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Americans. For this reason, a national panel of mutations is difficult to define.
Objective: The aim of this study was to describe genetic mutations found in patients attending at an Argentine CF Reference Center, and to assess the sensitivity of the different genetic methods used.
Methods: The genetic data from patients with confirmed CF diagnosis were analyzed. During the 2006–2016 period, a panel of 29 mutations was used. Since 2016, Next Generation Sequencing (NGS) and Multiplex Ligation dependent Probe Amplification (MLPA) was introduced. We reviewed all patients with this technique.
Results: 164 patients were included. The most common mutations in our cohort were: p.F508del: 60% (CI95% 54.5–65.4), G542X: 4.5% (CI95% 2.6–7.4), W1282X: 1.5% (CI95% 0.5–3.5) R334W: 1.2% (CI95% 0.3–3.1), 1811+1.6 Kb: 1.2% (CI95% 0.3–3.1), 1717 1G-A: 0.9% (CI95% 0.2–2.7) and 2789 + 1G-A: 0.9% (CI95% 0.2–2.7). With the 29 mutation panel and NGS with MLPA, we identified 80.7% (CI95% 76.1–84.9) (265 alleles) and 91.4% (CI95% 87.9–94.3) (300 alleles), respectively. We found both mutations for 67% (CI95% 59.3–74.2) and 86% (CI95% 79.7–90.9) of patients, using the 29 mutation panel and NGS with MLPA, respectively ($p < 0.01$). We were not able to identify the both mutations in 6 patients (3.6%) (CI95% 1.3–7.8)
Conclusions: NGS with MLPA was more sensitive than the 29 mutation panel to identify both mutated alleles in each confirmed CF patient. Argentine CF patients have an heterogeneous genetic profile.

P043
Genetic revision of Hungarian cystic fibrosis patients

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Objectives: Cystic fibrosis (CF) is one of the most common monogenic disease caused by over 2000 mutations in the *CFTR* gene. Molecular genetic analysis of *CFTR* mutations requires population specific test due to a strong allelic and and geographical heterogeneity. Our aim was to present an updated comprehensive estimation of the distribution of *CFTR* mutations in a cohort of 378 CF patients in Hungary of which 325 patients had two mutations (therefore not tested further), 49 had one detected mutation previously and 4 had no mutations detected before. Determination of the Hungarian mutation spectrum may increase the sensitivity of the diagnostic approach and is essential in mutation-specific therapy.
Methods: Different molecular genetic methods were used: Elucigene CF29 v.2 kit, allele specific PCR for *CFTR*dele2,3(21kb), Sanger sequencing, and *CFTR* targeted next generation sequencing DNA panels (Multiplicom, custom panel, Devyser) was performed. MLPA analysis was used to detect deletions/duplications.
Results: In our Hungarian cohort 67 different mutations were identified, including 6 novel likely pathogenic alterations (p.Lys95Glu, p.Asp984Val, p.Glu1044*, c.490-1G > C, p.Asp274Alafs*10, p.Thr438Asnfs*8). Five mutations reached a frequency >2%. F508del was detected in 69,53% followed by *CFTR*dele2,3(21kb) (3,96%) and p.Gly542* (3,30%) and c.2184insA (2,77%) and N1303K (2,11%). Sequencing and MLPA analysis revealed 13,19% of the *CFTR* mutations including *CFTR*dele2 (0,13%), *CFTR*dele19–21 (0,26%) and a deep intronic varint c.3718–2477C > T (0,13%) and other rare variants. In addition, sequencing revealed two CF-causing mutations in case of 4 patients who had no mutations detected before.
Conclusion: In conclusion, the updated mutational spectrum provides an effective diagnostic approach not only in the routine diagnostics but for the DNA testing in the newborn screening program. Supported by the Ministry of National Economy, Hungary GINOP-2.3.2-15-2016-00039.

P044
Clinical characteristics, gender differences and outcomes in adult-diagnosed cystic fibrosis and Cystic Fibrosis-Related disorders (CFRD)

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Introduction: Some patients are diagnosed as CF in adulthood and others develop a CFRD. We reviewed the characteristics and course of these two groups.
Results: Of 310 patients, from 2016 to 2018, 30 (9.7%) were diagnosed as classic CF at a mean age of 41.3 (18–71) years. Most were female (21 female: 9 male). Mean sweat chloride was 67.4 (18–106) mmol/L; 22 had one F508del mutation but none was homozygous F508del; 6 had R117H, 5 D1152H, and 3 P67L. Only 9 (30%) were pancreatic insufficient; 29 had bronchiectasis,13 sinusitis, 5 aspergillosis, 2 diabetes and 1hepatic steatosis; 7 of 9 men had confirmed infertility. Mean FEV_1 at diagnosis was 2.2 (0.9–5.1)L, 67.6 (38–118)%; 17 had *Pseudomonas* and 19 *Staphylococcus aureus* infections. Some improved with CF treatments but most had progressive bronchiectasis with a mean fall in FEV_1 of 16.2% over a mean follow-up of 9.4 years; two died of respiratory failure. A CFRD with no lung disease was diagnosed in 17 (5.5%); 13 were diagnosed late at a mean age of 25.6 (14–34) years, and 4 in childhood. Most were male (13 male: 4 female). Their mean sweat chloride was 71 (39–100)mmol/L; 8 had one F508del mutation; 4 R117H, 1 D1152H, 1 P67L and 3 G551D. Clinical features of CFRD were absent vas deferens 9, sinusitis 4, pancreatitis 4, liver disease 2, diabetes 1, aquagenic wrinkling 2. First FEV1 was normal at mean103 (80–148) % and none developed lung disease during a mean follow-up of 9.5 (2.2–20) years.
Conclusion: Despite overlap of genetic mutations and sweat chloride levels, these are distinct groups. Late diagnosed classic-CF patients often have progressive lung disease, though with a delayed trajectory at an older age. There are significant gender differences. For CFRD this is mainly due to presentation as male infertility, but there is an unexplained preponderance of females in late diagnosed CF which has been reported in several studies but is not fully explained.

P045
Results from a newborn screening (NBS) pilot study for cystic fibrosis in the Republic of Macedonia

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Objectives: There is wide agreement on the benefits of NBS for CF with respect to clinical outcomes and health economics. In May 2018, NBS for CF was introduced in Republic of Macedonia as a pilot study, included in the National program for mothers and children's care of the Ministry of Health.
Methods: Two steps IRT-IRT algorithm were performed, and then a sweat test for confirmation/exclusion of the CF diagnosis when IRT values were both over the cut off. In cases of positive or borderline sweat tests, mutation analysis of CFTR gene was performed (snapshot reaction for 11 most common regional CFTR mutations or extended gene analysis).
Results: During the period from May to November 2018, 9332 newborns were screened for CF. The IRT1 cut-off level of 70 ng/ml was established as 99.5th percentile of the IRT values obtained in a total of 2.058 newborns with birth weight >3000 grams, gestational age >38 weeks, and age >48 hours. For IRT2 a fixed cut off was used at 40 ng/ml. Recall rate was 0.45% (No = 42). The IRT2 was in normal range in 31 cases. Out of 11 screening positive cases, the diagnosis of CF was confirmed in 5 (sweat test results: 90..102..101..106..102 mmol/L), and 6 were false positives. All diagnosed cases at the end of the first month of life, already had symptoms consistent with diagnosis of CF. The patient's genotypes were: F508del/F508del (3), F508del/G1349D and F508del/G542X. In the same period, two symptomatic cases were diagnosed, born in a maternity hospital where the pilot study was not conducted (genotypes: F508del/R1158X and F508del/CFTRdel2,3).
Conclusion: The NBS for CF pilot study showed a high incidence of the disease (1:1860 live births) in our region. The pilot study demonstrated justification for the implementation of NBS for CF on the whole newborn population in the country. Early diagnosis of CF through NBS and the appropriate preventive and curative care management of affected children would be of great benefit for our patients.

CERTIFICATE OF ATTENDANCE

This is to certify that

Stojka Naceva Fushtikj

Attended the

42nd EUROPEAN CYSTIC FIBROSIS CONFERENCE
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We thank you for your participation.

Isabelle Fajac
ECFS President