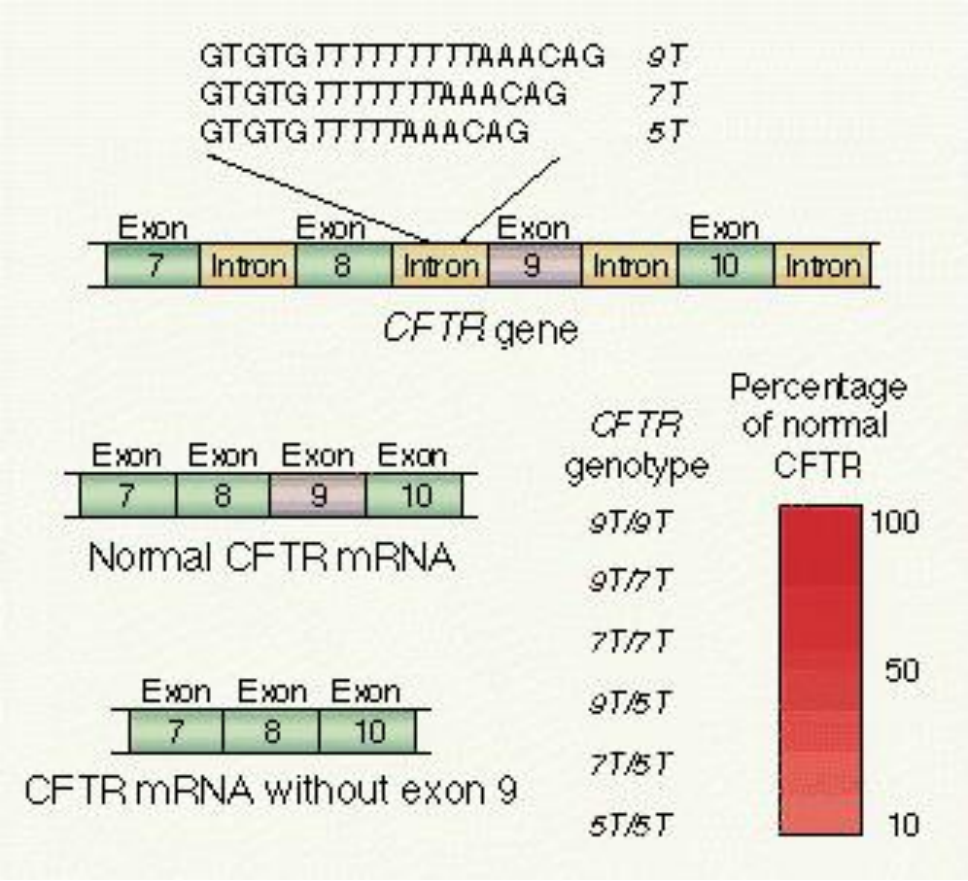
Invitation: join the 5T project

- Help increasing sample size and drawing conclusions as well as recommendations about follow up of 5T patients with more confidence
- Join if:
  - There are 5T patients in your center who underwent NPD measurement
  - It is possible to collect data on age, sweat test, FEV1, mutations and follow up
  - TG repeat analysis is possible or has been done
- Ask for contact information (or leave yours), today or tomorrow

Questions / Discussion / Comments

Background 5T

- 5T splice site variation
- Exclusion of exon 9 in 95% of mRNA



Methods

- 42 patients with 5T polymorphism underwent NPD (1996-now)

- Data: age, gender, symptoms, mutation analysis, ethnicity, sweat test results, FEV1, NPD results

Division according to mutations

Division according to mutations	Compound heterozygous 5T, N=20	Homozygous 5T, N=4	5T 'carrier', N=17
Mean age in years (range)	25 (3-58)	23 (16-32)	25 (7-65)
Gender, % males	75%	50%	65%
Mean sweat test result [mEq/l] (SD)	46 (19)	62 (32)	61 (21)
Mean FEV1 [%predicted] (SD)	88 (17)	89 (13)	85 (22)
Percentage abnormal NPD	75%	50%	29%
Improved symptoms in follow up	25%	33%	54%
Diagnosis (atypical) CF	75%	33%	33%

Division according to NPD results

Division according to NPD results		Abnormal NPD (exp ≥0.7) N=23	Normal NPD (exp <0.7) N=18
Mean age in years (range)		22 (3-64)	28 (7-65)
Gender, % males		74%	61%
Mean sweat test result [mEq/l] (SD)		55 (21)	48 (23)
Mean FEV1 [%predicted] (SD)		89 (16)	84 (22)
Mutations	Compound heterozygous	65%	26%
	Homozygous	9%	11%
	Carrier	26%	63%
Improved symptoms in follow up		29%	86%
Diagnosis (atypical) CF		86%	5%

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