Abstract S68 Table 1 Overview of solicited and unsolicited adverse events

	Group 1: 140 µg F-protein-FP/2 mg BLP		Group 2: 350 µg F-protein-FP/5 mg BLP		Placebo	
	Post prime (n=18)	Post boost (n=17)	Post prime (n=18)	Post boost (n=18)	Post prime (n=12)	Post boost (n=12)
n (% of subjects with events)						
Local solicited AEs						
Loss of smell	3 (16.7)	4 (23.5)	1 (5.6)	0	2 (16.7)	0
Nasal discomfort	2 (11.1)	3 (17.6)	3 (16.7)	4 (22.2)	3 (25.0)	1 (8.3)
Nasal pain	1 (5.6)	0	1 (5.6)	2 (11.1)	1 (8.3)	0
Rhinorrhea	8 (44.4)	4 (23.5)	6 (33.3)	4 (22.2)	3 (25.0)	2 (16.7)
stuffy nose	8 (44.4)	5 (29.4)	6 (33.3)	4 (22.2)	4 (33.3)	6 (50.0)
Sneezing	6 (33.3)	2 (11.8)	1 (5.6)	3 (16.7)	2 (16.7)	2 (16.7)
Sore throat	2 (11.1)	1 (5.9)	5 (27.8)	3 (16.7)	3 (25.0)	5 (41.7)
Solicited systemic AEs						
Arthralgia	1 (5.6)	2 (11.8)	1 (5.6)	1 (5.6)	0	0
Fatigue	9 (50.0)	7 (41.2)	6 (33.3)	6 (33.3)	7 (58.3)	5 (41.7)
Feeling feverish	2 (11.1)	1 (5.6)	1 (5.6)	1 (5.6)	1 (8.3)	1 (8.3)
Headache	8 (44.4)	4 (23.5)	8 (44.4)	8 (44.4)	4 (33.3)	2 (16.7)
Malaise	2 (11.8)	2 (11.8)	2 (11.1)	0	1 (8.3)	1 (8.3)
Myalgia	5 (27.8)	3 (17.6)	0	2 (11.1)	2 (16.7)	1 (8.3)
All unsolicited AEs						
Oro-pharyngeal pain	0	0	1 (5.6)	5 (27.8)	1 (8.3)	1 (8.3)
Cough	0	1 (5.6)	3 (16.7)	1 (5.6)	0	1 (8.3)

New approaches to characterising paediatric respiratory diseases

S69

GENETIC AND STRUCTURAL CHARACTERISATION OF OUTER DYNEIN ARM VARIANTS CAUSING PRIMARY CILIARY DYSKINESIA

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Introduction Primary ciliary dyskinesia (PCD) is a heterogeneous, recessive disease, characterised by dysfunction of motile cilia that arises from structural defects. Symptoms include chronic pulmonary disease, rhinosinusitis, otitis media, laterality defects, congenital heart disease and subfertility. The most commonly affected cilia structure is the outer dynein arm (ODA), a complex structure composed of a docking complex

and multiple heavy, light and intermediate dynein chains. An understanding of the relationship between the genetic and structural phenotype of ODA variants will allow patient stratification and improve diagnosis through verification of new candidate genes.

Methods 195 PCD patients were genotyped using next generation sequencing. Candidate variants were confirmed by Sanger sequencing and familial segregation analysis. For selected ODA mutations, electron tomography, an extension to transmission electron microscopy, was used to produce high-resolution 3D models of ciliary axonemal microtubular doublets and ODA volume ratios. The data were analysed to determine the impact of eight different gene mutations causing different structural defects of the ODAs.

Results 39% of patients had bi-allelic mutations identified which are associated with ODA structure. These include variants in known PCD genes: DNAH5 (n=39), DNAH11 (n=18), DNAI1 (n=8), DNAI2 (n=5), ARMC4 (n=3), CCDC114 (n=2), DNAL1 (n=1) and mutations in the novel candidate DNAH9. Variants in DNAH9 have been suggested as a cause of PCD previously but disregarded due to lack of phenotypic evidence. 3D models of the ODA complex identified genotype specific changes in the ODA complex in PCD. The ODA structure in PCD was different in the proximal region, in proximity to the microvilli, when compared to the distal region, towards the tip of the axoneme. A significant deficiency in the ODA volume was detected at the distal part of the axoneme in the patient with DNAH9 defects, whereas the proximal portion was unaffected, reflecting the protein position of DNAH9.

Conclusion 3D electron tomography can be used to detect subtle changes in the ultrastructure of the ODA in PCD patients with differences detected in the impact of mutations in proximal versus distal regions of the cilia.

S70

CHANGE IN LUNG CLEARANCE INDEX AND EXHALED NITRIC OXIDE AS MARKERS OF SYSTEMIC CORTICOSTEROID RESPONSE IN CHILDREN WITH SEVERE ASTHMA

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Introduction Children with severe therapy resistant asthma (STRA) have heterogeneous disease with variable response to steroids. Currently, spirometry (forced expiratory volume in 1 s (FEV₁)) is most widely used to assess treatment response. We hypothesised lung clearance index (LCI) would more sensitively assess steroid response than FEV₁ alone, using our multi-domain approach [JACI 2016;138:413–420] with the addition of LCI to measure response of distal airway disease.

Methods 39 children with STRA were recruited during a clinically-indicated admission for bronchoscopy and intramuscular triamcinolone injection. Prior to triamcinolone, they performed LCI, spirometry, FeNO, and filled in the asthma control test (ACT). They were followed up at 4 weeks and these tests repeated. ACT was considered abnormal if <20, LCI if ≥7.1, FEV₁ percent predicted below 80%, and FeNO if ≥24 parts per billion. Any domain which was abnormal at visit 2 was a non-response.

Results 26/39 (67%) patients had at least a partial response, see Table. There was strongest concordance of Results between FeNO and LCI (70%). 11/39 (28%) of patients had a response in at least two domains, 4/39 (10%) at least three, and 1 patient responded in all four domains.

Conclusions In this cohort, LCI, FeNO and FEV₁ were equally likely to be abnormal at baseline. FeNO and LCI were most likely to respond, (36% and 33% respectively), whereas FEV₁ was least responsive to systemic steroids. Using this multi-domain approach 67% improved over 4 weeks following treatment with systemic corticosteroid. The clinical significance of an LCI response remains to be determined. We speculate that this group may reflect a distal airway disease phenotype who may benefit from fine particle inhaled corticosteroids.

Abstract S70 Table 1 Patients with abnormal results in each of the 4 domains tested pre- and four weeks post-triamcinolone injection

Measurement	Visit 1 Abnormal	Visit 2 Abnormal
FEV ₁	23 (59%)	19 (49%)
LCI	20 (51%)	7 (18%)
ACT	37 (95%)	26 (67%)
FeNO	24 (62%)	10 (26%)

S71 ARE ETHNIC DIFFERENCES IN LUNG FUNCTION EXPLAINED BY DIFFERENCES IN RESPIRATORY MUSCLE STRENGTH IN CHILDREN?

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Background South Asian (SA) children have a reduction in forced vital capacity (FVC) of 9%–13% compare to white children. Ethnic differences in Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) could potentially explain this. One study in adults measured MIP (but not MEP) in four ethnic groups (not including South Asians) but failed to find any differences (Sachs, Enright et al. 2009).

Aim To investigate differences in spirometry and respiratory muscle strength between white and south Asian children.

Methods Children were recruited from primary schools. We measured height, weight, and spirometry. FEV₁ and FVC were expressed as Z-scores, based on predicted values for white children (Quanjer et al. 2012). For respiratory muscle strength measurements, the child breathed through a pneumotachograph attached to a shutter. To measure MIP, after several quiet breaths, the child exhaled maximally and the shutter was activated. The child made an inspiratory effort and peak pressure was recorded. The test was repeated several times. Measurements of MEP were similar, except that the child inhaled maximally and then made a forceful expiratory effort.

Results We studied 263 healthy children aged 5–11 year. We obtained valid spirometry on 229 (64 white, 165 SA); valid MIP on 203 (55 white, 148 SA); and valid MEP on 231 (64 white, 167 SA). FEV₁ and FVC were smaller in SA children than their white peers. There were no significant differences between unadjusted MIP and MEP in white and SA children.

This finding was unchanged after adjustment for age, height and weight (Table).

Conclusions Differences in spirometry were in accordance with previous reports. We did not find any significant differences in respiratory muscle strength between the two ethnic groups. The greater FVC in white children might have been attributable to increased inspiratory muscle strength, leading to a greater volume at the start of the manoeuvre, but this was not the case. An increase in expiratory muscle strength would be less likely to increase FVC, since the end of expiration occurs when there is airway closure. Elastic recoil might be an alternative explanation for ethnic differences in lung function.

Abstract S71 Table 1

	White	South Asian	p
FEV ₁ Z-score	0.13 (1.02)	−0.58 (0.96)	<0.000
FVC Z-score	0.34 (1.00)	−0.69 (0.95)	<0.000
MIP (unadjusted) (kPa)	7.31 (2.15)	7.10 (2.03)	0.54
MIP (adjusted) (kPa)	7.45 (1.92)	7.05 (1.91)	0.19
MEP (unadjusted) (kPa)	6.27 (1.56)	6.48 (1.73)	0.38
MEP (adjusted) kPa	6.33 (1.57)	6.46 (1.56)	0.59

Values are all Mean (SD)

S72 CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF SEVERELY ASTHMATIC CHILDREN WITH PERSISTENT AIRFLOW LIMITATION

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Introduction Severe therapy resistant asthma (STRA) in children is heterogeneous: many have normal lung function, however there is a group with persistent airflow limitation (PAL). Little is known about PAL in children and previous studies are limited by the definitions used. We hypothesised that when PAL is classified according to stringent criteria (post bronchodilator FEV₁ z score <−1.96 after a one-month systemic steroid trial (ERM 2011, Ch 5; 51–59) this group would have distinct clinical, inflammatory and pathological characteristics compared to children without PAL.

Methods Retrospective analysis of 103 STRA children. Patients were classified as STRA if they had ongoing poor control despite high dose inhaled corticosteroids plus at least one add on therapy having been assessed as part of a systematic protocol when modifiable factors such as poor adherence were identified and corrected. All children underwent bronchoscopy, bronchoalveolar lavage (BAL) and endobronchial biopsy and received intramuscular triamcinolone. Asthma control test score (ACT); inflammation (exhaled nitric oxide (FENO), induced sputum); spirometry (FEV₁, FVC) were measured on the day of bronchoscopy and 4 weeks later. The best FEV₁ in the year post triamcinolone was recorded.