WS13.1 Patients with mutations that permit 3% or more of wild-type CFTR function are associated with higher FEV_1

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Objectives: Quantifying the exact amount of CFTR function needed to escape lung disease in CF has been challenging. Establishing a threshold above which lung function improves provides a benchmark for molecular therapies that augment CFTR function.

Methods: Clinical and genetic data were collected on 39,696 patients enrolled in CF registries for the CFTR2 project. Functional consequences of 72 missense *CFTR* mutations were determined by short circuit current in Fischer Rat Thyroid cell lines expressing a single copy of *CFTR* cDNA. Mutations that introduce a premature termination codon (PTC) were presumed to have <1% wild-type (WT) CFTR function.

Results: Patients were grouped according to the function of their *CFTR* mutations relative to WT (Table 1). Patients with two mutations each having <1% WT CFTR function (includes F508del and PTC mutations) and patients with at least one mutation of ⩾3% CFTR function have a significant difference in FEV_1% predicted. Patients with CFTR function 4–15% also had higher FEV_1, but this was not different than the ⩾3% group.

Table 1. Comparison with <1%/<1%

	<1%/<1%	F508del/F508del	<1%/1–2%	<1%/2–3%	<1%/3–4%	<1%/4–15%
n	24947	16571	1459	241	134	612
Age	17.8±11.3	18.0±11.2	19.4±12.4**	19.7±12.0**	23.5±15.9**	24.2±16.7**
Sweat [Cl⁻]	101.8±16.1	101.9±15.6	102.7±16.3	99.8±16.7	79.9±25.0**	73.6±23.0**
Fraction PI	0.97	0.98	0.90**	0.77**	0.36**	0.37**
FEV1%pred.	74.3±25.3	74.5±25.3	75.2±24.6	73.3±23.9	82.6±27.0*	80.8±24.7**

*p<0.05, **p<0.001.

Conclusion: Patients with ⩾3% CFTR function had a clinically relevant difference in FEV_1, along with differences in sweat chloride concentration and rates of pancreatic insufficiency. These associations should be considered in evaluation of molecular therapies directed at low function *CFTR* mutations.

WS13.2 Change in FEV_1% predicted in one year in patients with nonsense mutations and patients homozygous for F508del

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We are at the dawn of personalized medicine for patients with cystic fibrosis (CF). Several trials with mutation or mutation class specific drugs are ongoing. However, it is unknown whether lung disease severity is worse in subjects with mutations belonging to specific classes.

Using the 2008–2009 European Cystic Fibrosis Society Patient Registry data, we evaluated the change in FEV_1 % predicted in one year in subjects with CF (patients 6 years old or more, without lung transplant) and a baseline lung function between 40 and 90% predicted. We compared the change (2008 to 2009) in FEV_1 % predicted in subjects having at least one nonsense mutation (group I; n=912) and in subjects homozygous for F508del (group II; n=3717). The change in FEV_1 % predicted was similar in the two groups: the median of the change was −0.74% predicted (IQR −5.93; +4.37) in group I, and −0.85% predicted (IQR −6.62; +4.61) in group II. In group I the median change in FEV_1 % predicted was positive in the age categories 6–9 and 10–14 years, and negative from 15–19 up to 40–44 years; in group II the median change of FEV_1 % predicted was positive in the age categories 6–9 and 40–44 years, and negative from 10–14 up to 35–39 years. Expressed as percentage from baseline year 2008, the median changes were 1.17% (IQR −9.35%; 6.38%) in group I and 1.29% (IQR −10.2%; +6.82%) in group II, again without group differences (Kruskal-Wallis test: p=0.59).

In conclusion, in patients with CF and baseline lung function between 40 and 90% predicted, we did not find evidence for difference in change in FEV_1 % predicted over 1 year between patients with nonsense mutations or patients homozygous for F508del.

WS13.3 Magnetic resonance imaging detects changes in structure and perfusion, and response to therapy in early cystic fibrosis lung disease

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Objectives: Recent studies in infants and preschool children with cystic fibrosis (CF) suggest that non-invasive monitoring will be important for patients who may benefit from early therapy to prevent structural lung damage. Magnetic resonance imaging (MRI) detects structural and functional abnormalities in lungs from older CF patients without radiation exposure. Aim of this study was to evaluate the potential of MRI to detect abnormal lung structure and perfusion in infants and young children with CF, and monitor response to therapy for pulmonary exacerbation.

Methods: MRI studies were performed in 50 children with CF (age 3.1±2.1years, range 0–6years) in stable clinical condition (n=40) or pulmonary exacerbation before and after antibiotic treatment (n=10), and in 26 non-CF controls (age 2.9±1.9years). T1- and T2-weighted sequences before and after intravenous contrast and first-pass perfusion imaging were acquired, and assessed using a dedicated morpho-functional score.

Results: MRI demonstrated bronchial wall thickening/bronchiectasis, mucus plugging and perfusion deficits from the first year of life in most stable patients with CF (global score 10.0±4.0), but not in non-CF controls (score 0.0±0.0; $P < 0.001$). In patients with exacerbations, the global MRI score was increased to 18.0±2.0 ($P < 0.001$), and was significantly reduced to 12.0±3.0 ($P < 0.05$) after antibiotic therapy.

Conclusion: MRI detected abnormalities in lung structure and perfusion, and response to therapy for exacerbations in infants and preschool children with CF. These results support the development of MRI for non-invasive monitoring and as an endpoint in interventional trials for early CF lung disease.

WS13.4 Small-airway disease in cystic fibrosis studied with multidetector CT and microCT

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Introduction: Little is known on the site and nature of CF small-airway disease (SAD). Small airways can be studied at two levels of resolution: Multidetector Computed Tomography scans (MDCT) with a resolution down to 1 mm and MicroComputed Tomography (μCT) to allow 3D morphometry of terminal bronchioles (TB) (<1 mm in diameter).

Aim: To study SAD in CF using MDCT and μCT.

Methods: CF explant lungs (n=8) and control lungs (n=6) were inflated to total lung capacity and fixed in the fumes of liquid nitrogen. On MDCT and utilizing Osirix 4.1, the number and diameter of visible and obstructed airways were counted per airway generation (method: Verleden et al. AJRCCM 2013). Using μCT (Skyscan 1172), the number per milliliter (mL), minimal diameter and cross-sectional area (CSA) of TB were assessed in lung cores (on average 10/lung; each core 1.5 cm diameter).

Results: CF lungs had significantly more visible airways on MDCT than controls (mean total 606 vs 316, p=0.02). Airway dilatation was found downstream from generation 6 with cumulative airway diameter of 209 cm per lung in CF versus 78 cm in controls (p=0.004). Obstructive lesions were seen from generation 5–6 onwards; 75% (SD 20%) of total airways or around 40% of airways per generation were obstructed. μCT showed a significant reduction in the number (2.9 vs 5.6/mL; p<0.001), diameter (212 vs 363 μm; p<0.001) and CSA of TB (92 vs 177 μm²; p<0.001) in CF versus control.

Conclusion: We studied CF SAD using MDCT and μCT. Dilatation and obstruction of airways from generation 5–6 onwards as well as narrowing and disappearance of TB were found. Ongoing research will correlate μCT TB lesions with histological findings.