Epidemiology/Registry

P032

The dynamics of DNA diagnosis availability for cystic fibrosis patients in the Russian Federation, and genetic variation analysed using the National Disease Registry between 2013–2018

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Objectives: To analyse the dynamics of detecting genetic variants of *CFTR* gene based on data from the Registry between 2013 and 2018 in the Russian Federation (RF).
Methods: Registry for 2013 year contained data of 1968 patients from 74 different regions, for 2018 year - 3142 patients from 81 RF regions.
Results: 94.3% out of all CF patients underwent genetic testing in 2018 compared to 87.5% in 2013. Children who underwent the testing composed 94.6%, adults –93.6% of the cases in 2018 (compared to 87.5% for children and 91.0% for adults in 2013). The overall frequency of allele identification made up to 89.3% (79.1% in 2013). Out of the entire group of patients who underwent genetic testing, 82.4% had 2 variants of DNA sequence of the *CFTR* gene (66.1% in 2013), 14% had only one variant, and in 3.7% none of the genetic variants was identified (in 2013, 25.9% had one, 8% had none). A total of 212 genetic variants were revealed (112 in 2013). The most common genetic variants are F508del - 53.05%, CFTRdele2,3 - 6.09%, E92K - 3.04%, 3849+10kbC->T - 2.38%, 2143delT - 2.11%, 2184insA - 1.84%, 1677delTA - 1.77%, W1282X - 1.75%, N1303K - 1.55%, G542X - 1.48%. «Mild» genotypes were observed in 23% of the patients. «Severe» genotypes were predominant among children and adults, 82.4% and 62.5%, respectively.
Clinical characteristics and functional evaluation of the chloride channel first described in patients with pathogenic variants: c.831G>A, c.1083G>A, 3272-16T>A, D579Y and c.1585-94124A>G.
Conclusion: The number of *CFTR* gene variants in RF has increased by 101 variants throughout the last 5 years due to the introduction of sequencing and increased genetic testing. Also 49 rare mutations were observed and the number of patients with one or two undetected mutations accordingly decreased. The use of functional tests (Intestinal current measurement) allows for a better understanding of the pathologic manifestation of the different genetic variants.

P033

Epidemiological features "Middle - Ural" variant L138ins in the CFTR gene at cystic fibrosis in Russia

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The allele frequency (AF) of the L138ins, according CFTR2, was only 0.00014% (https://cftr2.org). The L138ins in Russian CF patients was describing since 2005 - with an AF of 0.2% (Kapranov N. et al., 2005). In 2009, the AF of the L138ins in the European part of Russia determined to 0.004%, in the Siberian Federal District - 0.01% (Petrova N., 2009). Since 2009, the L138ins has been included in the routine CFTR gene analysis in Russia.
Objectives: To study the epidemiological characteristics of L138ins in CF patients in Russia.
Methods: The National Register of CF Patients in the Russian Federation (RF) for 2017 was analysed.
Results: In the National Register were 196 different variants in the CFTR gene. The L138ins was found in 70 patients and took 11th place in the AF of the CFTR gene variants in Russia (1.2%). Among children - in 10th place (1.1%), among adults - 7th place (1.6%).The AF of the L138ins in the regions of RF was different: in the Perm Region - 5.4%, in the Chelyabinsk Region - 4.1%, in the Sverdlovsk Region - 3.3%. The highest AF of the L138ins was in the Republic of Mordovia, however, L138ins was found there in only two patients. Also, a high frequency was in Kurgan (6.3%) and in Kirov (5.6%) regions - but one patient in each region. In the remaining regions, the L138ins was found in isolated cases or was absent.
Conclusion: The L138ins is a rare variant CFTR in the world, but it is often found in CF patients in the RF, to a greater extent in adult patients. The widespread introduction of DNA diagnostics, the inclusion of the L138ins in the panel of common variants in the CFTR, the detection of CF among adults has significantly increased the diagnosis of this variant in Russia. The L138ins was more common in CF patients living in the Middle Urals. We would like to thank CF Patient Registry of the RF for providing access to patient data and thank the individual regional CF centres' representatives for allowing use of data (http://mukoviscidoz.org/).

P034

Prevalence of cystic fibrosis paediatric patients with p.Arg1162X mutation in southern Brazil: a migration flow outcome

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There are more than 2000 mutations reported in CF. Brazilian population is a mix of African, European and Indigenous populations forming a particular genetic background. One of the top 5 CF pathogenic variants in Brazil is the stop codon mutation p.Arg1162X or R1162X.
Methods and objectives: Here we present data of CF paediatric patients from a referral center in the South of Brazil with at least 1 allele of p. Arg1162X. The objective of this study was to report the prevalence of this variant in Brazil and relate it to migration flows.
Results: In our database of 87 CF paediatric patients, p.Arg1162X is the second most common (4.4%) mutation, a higher prevalence than that in the whole country database (1.8%, p = 0.01). Seven of the patients have at least 1 allele and 1 of them is homozygous for this mutation. The mean current age of patients is 10y. The majority of diagnosis was made after newborn screening (58%). In the latest Brazilian CF Registry report, approximately 70% of CF patients live in the south and southeast regions, where the majority of European immigrants were settled in the past. The heterogeneity of Brazilian genetic background is principally influenced by immigration flows. Italian immigration to our region peaked in the 1880s and more than half of immigrants were from the Veneto region. Italian studies show that the pathogenic variant p.Arg1162X is very common in Veneto and Trentino regions (close to 10%).
Conclusion: Our higher prevalence of the p.Arg1162X mutation is probably due to a greater immigration of Veneto people to southern Brazil.

P035

Comparison of clinical findings of the patients with cystic fibrosis in terms of diagnosed with and without neonatal screening

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Objectives: Newborn screening (NBS) for cystic fibrosis (CF) was implemented on January 2015 in Turkey. The aim of this study was to compare the clinical findings of CF patients diagnosed by NBS and patients who were diagnosed without or negative NBS in CF Registry of Turkey (CFRT).
Methods: The total number of patients in the CFRT was 1488 in 2018. Three hundred and fifty-nine of these patients were included into the study who were born after NBS implementation. Age at diagnosis, gender, history of meconium ileus (MI), results of sweat chloride test, and faecal elastase, colonisation status were compared in patients diagnosed with NBS and patients without or negative NBS. NBS positive patients were classified as group 1, NBS negative patients as group 2, and patients without NBS as group 3.
Results: There were 299 (83.3%) patients in group 1, 40 (11.1%) patients in group 2 and 20 (5.6%) patients in group 3. The mean age at diagnosis was 0.2 ± 0.4 in group 1, 0.9 ± 2.0 in group 2, and 0.5 ± 0.6 months in group 3. The mean age at diagnosis was significantly higher in group 2 and 3 than group 1 (p:0.001). Seventeen (5.6%) patients in group 1, two (5%) patients in group 2 and five (25%) patients in group 3 had MI. MI was more common in group 3 than the others (p: 0.018). Two hundred and sixty-six patients in group 1, 26 patients in group 2 and 18 patients in group 3 had pancreatic insufficiency and it was more common in group 2 and group 3 than group 1 (p:0.001). Chronic *S. aureus* infection was present in 16% patients in group 1, 7% patients in group 2, 40% patients in group 3 and there were significant difference between the group 3 and the others (p:0.004). Sweat chloride tests results were higher (p:0.009) and faecal elastase results were lower (p:0.033) in group 1 than the others.
Conclusions: NBS provides early diagnosis and patients could be diagnosed before the occurrence of pancreatic insufficiency findings and pulmonary complications such as *S. aureus* colonisation.

P036

Relationship between phenotype and genotype in an older cystic fibrosis cohort

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Objectives: The evolution of CF demography over time has seen an exponential improvement in survival and an ageing CF population. The CF registry reported that 56.2% of patients in the UK in 2018 were adults and the number of older adults with CF continues to increase. It is therefore important to consider the specific demographics of the older CF population, in order to better understand this group and their potential complexities and trajectories.
Methods: Data were retrospectively collected for patients ≥40 years of age at a large adult CF centre in the UK, including age at diagnosis, genotype, pancreatic status, BMI and %predicted FEV_1. In addition, prospective sweat testing, using pilocarpine iontophoresis (Wescor Macroduct), was performed to examine the relationship between sweat chloride and other demographics within this older CF patient cohort.
Results: Data were collated for 91 patients, with 58 of these patients undergoing sweat test analysis. Patient data were analysed in three age groups (40–49; 50–59; ≥60 years) using one-way ANOVA, revealing differences in sweat chloride ($p = 0.025$) and age of diagnosis ($p < 0.001$) between groups. Lower sweat chloride, later age of diagnosis and higher prevalence of pancreatic sufficiency was seen with advancing age. There was no significant difference in BMI and baseline $\%FEV_1$ between age groups. Genotype analysis reveals a difference in the prevalence of less severe CFTR mutations (defined as ≥1 class IV-V mutation) between age groups 40–59 years and ≥60 years ($p = 0.002$).
Conclusion: CF patients over 40 years of age have a heterogeneous phenotype. Those greater than 60 years are more likely to have been diagnosed in later life, be pancreatic sufficient, have lower sweat chloride and a less severe genotype. Within the older CF patient cohort there exists a distinct group with sufficient CFTR function to delay clinical presentation for several decades.

P037

Cystic fibrosis in Cyprus: results from the national patients' Registry

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Objectives: Since the early 1990s, systematic recording of cystic fibrosis (CF) patients' data has been implemented in Cyprus. Recently, we have established and maintained a national patients' registry. We aim to present a wide spectrum of genotypic and phenotypic features of CF patients in Cyprus from the most recent data collection in 2019.
Methods: Patients' core data (demographics, diagnosis, genotype) and annual report data (growth, lung function, microbiology, complications, treatment) were systematically collected, recorded, and analysed following the specifications of the European patients' registry online software system.
Results: Overall, data from 50 CF cases are presented, 5 of whom have deceased and 13 have been lost to follow-up in last years. Mean ± SD age at diagnosis was 6.2 ± 10.8 years, and mean ± SD age by the end of 2019 was 21.5 ± 14.3 years. Most commonly, patients presented at diagnosis with acute or persistent respiratory symptoms (46%), failure to thrive or malnutrition (42%), and dehydration or electrolyte imbalance (34%). In all cases, diagnosis was confirmed by genotyping. p.F508del was the most common mutation (45.2%), followed by p.Leu346Pro (6.7%), a mutation detected solely in individuals of Cypriot descent. According to the 2019 annual report, mean ± SD BMI-for-age z-score was 0.07 ± 1.3, whereas mean ± SD best FEV_1% predicted was 78 ± 19.9. *Haemophilus influenzae* was the most common pathogen isolated in sputum cultures across all age groups (>60% of examined patients). Chronic colonisation with *Pseudomonas aeruginosa* and *Staphylococcus aureus* was confirmed in 37.5% and 50%, respectively, in patients who underwent a sufficient number of sputum cultures.
Conclusion: Systematic recording of patients' data is necessary for the optimisation of healthcare for CF patients and for the overall improvement of disease prognosis.