Abstract ID:- 575

Abstract Title:- Genetic variant landscape of Childhood Interstitial Lung Diseases in India

Presenting author name :- Madhumita Roy Chowdhury

Presenting author institute:- Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

Co-authors name:- Anjali Bajaj, Indu Kumari, Divya Bhalla, Vamsi K. Yenamandra, Rakesh Lodha, Nitin Dhochak, Kana Ram Jat, Neerja Gupta, Madhulika Kabra, Sushil K. Kabra

Co-authors name institute:- Pediatrics MGM Medical College, Aurangabad, India, CSIR-Institute of Genomics and Integrative Biology, New Delhi, India, Academy of Scientific and Innovative Research, Ghaziabad, India

Aims:- Childhood Interstitial Lung Diseases (chILD), are a diverse group of incurable diseases characterized by chronic lung inflammation and fibrosis, resulting in progressive and irreversible decline in lung function with poor survival rates. While environmental and occupational exposures are known risk factors for adult ILD cases, there is increasing evidence for genetic predisposition in chILD patient cohorts (including familial and sporadic cases) with the identification of several candidate genes involved in surfactant production, telomerase maintenance, immune and lung barrier function. Given the lack of molecular studies in Indian chILD patients, our aim is to

Aim: To identify the genetic variant landscape in Indian chILD patients.

Methods:- We carried out whole exome sequencing (WES) as per manufacturer's protocol (Twist Biosciences Inc.) to discover the genetic variant landscape in a cohort of 34 radiologically confirmed chILD patients (aged 1-16 years) recruited from Pediatric Pulmonology OPD & Clinic at AIIMS, New Delhi. The average sequencing coverage was 73.1±21.8x with a median of 1,25,883 variants captured per sample. A merged variant file (15,41,374 variants) was generated for all patient samples and a candidate gene-based filtering strategy was employed for variant prioritization against a list of 183 genes known to be implicated in ILD based on literature evidence.

Results:- A total of 269 variants in 85 ILD genes were selected based on functional significance (loss of function and non-synonymous variants); in-silico prediction tools [SIFT (D), PolyPhen (D/P) and CADD (>15)]; minor allele frequency (<0.05) in population datasets (gnomAD and IndiGen) and previously reported pathogenic variants (ClinVar). Four patients (12%) had previously reported pathogenic variants in CFTR, STING1, NF1 and NPRL3 genes. Current functional evidence precluded us from prioritizing causative variants in the remaining patients, but a striking observation among our cohort was the rare deleterious variant enrichment in mucin genes (MUC5B, MUC17), surfactant proteins (SFTPC, ABCA3), host defense (ATP11A, TOLLIP, OTOP1), cell adhesion (DSP, DPP9) and others (HRNR, SMPD4, CSPG4, LAMA5).

Conclusions:- Building on this data and identifying such gene variants in additional chILD patients coupled with functional analyses would help in ascertaining their significance in chILD pathogenesis. Rapid advances and dwindling costs of genome sequencing technologies is enabling clinicians to decipher the underlying genetic determinants of complex and idiopathic systemic diseases.

Conclusion: In the absence of effective therapies, such precise molecular characterization studies in chILD patients could offer invaluable insights into disease prognostication and prevention strategies in addition to discovering molecular targets for early therapeutic interventions.