SOCIETATEA ROMÂNĂ DE GENETICĂ MEDICALĂ

UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE DIN CRAIOVA

AL VI LEA CONGRES DE GENETICĂ MEDICALĂ CU PARTICIPARE INTERNAŢIONALĂ

CRAIOVA, 22-25 SEPTEMBRIE 2022

CURS PRACTIC DE GENETICĂ MOLECULARĂ "TEHNICI AVANSATE DE GENETICĂ MOLECULARĂ"

CRAIOVA, 19-21 SEPTEMBRIE 2022

VOLUM DE REZUMATE

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CRGM DOLJ

SRGM Societatea Romana de Genetica Medicala

Universitatea de Medicină și Farmacie din Craiova
Strada Petru Rareș 2, Craiova 200349

CRGM DOLJ UMF CRAIOVA

AL VI-LEA CONGRES DE GENETICĂ MEDICALĂ CU PARTICIPARE INTERNAŢIONALĂ

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”Tehnici avansate de Genetică Moleculară”

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VOLUM DE REZUMATE

LOGO ORGANIZATORI SI SPONSORI

ORGANIZATORI

SRGM
Societatea Romana
de Genetica Medicala

UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE CRAIOVA

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Dragi prieteni și colegi,

În numele Comitetului de Organizare ne revine deosebita plăcere de a vă invita la cel de-**al VI-lea Congres de Genetică Medicală cu Participare Internațională** care se va desfășura la Craiova, în cadrul **Universității de Medicină și Farmacie din Craiova,** în perioada **22-25 Septembrie 2022.**

Congresul va fi precedat de **Cursul practic "Tehnici avansate de Genetică Moleculară"** adresat medicilor rezidenți și tinerilor specialiști. Cursul se va desfășura în perioada **19-21 Septembrie 2022** în cadrul **Centrului Regional de Genetică Medicală Dolj**.

Genetica umană este un domeniu cu dezvoltare rapidă a metodelor de investigație moleculară care pun permanent în evidență noi patologii, dar și strategii de tratament. Congresul de anul acesta ne va oferi ocazia să împărtășim din experiența colegilor, să aflăm informații despre noi direcții științifice și, nu în ultimul rând, să ne bucurăm împreună de zilele de septembrie petrecute în Craiova. Manifestările științifice se adresează deopotrivă profesioniștilor și beneficiarilor domeniului medical interesați de patologia genetică.

Participarea dumneavoastră ne onorează!

Informații suplimentare puteți găsi pe paginile web:

www.geneticamedicala.ro și www.srgm.ro.

Vă așteptăm cu drag să împărtășim acest moment de excelență științifică!

Președinți Congres și Curs

Prof.univ.dr. Eusebiu Vlad Gorduza și Prof.univ.dr. Mihai Ioana

COMITET DE ORGANIZARE

Președinte: Prof.univ.dr. Florin Burada

Adina Barbu	Ana Maria Bugă	Alex. Calotă-Dobrescu	Monica Laura Cara
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Simona Șoșoi	Isabela Tudorache		

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Președinte: Prof.univ.dr. Maria Puiu

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CURS PRACTIC DE GENETICĂ MOLECULARĂ
”Tehnici avansate de Genetică Moleculară”

CRAIOVA, 19 - 21 SEPTEMBRIE 2022

LUNI, 19 SEPTEMBRIE, 2022

10:00 – 11:30	Cazare și Înregistrare Participanți
12:00 – 14:00	**Deschiderea Oficială a Cursului** Mihai Ioana, Florin Burada, Vlad Gorduza, reprezentanți centre universitare medicale **12:00 – 12:20** – Cursul ca o prezentare a opțiunilor unui tânăr genetician în „piața” biomedicală românească – Mihai Ioana **12:20 – 14:00** – Cine suntem noi, centru cu centru?
14:00 – 14:30	**Pauză de Cafea**
14:30 – 16:30	**Oncogenetică și medicină personalizată. Cancere Rare** **14:30 – 15:30** – Importanţa testării genetice în managementul pacientului oncologic - Michael Schenker **15:30 – 16:30** - Building blocks for personalised healthcare - Marius Geantă
16:30 – 17:00	**Pauză de Cafea**
17:00 – 19:30	**Organizarea unui centru regional de Genetică Medicală în context universitar. Fluxuri de lucru în Laboratorul de Genetică Medicală. Ambulatoriu. Compartiment. Laborator de cercetare și spații de învățământ.** Ioana Streață, Mihai Cucu, Anca Costache, Răzvan Pleșea, Andrei Pîrvu, Simona Șerban Șoșoi, Ana Maria Bugă, Monica Cara, Amelia Dobrescu, Florin Burada, Mihai Ioana
19:30 – 19:45	**Sinteză** Mihai Ioana

MARȚI, 20 SEPTEMBRIE, 2022

09:00 – 11:00	**Diagnostic genetic prenatal & postnatal I** **09:00 – 09:30** – Importanţa extracției ADN pentru rezultatul final în testarea genetică – Bogdan Iancu **09:30 – 10:00** - Sudden cardiac death: insights on the genetic of channelopathies and cardiomyopathies - Cristina Skrypnyk (Online) **10:00 – 10:30** – Emergency in clinical genetics - Daniela Iancu **10:30 – 11:00** – Simpozion sponsor – MEDISON – Fibroza chistică - Amelia Dobrescu
11:00 – 11:30	**Pauză de Cafea**
11:30 – 13:30	**Diagnostic genetic prenatal & postnatal II** *Tehnici avansate de Genetică Moleculară - de la date clinice, probă, rezultat, interpretare și buletin – QF-PCR. MLPA. aCGH. Real Time PCR și NGS în patologia infecțioasă.* Ioana Streață, Mihai Cucu, Anca Costache, Răzvan Pleșea, Andrei Pîrvu, Simona Șerban Șoșoi, Ana Maria Bugă, Monica Cara, Amelia Dobrescu, Florin Burada, Mihai Ioana
13:30 – 14:30	**Prânz**
14:30 – 15:30	**Genetica în patologia infecțioasă** **14:30 – 15:00** - *Impactul variantelor virale asupra evoluției pandemiei COVID 19* – Simona Ruță **15:00 – 15:30** - *Impactul pandemiei COVID 19 asupra diagnosticului molecular în bolile infecțioase* – Dan Oțelea
15:30 – 15:45	**Pauză de Cafea**
15:45 – 18:45	**Diagnostic genetic prenatal & postnatal III. Oncogenetică** *Tehnici avansate de Genetică Moleculară - de la date clinice, probă, rezultat, interpretare și buletin – Secvențiere capilară, NGS – NIPT / panel gene /WES /oncogenetică* Ioana Streață, Mihai Cucu, Anca Costache, Răzvan Pleșea, Andrei Pîrvu, Simona Șerban Șoșoi, Ana Maria Bugă, Monica Cara, Amelia Dobrescu, Florin Burada, Mihai Ioana
18:45 – 19:00	**Sinteză** Mihai Ioana

MIERCURI, 21 SEPTEMBRIE, 2022

09:00 – 11:00	**Genomică** **09:00 – 10:00** - Genomica în context - Horia Stănescu **10:00 – 11:00** - Pharmacogenetics - Katja Just (Online)
11:00 – 11:30	**Pauză de Cafea**
11:30 – 13:30	**Workshop interpretare rezultate NGS Oncogenetică I – Illumina TSOncology 500 (ELTA 90 MR)** Anca Costache
13:30 – 14:30	**Prânz**
14:30 – 16:00	**Workshop interpretare rezultate NGS Oncogenetică II - Illumina TSOncology 500 (ELTA 90 MR)** Anca Costache, Bogdan Mirăuță
16:00 – 16:15	**Pauză de Cafea**
16:15 – 18:30	**A complete workflow for MSI Biomarker detection - Workshop PROMEGA (DEXTER)** Armin Ziga
19:00 – 22:00	**Antropogenetică. Genetica populaţiilor.** Mihai Netea, Mihai Ioana, Florin Ridiche, Irina Popescu **Închiderea Oficială a Cursului** Mihai Ioana, Florin Burada, Vlad Gorduza

AL VI-LEA CONGRES DE GENETICĂ MEDICALĂ CU PARTICIPARE INTERNAŢIONALĂ CRAIOVA, 22-25 SEPTEMBRIE 2022

JOI, 22 SEPTEMBRIE 2022

12:00 – 14:00 – **ÎNREGISTRAREA PARTICIPANŢILOR**

14:00 – 15:00 – **DESCHIDEREA OFICIALĂ A CONGRESULUI**
Mihai Ioana, Florin Burada, Maria Puiu, Vlad Gorduza, reprezentanți UMF Craiova

14:45 – 15:00 - *What Can Neanderthal DNA Teach Us about Membranous Nephropathy*? - Cătălin D Voinescu, Monika Mozere, Giulio Genovese, Mallory Downie, Sanjana Gupta, Daniel Gale, Detlef Böckenhauer, Robert Kleta, Mauricio Arcos-Burgos, Horia Stănescu

15:00 – 17:30 – **SESIUNEA PLENARĂ 1**
MEDICINA PERSONALIZATĂ ÎN BOLI GENETICE ŞI BOLI RARE. ONCOGENETICĂ
Claudia Bănescu, Vlad Gorduza

15:00 – 15:20 - *Etapele evolutive ale medicinei personalizate in oncologie - de la 1.0 la 4.0* – Marius Geantă
15:20 – 15:40 - *Diagnosticul genetic (molecular) - componentă obligatorie a PNCC* - Michael Schenker
15:40 – 15:50 - *Genetic Testing in non-BRCA Hereditary Breast and Ovarian Cancer* - Cătană Andreea, Trifa Pavel Adrian, Achimas- Cadariu Patriciu, Bolba Morar Gabriela, Antone Nicoleta, Munteanu Maximilian, Kutasi Eniko, Iordănescu Irina, Militaru Sanda Mariela
15:50 – 16:00 - *The importance of genetic testing in breast cancer* - Loredana Ștefania Negoianu, Mădălina Elisabeta Drăgănescu
16:00 – 16:10 - *The value of genetic testing and counseling in breast and ovarian cancer using the multi-cancer panels by Next-Generation Sequencing* - Gug Miruna, Stoicănescu Dorina, Gug Cristina

16:10 – 16:20 - *The spectrum of genetic mutations in acute myeloid leukemia progression from myelodysplastic syndrome* - Claudia Bănescu, Andrei Crauciuc, Alina Bogliș, Florin Tripon

16:20 – 16:30 - *BRCA1 and BRCA2 testing through next generation and capillary sequencing for diagnosis and family intervention of hereditary breast and pancreas cancers - CRGM Dolj update* - Ionuț Gavrilă, Anca-Lelia Riza, Ioana Streata, Răzvan Pleșea, Andreea Mituț, Stefania Dorobanțu, Adina Barbu, Mihai Cucu, Andrei Pirvu, Amelia – Mihaela Dobrescu, Monica – Laura Cara, Ana Maria Buga, Georgiana Camen, Michael Schenker, Florin Burada, Mihai Ioana

16:30 – 16:50 - DNBSEQ Technology: MGI potential in the world of Genomics - Bernard Okere – Simpozion AGILROM

16:50 – 17:10 – Decoding genomic profiling - a solid base of personalised healthcare – Florina Nedelea - Simpozion ROCHE

17:10 – 17:30 – Hematological malignancies and genomic testing - Konstantinos Lilakos - Simpozion ANTISEL

17:30 – 18:00 – **COFFEE BREAK**

18:00 – 19:30 - **SESIUNEA PLENARĂ 2**
GENOMICĂ
Claudia Jurcă, Adela Chiriță – Emandi, Viorica Rădoi

18:00 – 18:10 - *Panel next generation sequencing and genetic diagnosis in hereditary lipid metabolism disorders - CRGM Dolj update* – Diana-Stefania Ristea, Anca-Lelia Riza, Andreea Constantin, Ioana Streata, Alexandru Prica, Stefania Dorobantu, Adina Barbu, Ionut Gavrila, Bogdan Geamanu, Andra Dan, Razvan Plesea, Simona Serban-Sosoi, Mihai Cucu, Andrei Pirvu, Amelia – Mihaela Dobrescu, Monica – Laura Cara, Ana Maria Buga, Florin Burada, Ioan Gherghina, Mihai Ioana

18:10 – 18:20 – *Pathogenic VHL variant associated with Von Hipple-Lindau syndrome detected by NGS sequencing in a patient with paraganglioma - clinical case* - Truica Radu-Alexandru, Cojocaru Alexandra, Caragea Andreea-Mirela, Chelu Gratiela-Paula, Filimon Simona, Popa Mihaela, Perioc Andra-Rodiana, Ionescu Andreea-Carmen, Riurean Patricia-Ioana, Bohiltea Laurentiu-Camil, Ursu Radu-Ioan

18:20 – 18:30 - *Applications of next generation sequencing in cardiomiopathy - CRGM Dolj update* - Alexandru Prica, Anca-Lelia Riza, Ioana Streata, Stefania Dorobantu, Adina Barbu, Ionut Gavrila, Bogdan Geamanu, Andra Dan, Diana – Stefania Ristea, Razvan Plesea, Mihai Cucu, Andrei Pirvu, Amelia – Mihaela Dobrescu, Monica – Laura Cara, Ana Maria Buga, Florin Burada, Ruxandra Jurcuț, Mihai Ioana

18:30 – 18:40 - *Molecular karyotype in clinical cases of SMA* - Iulia Coliban, Daniela Blăniță, Svetlana Hadjiu, Natalia Ușurelu, Ninel Revenco, Victoria Sacară

18:40 – 18:50 - *The ESHG-Y Committee and our impact in empowering young geneticists across Europe* - Ileana - Delia Săbău, Can Ding, Juliana Xavier de Miranda Cerqueira, Mridul Johari, Ana Raquel Gouveia Freitas da Silva, Elena Avram, European Society of Human Genetics - Young Committee

18:50 – 19:10 – Abordarea multidisciplinară și îngrijirea integrata în bolile rare, recomandări europene și deziderate nationale – Maria Puiu - Simpozion ASTRA ZENECA

19:10 – 19:30 – Diagnostic and management in achondroplasia - international guidelines and consensus statements – Ioana Streață - Simpozion BIOMARIN

20:30 – CINA RESTAURANT EPOCA

VINERI, 23 SEPTEMBRIE 2022

09:00 – 11:00 – SESIUNEA PLENARĂ 3
STRATEGIA NAŢIONALĂ PENTRU PREVENŢIA ŞI MANAGEMENTUL BOLILOR GENETICE ŞI BOLILOR RARE
Mihai Ioana, Gindrovel Dumitra, Ștefan Bușnatu, Maria Puiu, Emilia Severin, Dorica Dan, Vlad Gorduza
Reprezentanți UMF Craiova
Ministrul Sănătății: Prof. Univ. Dr. Alexandru Rafila (Online)
Primarul Municipiului Craiova – Lia Olguța Vasilescu
Președintele Consiliului Județean Dolj – Cosmin Vasile
Reprezentanți SCJU Craiova

The true story of rare diseases in Romania – Emilia Severin, Dorica Dan

EU4HEALTH Programme – 2022 Joint Actions for rare diseases – Mihai Ioana

11:00 – 11:30 – COFFEE BREAK, EXPOZIŢIE, VIZUALIZAREA POSTERELOR

11:30 – 11:45 – How genomics can improve patients care – Boutros Maroun – Illumina - Simpozion ELTA 90 MR
11:45 – 12:00 – Comprehensive view of the tumor – Alexander Kirpiy – Illumina - Simpozion ELTA 90 MR

12:00 – 13:30 - SESIUNEA PLENARĂ 4
STANDARDIZAREA ŞI ORGANIZAREA DIAGNOSTICULUI GENETIC ÎN BOLILE GENETICE ŞI BOLILE RARE DE CAUZĂ GENETICĂ: REGISTRE, STANDARDE, REŢELE EUROPENE DE REFERINŢĂ
Alain Verloes, Klea Vyshka, Dorica Dan, Maria Puiu, Emilia Severin, Mihai Ioana

12:00 – 12:30 – *ERNs and their role in the national health systems* – Alain Verloes
12:30 – 12:50 - *ERN ITHACA* - Klea Vyshka
12:50 – 13:10 - *Romanian Network of Multiple Congenital Anomalies with Intelectual Disabilities (Ro-NMCA-ID)* - Adela Chiriță – Emandi, Maria Puiu

13:10 – 13:40 – *Registries importance in genetic and rare diseases* - Domenica Taruscio (Online)

13:40 – 14:30 – **PRÂNZ**

14:30 – 16:30 - **SESIUNEA PLENARĂ 5**
PARTENERUL ÎN BOLILE GENETICE ȘI BOLILE RARE: ASOCIAȚIILE DE PACIENȚI
Dorica Dan, Isabela Tudorache, Anne Hugon

14:30 – 15:00 – *Patients vision within the ERNs – ITHACA* - Anne Hugon
15:00 – 15:20 – An *integrated care pilot project for people affected by rare diseases in Romania* - Dorica Dan, Lidia Onofrei, Maria Puiu
15:20 – 15:35 - *Coffin-Lowry Syndrome – A Rare Disease Now Easier To Diagnose* – Iuliana Dumitriu
15:35 – 15:50 – *Starea de bine ca stare de fapt, factor de influență în evoluția stării de sănătate a copilului și tânărului DMD/DMB* - Isabela Tudorache
15:50 – 16:10 - *Proiecte norvegiene derulate sub umbrela MS, vizând bolile genetice rare – Maria Puiu*

16:10 – 16:30 – Simpozion BLUEPRINT GENETICS

16:30 – 17:00 – **COFFEE BREAK, EXPOZIȚIE, VIZUALIZAREA POSTERELOR**

17:00 – 19:30 – ADUNAREA GENERALĂ A MEMBRILOR SRGM

SÂMBĂTĂ, 24 SEPTEMBRIE, 2022

09:00 – 10:30 - **SESIUNEA PLENARĂ 6**
GENETICA REPRODUCERII. DIAGNOSTIC GENETIC PRENATAL
Florin Burada, Mariela Militaru, Diter Atasie

09:00 – 09:15 – *Examinarea ecografică și genetica prenatală. Unde ne întâlnim, unde ne despărțim* - Marina Dinu, Andreea Cismaru-Stăncioi , Comănescu Alexandru, Căpitănescu Răzvan, Pătru Ciprian, Sîrbu Ovidiu, Ștefania Tudorache

09:15 – 09:25 – *Is conventional karyotyping still required as a routine test for prenatal diagnosis? LGU-UMF Craiova/ CRGM DOLJ experience* - Florin Burada, Gabriela Popescu-Hobeanu, Anca-Lelia Riza, Alexandru Comănescu, Ștefania Tudorache, Dominic Iliescu, Cornelia Pascu, Ramona Cotulbea-Popa, Elisa Simona Popa, Simona Serban Sosoi, Amelia Dobrescu, Mihai Cucu, Ioana Streață, Mihai Ioana

09:25 – 09:35 – *Diagnostic difficulties in sexual differentiation disorders with prenatal onset - case report* - Mariela Militaru, Eleonora Dronca,Viorel Suciu, Irina Iordanescu, Zina Cuzmici, Mihai Militaru, Emanuela Braha, Andreea Cătană

09:35 – 09:45 – *Newborn screening for spinal muscular atrophy in Romania: a pilot project* - Neagu E, Bălănescu O, Bercu E, Bădină M, Shelby S, Moisă M, Leancă M, Axente M, Dima V, Șerban M, Toma A, Stoicescu S, Pădure L, Mirea A

09:45 – 09:55 – *Prenatal screening - combined test and NIPT - and diagnosis for fetal aneuploidies - CRGM Dolj update* - Bogdan Geamanu, Anca Lelia (Riza) Costache, Stefania Dorobantu, Raluca Tutunaru, Ioana Streata, Razvan Plesea, Mihai Cucu, Andrei Pirvu, Amelia – Mihaela Dobrescu, Monica - Laura Cara, Ana Maria Buga, Dominic Iliescu, Stefania Tudorache, Florin Burada, Mihai Ioana

09:55 – 10:05 - *Rare partial Xq chromosome deletion in an infertile patient* - Cojocaru Alexandra, Truica Radu-Alexandru, Caragea Andreea-Mirela, Chelu Gratiela-Paula, Filimon Simona, Popa Mihaela, Perioc Andra-Rodiana, Ionescu Andreea-Carmen, Riurean Patricia-Ioana, Bohiltea Laurentiu-Camil, Ursu Radu-Ioan

10:05 – 10:30 - Diagnostic pathway and current screening options for aromatic L-amino acid decarboxylase deficiency - Neagu Elena - Simpozion MEDISON

10:30 – 10:50 – COFFEE BREAK, EXPOZIŢIE, VIZUALIZAREA POSTERELOR

10:50 – 13:30 - **SESIUNEA PLENARĂ 7**
GENETICĂ CLINICĂ
Maria Puiu, Emilia Severin, Marius Bembea

10:50 – 11:20 - *Genetics of speech and language* - Marius Bembea, Codruța Petcheși, Kinga Kozma, Ramona Hodișan, Dan Bembea, Alina Sklerniacof, Claudia Jurca
11:20 – 11:30 - *The utility of aCGH in the diagnosis of patients with syndromic intellectual disability - data from a small Romanian cohort* – Ioana Streață, Alexandru Cărămizaru, Andrei Pîrvu, Simona Șerban – Șoșoi, Anca – Lelia Riza, Mihai Cucu, Răzvan Pleșea, Monica Laura Cara, Ana Maria Bugă, Amelia – Mihaela Dobrescu, Florin Burada, Mihai Ioana
11:30 – 11:40 - *Investigation of neurodevelopmental disorders within the Medical Genetics Laboratory of "Victor Babes" National Institute of Pathology, Bucharest* – Magdalena Budisteanu, Sorina Mihaela Papuc, Alina Erbescu, Maria Dobre, Gisela Gaina, Lucian Albulescu, Adelina Glangher, Emanuela Andrei, Florentina Linca, Doina Ioana, Cristina Nedelcu, Florina Rad, Aurora Arghir
11:40 – 11:50 - *Cauze genetice ale hipostaturii* – Miclea Diana, Popp Radu, Bucerzan Simona, Lazea Cecilia, Pașcanu Ionela, Crișan Mirela, Nazarie Florina, Stefan Delia, Muntiu Maria, David Ana, Maios Flavia, Alkhzouz Camelia
11:50 – 12:00 - *De la fenotip la genotip* – perspective curente şi de viitor în epilepsiile genetice - Eugenia Roza, Oana Vladacenco, Raluca Ioana Teleanu
12:00 – 12:10 - *Evolutia fenotipurilor la pacienții pediatrici cu AMS în contextul schimbării paradigmei terapeutice* - Oana Vladacenco, Eugenia Roza, Raluca Ioana Teleanu
12:10 – 12:30 - Biological therapy in X-linked hypophosphatemia - Jurca Claudia, Iuhas Oana, Kozma Kinga, Petchesi Codruța, Hodisan Ramona, Jurca Aurora, Bembea Marius - Simpozion KYOWA KIRIN

12:30– 13:30 – Simpozion GENESIS PHARMA
12:30 – 12:45 - Terapia siARN in Bolile Rare - Maria Puiu

12:45 – 13:00 - Descoperind Porfiria Hepatica Acuta – Ioana Streață
13:00 – 13:15 - O nouă perspectivă în managementul Amiloidozei hATTR – Valerica Tudorică
13:15 – 13:30 - Terapia chaperon in managementul bolii Fabry – Robert Dinu

13:30 – 14:30 – **PRÂNZ**

14:30 – 16:30 - **SESIUNEA PLENARĂ 8**
DIAGNOSTIC GENETIC AVANSAT
Ioana Streață, Nicoleta Andreescu, Laima Ambrozaityte

14:30 – 15:00 - *Next Generation Sequencing Based Genetic Diagnostics for Rare Diseases* - Laima Ambrozaityte
15:00 – 15:30 – *Implementation of personalized medicine (focus on pharmacogenomics) in different therapeutic areas* – Mandana Hasanzad (Online)
15:30 – 15:40 – *The Importance of Extensive Molecular Testing in Rare Genetic Disorders* - Cătană Andreea, Barbaș Cuzmici Zina, Dronca Eleonora, Iordănescu Irina, Kutasi Eniko, Militaru Diana, Braha Emanuela, Militaru Sanda Mariela

15:50 – 16:20 – Diagnosis of MSI status with the Gold Standard markers using OncoMate™ MSI Dx Analysis System CE-IVD – Monica Sevilliano – Simpozion PROMEGA (DEXTER) (Online)
16:20 – 16:40 – Simpozion CHIESI
16:20 – 16:30 - Alfa manozidoza- de la un semn discret la diagnosticul precoce in bolile rare – Maria PUIU
16:30 – 16:40 - Cum recunoaștem cistinoza? – Adela CHIRITA-EMANDI

16:40 – 17:00 – **COFFEE BREAK, EXPOZIŢIE, VIZUALIZAREA POSTERELOR**

17:00 – 19:00 - **SESIUNEA PLENARĂ 9**
VARIA
Radu Popp, Amelia Dobrescu, Cristina Rusu

17:00 – 17:20 – Simpozion MEDICAI

17:20 – 17:30 - *MLPA Genetic Testing: available kits and positive cases, an update at CRGM Dolj* - Mihai Gabriel Cucu, Andrada Maria Gheorghe, Adela Cucu, Adina Maria Dragos, Alexandru Calotă – Dobrescu, Andrei Pîrvu, Simona Șerban – Șoșoi, Ioana Streață, Anca - Lelia Riza, Răzvan Pleșea, Monica – Laura Cara, Ana Maria Bugă, Amelia-Mihaela Dobrescu, Florin Burada, Mihai Ioana
17:40 – 17:50 - *Clinical case: hemyzygous CYBB gene variant in an infant with recurrent family affected males* - Alina Georgiana Mitrut, Nadejda Bîrlădeanu, Oana Maria Farkas, Alexis Cochino
17:50 – 18:00 – *Genetic Diagnosis of Dravet syndrome using next generation, capillary sequencing and multiplex-ligation dependent probe amplification* - CRGM Dolj update – Alexandru Calotă – Dobrescu, Anca-Lelia Riza, Ioana Streață, Mihai Cucu, Andrada Gheorghe, Alexandru Pricã, Stefania Dorobantu, Adina Barbu, Andra Dan, Magdalena Budișteanu, Catrinel Iliescu, Carmen Burloiu, Andra Grigorescu, Amelia-Mihaela Dobrescu, Eugenia Roza, Oana, Vladacenco, Florin Burada, Raluca Teleanu, Mihai Ioana
18:00 – 18:10 – *Clinical case of CHARGE syndrome genetically diagnosed* - Viorica-Elena Rădoi, Ileana- Delia Sabau, Mihaela Țurcan
18:10 – 18:20 – *Clinical case of two siblings – complex immunological manifestations of a new DADA2 variant* - Nadejda Bîrlădeanu, Oana Maria Farkas, Andreea Ioan, Onda Tabita Lupu, Mihaela Dragomir, Ana Mihalache, Alexis Cochino
18:20 – 18:30 - *NGS and inherited metabolic disorders – Focus on PKU* - Andra Dan, Anca-Lelia Riza, Alin Iuhaș, Ioana Streata, Stefania Dorobantu, Adina Barbu, Alexandru Pricã, Ionuț Gavrilă, Bogdan Geamanu, Andra Dan, Diana – Stefania Ristea, Razvan Pleșea, Mihai Cucu, Andrei Pîrvu, Amelia – Mihaela Dobrescu, Monica – Laura Cara, Ana Maria Buga, Kinga Kosma, Claudia Jurcă, Florin Burada, Marius Bembea, Mihai Ioana

20:30 – CINA SMART PUB

DUMINICĂ, 25 SEPTEMBRIE, 2022

10:00 – 11:00 EXPOZIŢIE, VIZUALIZAREA POSTERELOR

11:00 – 11:30 PREMIERE POSTERE. CONCLUZII

11:30 – 12:00 CEREMONIA OFICIALĂ DE ÎNCHIDERE

AL VI-LEA CONGRES DE GENETICĂ MEDICALĂ CU PARTICIPARE INTERNAŢIONALĂ CRAIOVA, 22-25 SEPTEMBRIE 2022

PREZENTĂRI ORALE

What Can Neanderthal DNA Teach Us about Membranous Nephropathy?

Cătălin D Voinescu, Monika Mozere, Giulio Genovese, Mallory Downie, Sanjana Gupta, Daniel Gale, Detlef Böckenhauer, Robert Kleta, Mauricio Arcos-Burgos, Horia Stănescu

University College London

Alleles at the HLA-DQA1 and PLA2R1 loci underlie the genetic basis of autoimmunity in a large proportion of Membranous Nephropathy (MN) cases, presumably by dysregulating the levels of PLA2R antigen.

We show that a relatively long region in high LD in the PLA2R1 gene region appears to be the result of introgression from Neanderthal into the modern human genome. Based on variants imputed from our previous genome-wide association study (2011) we show significant differences in the distribution of Neanderthal variants between MN cases and controls: archaic alleles exhibit a significant overrepresentation of MN risk-lowering (protective) alleles.

This is in contrast to the typical direction of effect of introgressed Neanderthal genetic material, which previous studies largely identify as risk factors in autoimmune conditions.

These findings suggest that Neanderthal genetics may contribute to the modern human renal pathogenesis. We hereby underline the importance of understanding the relationship between environmental conditions and evolution as the ultimate force shaping the natural history of diseases.

Genetic Testing in non-BRCA Hereditary Breast and Ovarian Cancer

Cătană Andreea[1,2,3.], Trifa Pavel Adrian[1,2.], Achimas- Cadariu Patriciu [1,2.], Bolba Morar Gabriela[2], Antone Nicoleta[2], Munteanu Maximilian[1,2.], Kutasi Eniko[1], Iordănescu Irina[3], Militaru Sanda Mariela [1,2,3.]

[1]UMF Iuliu Hatieganu Cluj, [2]IOCN Cluj, [3]RPS Regina Maria

Introduction. Hereditary Breast and Ovarian Cancer (HBOC) accounts for 7-15% of all diagnosed cases. Multigene sequencing rapidly replaced BRCA1 and BRCA2 specific tests for patients with breast cancer, yielding a significantly greater detection of cancer-causing gene mutations.

Materials and Methods. Retrospective study from the Oncogenetic Department of the Oncology Institute Cluj-Napoca between 2020-2021. Out of 253 patients, 147 meet the specific criterias for subsequent genetic testing (according to NCCN guidelines: early-onset breast cancer (<45 years), first-degree relative diagnosed with breast cancer, breast cancer associated with ovarian cancer or other neoplasms, familial association of neoplasms, relatives of pathogenic mutation carriers, etc). All patients were tested using a Multigene Panel analysis (Illumina NextGen) including 100 genes associated with breast, ovarian, prostate, pancreas, stomach, uterus, colon cancer and melanoma. The presence of pathogenic mutations identified throughs NGS have been confirmed by Sanger sequencing.

Results. As expected, the most prevalent mutations were found in BRCA1 and BRCA2 genes (63%), but high-risk and moderate-risk penetrance variants were identified in other HBOC-related genes: CHEK2, PMS2, PTEN, MSH2, CDH11, RAD51, BARD1 and TP53

Conclusion. Our findings demonstrated that multigene panel resting for HBOC offers the potential advantage of more clinically valuable information and increases the quality of genetic counselling and oncologic management.

The importance of genetic testing in breast cancer

Loredana Stefania Negoianu, Madalina Elisabeta Draganescu

"Prof Dr. Alexandru Trestioreanu" Institute of Oncology, Bucharest, Romania

Introduction. Some people inherit mutation in certain genes that increase their risk of breast cancer, the most important are in the BRCA1 and BRCA.

Materials and method. Genetic counselling and testing for germline BRCA1 and BRCA2 mutations should be offered to breast cancer patients in high-risk groups with: strong family history of breast cancer, ovarian, pancreatic and/or high grade/metastatic prostate cancer, diagnosis of breast cancer before the age of 50, diagnosis of TNBC cancer before the age of 60, personal history of ovarian cancer or second breast cancer.

Results and Conclusions. Genetic testing is a powerful tool that allows for the detection of BRCA and non-BRCA germline mutations in individuals with high risks of breast cancer, wich in turn aids in the individualisation of treatment. Cost is an part of the genetic testing process and depend of the individual risk factors, laboratory pricing, insurance.

Keywords: genetic testing, BRCA 1, BRCA 2, mutation, breast cancer

The value of genetic testing and counseling in breast and ovarian cancer using the multi-cancer panels by Next-Generation Sequencing

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Department of Microscopic Morphology, University of Medicine and Pharmacy "Victor Babeș, 300041 Timișoara, Romania

International guidelines recommend that genetic testing for hereditary cancers be accompanied by genetic counseling. The aim of the study is to determine the value of genetic counseling for people undergoing genetic testing for breast cancer and to record the genes in which pathogenic variants were identified in a group of patients from western Romania.

Method: A retrospective study was carried out through the genetic-clinical evaluation of patients tested for breast cancer in the period 1.10.2019-31.08.2022. The biological samples were sent to INVITAE where a panel of 150 genes associated with hereditary cancers was used for Next-Generation-Sequencing(NGS) analysis.

Results: 46 patients were tested through multi-cancer panels, of which 20(43.5%) had a diagnosis of breast/ovarian cancer and 26(56.5%) healthy individuals who had a suggestive family history. The completely negative results, present in 6/20 (33%) patients, helped us to exclude hereditary genetic etiology. The positive results were represented by the pathogenic variants identified in the following genes: BRCA1(9 cases), BRCA2(8 cases), RAD50(7 cases), MRE11(5

cases), CHEK2(4 cases), ATM(3 cases), SMARCA4(2 cases) and 1 for REQUOL, XRCC2 and FANCC. In 9 cases family testing was continued, testing a total of 27 relatives. Some of the variants have undergone reclassification over time.

Conclusions: Genetic counseling offers significant psychosocial and medical benefits, related to the clinical decisions of affected patients or the screening of carriers of pathogenic variants. In addition, the molecular details allow the exploration of phenotype-genotype correlations and the completion of the database of pathogenic variants associated with breast and ovarian cancer in our country.

The spectrum of genetic mutations in acute myeloid leukemia progression from myelodysplastic syndrome

Claudia Banescu, Andrei Crauciuc, Alina Boglis, Florin Tripon

Genetics Laboratory, Center for Advanced Medical and Pharmaceutical Research, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania

Acute myeloid leukemia (AML), a complex and aggressive hematological neoplasm, characterized by genomic instability and by frequent somatic gene mutations may arise de novo or can be secondary AML, arising from a previous hematologic disorder, mostly from a myelodysplastic syndrome (MDS). Recent studies have revealed that chromosomal abnormalities (such as monosomy 7, complex karyotype, loss of 5q, 7q, and 17p) and gene mutations are important factors for prognosis, overall survival, and response to the treatment.

Recent investigations have revealed recurrent gene mutations, such as those found in genes involved in RNA splicing (SF3B1, SRSF2, U2AF1), DNA methylation (DNMT3A, TET2, IDH1, IDH2); genes involved in chromatin modification (ASXL1, EZH2); signal transduction (KRAS, JAK2); transcriptional regulation (GATA2, RUNX1), etc. Mutation profiles change during MDS transformation to AML and new gene mutations emerge. Several pieces of evidence suggest that uncovering gene mutations predicting leukemic progression and patient survival will improve disease stratification, leading to tailored and efficient treatment approaches. The present work summarizes the current understanding of cytogenetic aberrations and somatic gene mutations regarding their relevance for disease evolution to acute myeloid leukemia from myelodysplastic syndrome.

BRCA1 and BRCA2 testing trough next generation and capillary sequencing for diagnosis and family intervention of hereditary breast and pancreas cancers – CRGM Dolj update

Ionuț Gavrilă[1], Anca-Lelia Riza[1,2], Ioana Streata[1,2], Răzvan Pleșea[1,2], Andreea Mituț[1], Stefania Dorobanțu[1,2], Adina Barbu[1,2], Mihai Cucu[1,2], Andrei Pirvu[1,2], Amelia – Mihaela Dobrescu[1,2], Monica – Laura Cara[1,2], Ana Maria Buga[1,2], Georgiana Camen[2], Michael Schenker[2], Florin Burada[1,2], Mihai Ioana[1,2]

[1] *Regional Centre for Medical Genetics Dolj (CRGMDJ), County Emergency Hospital Craiova, Romania*
[2] *University of Medicine and Pharmacy of Craiova, Romania*

Background/Objectives: The BRCA1 and BRCA2 pathogenic variants are key players in the hereditary predisposition and therapeutic response for breast cancer. Beyond breast cancer, they increase the risk for pancreatic cancer, the third most common cancer type related to the early onset BRCA gene mutation in breast cancer.

Methods: We are reporting 44 patients with a diagnosis of **breast cancer**, referred to CRGM-Dolj between 2019 and 2021.Testing options consist of Illumina BRCA next generation sequencing (NGS) panel on an Illumina NextSeq550 IVD sequencer and in-house capillary sequencing on a Thermo Fisher 3730xl DNA Analyzer. Data analysis uses our bioinformatics pipeline based on nf-core/sarek v2.7.1 (GATKv4.1.7.0) and Ensembl VEP v104.3, and Mutation Surveyor v.5.1.

Results: NGS identified 6 pathogenic and 1 variant of uncertain significance (VUS) in genes associated with the phenotype for 10 subjects (47.6%). Capillary sequencing was offered to screen the extended family for the identified variants.

Conclusion: Genetic testing is a powerful tool that allows detection of BRCA mutations. These tests are expanding in clinical oncology centers worldwide. The inclusion of BRCA testing in the routine management of patients with breast and pancreatic cancer is playing an important

Funding: This work is supported by the National Health Programe XIII.2.2.3. and POCU ProGeneRare - SMIS code 108073.

Panel next generation sequencing and genetic diagnosis in hereditary lipid metabolism disorders – CRGM Dolj update

Diana – Stefania Ristea[1], Anca-Lelia Riza[1,2], Andreea Constantin[3], Floana Streata[1,2], Alexandru Prica[1], Stefania Dorobantu[1,2], Adina Barbu[1,2], Ionut Gavrila[1], Bogdan Geamanu[1], Andra Dan[1], Razvan Plesea[1,2], Simona Serban-Sosoi[1,2], Mihai Cucu[1,2], Andrei Pirvu[1,2], Amelia-Mihaela Dobrescu[1,2], Monica -Laura Cara[1,2], Ana Maria Buga[1,2], Florin Burada[1,2], Ioan Gherghina[3], Mihai Ioana[1,2]

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Background: Familial hypercholesterolemia is a frequent, inherited, potentially fatal disorder of cholesterol metabolism that leads to premature morbidity and mortality due to atherosclerotic cardiovascular disease. Familial hypercholesterolemia is characterized by a high low-density lipoprotein cholesterol level, xanthomas, and premature coronary heart disease. Multiple mutations in various genes have been reported in patients with this disease.

Methods: We are reporting 21 patients with a presumed diagnosis of familial hypercholesterolemia, referred to CRGM-Dolj between 2019 and 2021. Illumina TruSight Cardio next generation sequencing (NGS) panel was used. Sequencing was run on an Illumina NextSeq550 IVD sequencer and in-house capillary sequencing on a Thermo Fisher 3730xl DNA. Analyzer. Data analysis uses our bioinformatics pipeline based on nf-core/sarek v2.7.1 (GATKv4.1.7.0) and Ensembl VEPv104.3, and Mutation Surveyor v.5.1.

Results: NGS identified 4 pathogenic, 2 likely pathogenic and 5 variants of uncertain significance (VUS) in genes associated with the phenotype for 10 subjects (47.6%). Capillary sequencing was offered to screen the extended family for the identified variants.

Conclusion: Early diagnosis and treatment mitigate the high risk of premature atherosclerotic heart disease in people carrying a gene associated with familial hypercholesterolemia. Genetic testing for familial hypercholesterolemia is becoming more widely available and cheaper. Understanding the scope of genetic determinants of familial hypercholesterolemia has expanded substantially. Advances in molecular technologies have provided novel insights into the role of NGS.

Funding: This work is supported by the National Health Programe XIII.2.2.3. and POCU ProGeneRare - SMIS code 108073.

Pathogenic VHL variant associated with Von Hipple-Lindau syndrome detected by NGS sequencing in a patient with paraganglioma - clinical case

Truica Radu-Alexandru[1, 2], Cojocaru Alexandra[2], Caragea Andreea-Mirela[1, 3], Chelu Gratiela-Paula[2], Filimon Simona[2], Popa Mihaela[2], Perioc Andra-Rodiana[2], Ionescu Andreea-Carmen[2], Riurean Patricia-Ioana[2], Bohiltea Laurentiu-Camil[1], Ursu Radu-Ioan[1, 2]

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Background: Von Hippel-Lindau syndrome (VHLS, OMIM #193300) is an autosomal dominant familial cancer syndrome, predisposing to a variety of malignant and benign tumors, caused by pathogenic variants in the VHL gene. The tumors are usually benign, but some can become malignant. The global incidence is 1 in 36,000 births affecting males and females from all ethnic groups equally.

Clinical case presentation: We present the case of a 44 y.o. female patient with the clinical suspicion of paraganglioma, referred to our medical genetics laboratory for genetic testing (Next Generation Sequencing using a 14 genes endocrine tumor panel).

Genetic testing results: The result of the analysis identified the NM_000551.3:c.598C>T / NP_000542.1:p.Arg200Trp / R200W / rs28940298 heterozygous missense pathogenic (class 5, P) variant within exon 3 of the VHL gene (von Hippel-Lindau tumor suppressor, OMIM #608537, cytogenetic location 3p25.3). The detected mutation is associated in a heterozygous state in the OMIM database with the von Hippel-Lindau syndrome (OMIM #193300) and pheochromocytoma (OMIM 171300), autosomal dominant disorders.

Conclusions: In conclusion, the detected VHL c.598C>T mutation is classified as a pathogenic variant (class 5, P), most probably representing the genetic cause for the patient`s phenotype. Genetic counselling is recommended for the clinical interpretation of the result and for family testing (targeted testing for the known mutation VHL c.598C>T).

Key words: paraganglioma; Next Generation Sequencing (NGS); pheochromocytoma; hereditary tumors; VHL gene; von Hippel-Lindau syndrome.

Applications of next generation sequencing in cardiomyopathy - CRGM Dolj update

Alexandru Prica[1], Anca-Lelia Riza[1,2], Ioana Streata[1,2], Stefania Dorobantu[1,2], Adina Barbu[1,2], Ionut Gavrila[1], Bogdan Geamanu[1], Andra Dan[1], Diana – Stefania Ristea[1], Razvan Plesea[1,2], Mihai Cucu[1,2], Andrei Pirvu[1,2], Amelia – Mihaela Dobrescu[1,2], Monica – Laura Cara[1,2], Ana Maria Buga[1,2], Florin Burada[1,2], Ruxandra Jurcuț3, Mihai Ioana[1,2]

1. Regional Centre for Medical Genetics Dolj (CRGMDJ), County Emergency Hospital Craiova, Romania
2. University of Medicine and Pharmacy of Craiova, Romania
3." Carol Davila" - University of Medicine and Pharmacy, Bucharest

Background/Objectives: Cardiomyopathies, having age-dependent expression, variable penetrance and overlapping phenotypes**,** account for a considerable yet underestimated portion of the global burden of disease. They comprise the cause for close to 50% of fatalities and cardiac transplants in adolescent and younger patients. Recent advances concerning the molecular etiologies of cardiac remodeling have opened the way towards precision medicine in cardiomyopathies.

Methods: We are reporting 21 patients diagnosed with various types of cardiomyopathies, referred to CRGM-Dolj between 2019 and 2021. Genetic testing was performed using Illumina TruSight Cardio next generation sequencing (NGS) panel on an Illumina NextSeq550 IVD sequencer and in-house capillary sequencing on a Thermo Fisher 3730xl DNA Analyzer. Data analysis uses our bioinformatics pipeline based on nf-core/sarek v2.7.1 (GATKv4.1.7.0) and Ensembl VEP v104.3, and Mutation Surveyor.

Results: NGS identified 36 variants: 11 pathogenic, 2 likely pathogenic and 23 variants of uncertain significance, all in genes associated with the phenotype for 20 subjects (95%). Capillary sequencing was offered to screen the extended family for the identified variants and was accepted by only a few.

Conclusion: Comprehensive clinical and imagistic phenotyping is essential for interpreting results. Genetic assessment of patients with severe cardiomyopathies can be a powerful tool for clinicians, as it eliminates diagnostic ambiguity and can have implications in the management, clinical screening and counseling of patients and their families, especially those before the age of disease onset.

Funding: This work is supported by the National Health Programe XIII.2.2.3. and POCU ProGeneRare - SMIS code 108073.

MOLECULAR KARYOTYPE IN CLINICAL CASES OF SMA

Iulia COLIBAN[1], Daniela BLĂNIȚĂ[1], Svetlana HADJIU[1],
Natalia UȘURELU[1], Ninel REVENCO[2], Victoria SACARĂ[1]

[1] *PMSI Institute of Mother and Child*
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Introduction. Spinal muscular atrophy (SMA) is an autosomal recessively inherited progressive neuromuscular disease caused in 95% of deletions of the SMN1 gene.

Materials, methods and results. We report 2 cases of 2 mo and respectivelly 16 mo boys born at term in a no-consanguineous families. Both children presented with severe hypotonia with lack of reflexes and dynamics, suggesting SMA and other clinical manifestations.

The molecular–genetic examination of SMN1 gene through PCR-RFLP/qPCR methods showed deletions of exons 7 and 8 for one of them but not for the other patient. At the same time, considering other clinical manifestations the constitutional and molecular karyotype investigation was indicated. Subsequent the result of the constitutional karyotype was normal (46 XY) for both.

Molecular karyotype, trough Array-CGH method, identified the following unbalanced haploinsufficient genetic changes: a 1398 Kb microdeletion in the region of chromosome 5q13.2 (of which SMN1, NAIP, GTF2H2, SERF associated with SMA) and a microdeletion of 4832 Kb in the region of chromosome 10q11.22-q11.23 for patient without SMA diagnosed and for patient of 2 mo, with SMA diagnosed, there have been identified unbalanced genomic abnormalities (461kb duplication on chr1q and 1.78Mb deletion on chr5q, among them are the SMN1 and SMN2) and regions with LOH (3.6Mb region on chr1p and 4.8Mb region on chr14q).

Conclusion. Molecular karyotype is extremely important in clinical utility for patients such as this cases, a detailed phenotypic and genotypic approach revealed that the diagnosis or suspection of SMA was mimicked by much more complex genomic abnormalities.

The ESHG-Y Committee and our impact in empowering young geneticists across Europe

Ileana - Delia Săbău[1,9] , Can Ding[2,9] , Juliana Xavier de Miranda Cerqueira[3,4,9], Mridul Johari[5,6,9], Ana Raquel Gouveia Freitas da Silva[7,9],Elena Avram [8,9], European Society of Human Genetics - Young Committee[9]

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The European Society of Human Genetics – Young Committee (ESHG-Y) is made up of early-career professionals in Human Genetics who aim to support their generation of young geneticists by developing strategies and programs for a better education and creating a strong network in all European countries. Our structure is as follows: 7 active members, associate members and consultant members elected every two years.

Our goals were to organize different scientific events like ESHG-Y educational sessions at the ESHG Annual Conference, the European Dysmorphology Meetings and a virtual session in collaboration with the European Board of Medical Genetics (EBMG). The virtual session in collaboration with EBMG was about becoming European Board Certified in Medical Genetics, passing the exam called European Certification in Medical Genetics and Genomics (ECMGG). The ECMGG exam proposes to be a remarkable assessment tool for young geneticians and to establish world-class standards in our specialty for all the European countries.

The ESHG-Y social media platforms have regularly promoted relevant activities and we succeeded to create an active young geneticist network.

In the last 4 years our representatives have had a supportive role in the ESHG Board, the ESHG Scientific Programme Committee, the ESHG Education Committee and the EBMG. We have also supported organizations like: ERN-Ithaca, Unique, Orphanet, EuroGEMS and MOOC BIG.

To conclude, we state that the ESHG-Y has successfully achieved its objectives, honouring young geneticians in Europe and will countinue to grow and to help inspire more and more early-career geneticists.

The True Story of Rare Diseases in Romania

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[1] *Carol Davila university of Medicine and Pharmacy*
[2] *Romanian Prader Willi Syndrome Association*

The beginning of the story stars in 2003 when a mother of a girl with undiagnosed disease experienced a long journey in getting an accurate diagnostic for her child. She wanted no one to go through this experience and this is how the Romanian Prader Willi Syndrome association was born.In 2007, Romanian National Alliance for RDs was established at the initiative of Romanian Prader Willi Syndrome Association as a strong voice of people with rare diseases.

In the same year, Romania joined the European Union and harmonized its legislation with EU requirements. Therefore, new strategic directions and priorities for health system reform had to be established, including RDs.

The number of Romanians living with a rare disease is estimated to be up to 1 million, both children and adults. This estimate shows that while individual diseases may be rare, collectively are common. Thus, “the paradox of rarity” highlights rare conditions as a priority of the public health care system in Romania. Patient organizations, healthcare professionals, and academics speaking with one strong voice, Romanian National Alliance for RDs, have played an active role in the establishment of a national plan for RDs. The European Council and EUROPLAN project recommendations for the development of a national plan for RDs were used and adapted to the national situation. In 2013, the Ministry of Health adopted the National Plan for Rare Diseases as a strategic document including it in the National Public Health Strategy. The strategy established a regulatory, political framework that generates a system to integrate health and social services. The Government approved, by Decision the national programs for rare diseases to be carried out and funded by the Ministry of Health and National Health Insurance House.

In 2016, the Ministry of Health started to implement the national evaluation of Centers of Expertise for RDs, using the EUCERD Recommendation on Quality Criteria for Centers of Expertise adapted to the national situation, and the application for ERN membership. In 2021, the new National Plan for Rare diseases has become part of the new Public Health National Strategy. It has been a long road from 2007 until now, with many preliminary stages, but in the end, Romania has a political framework that shapes and controls the health care services dedicated to people with rare diseases.

Thanks to all Romanian National Alliance for Rare Diseases

Integrated care pilot project for people affected by rare diseases in Romania

Dorica Dan, Lidia Onofrei, Maria Puiu

National Alliance for Rare Diseases

More than 1 million people are affected by severe disabilities produced by rare diseases and rare cancers in Romania. They are mainly cared by their families. This means that 4 million or almost 20% of the Romanian population are affected by the current situation. Almost 50% of the Romanian population live in villages with no access to medical and social services so, it is hard to believe that they are diagnosed and properly cared. Only 10 % of the patients are included in national programs for health and social services, either because they have no treatment (only 5% of the rare diseases have treatment).

Being affected by a rare disease means for the families to be threatened by poverty, care givers risk to be abandoned by their loved ones, become a patient themselves, often suffering from depression. A large majority of the people affected by rare diseases are persons with severe and complex disabilities.

Romanian Prader Willi Association www.apwromania.ro opened the NoRo Center in 2011 to improve the quality of life for people living with rare diseaes and their families. NoRo Center is accreditated for social, medical and educational services and it is one of the Centers of Expertise for Rare Diseases since 2017: www.centrulnoro.ro.

Our goal is to shorten waiting time it takes for people with disabilities produced by rare disease to get the correct diagnose and care through bridging the gaps between medical, educational and social services, while advocating for a national strategy for rare diseases.

Coffin-Lowry Syndrome – A Rare Disease Now Easier To Diagnose

Iuliana Dumitriu

Asociatia Sindromul Coffin-Lowry

Coffin-Lowry Syndrome is one of the 6000 rare diseases. It has an incidence of 1:50 000 cases, which means that we expect more than 300 cases in Romania. However only 4 are reported to this date. All are children below 8 years old and have been diagnosed in the last year.

The increased availability and price decreases of molecular tests made this possible. Current globalization has connected these patients in a global support network and we are organized in a national association, collaborating with Alianta Nationala de Boli Rare, as well as with Eurordis and NORD to improve access to information, support, treatments, therapies and social inclusion.

Today we want to present the clinical markers that are distinct for this syndrome. These become easily recognizable starting with early ages and accompany the unspecific symptoms. We hope that this will help increasing the number of diagnosed cases in Romania.

Even if the initial clinical signs are unspecific, like delayed mile stones, the facial treats start to become specific as early as 1 year old, becoming really specific by the age of 3 when they can raise a strong diagnostic suspicion. This is demonstrated by the pictures attached in the presentation.

In the past years molecular tests have become more accessible for patients, even in the private medical sector. Here the prices for intellectual disabilities multi gene panels have decreased to as low as 250 euros in some clinics. This of course accompanies the public sector tests available now in Romania.

Proiecte norvegiene derulate sub umbrela MS, vizând bolile genetice rare

Maria Puiu[1,2], Nicoleta Andreescu[1,2], Dorica Dan[3], Adela Chiriță Emandi [1,2], Simona Farcaș [1], Alexandra Dan [3], Lisen Julie Mohr [4]

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[3]*Asociatia Prader-Willi Romania, Alianța Națională pentru Boli Rare România*
[4] *Frambu,Siggerud, Norvegia*

Proiectul Extinderea serviciilor medicale și comunitare pentru persoanele afectate de boli genetice și rare (MEDI.COM-RARE), având ca sursă principală de finanțare: Mecanismul Financiar al Spatiului Economic European a fost depus de către Universitatea de Medicina si Farmacie Victor Babes Timisoara, in parteneriat cu Spitalul Clinic de Urgență pentru Copii "Louis Țurcanu, Asociația Prader-Willi Romania și Frambu, Norvegia.

Proiectul are ca scop dezvoltarea politicilor de sănătate și a serviciilor pentru prevenirea bolilor genetice și rare în vederea îmbunătățirii accesului la servicii de îngrijire a sănătății pentru persoanele afectate, inclusiv romi și persoane din mediul rural și zone izolate, folosind modelul norvegian. Dezvoltarea de servicii de formare în domeniul bolilor genetice și rare după modelul norvegian va fi facilitată de organizarea unor mese rotunde virtuale și față-n față cu partenerul norvegian.

Implementarea Planului de formare pentru 100 de medici de familie, 500 de asistenți medicali comunitari și a 50 de mediatori sanitari, implicați în proiect va asigura o mai bună coordonare a diagnosticului și îngrijirii pacienților cu boli genetice și rare. Proiectul își propune și îmbunătățirea accesului la serviciilor de sănătate de tip preventiv (teste genetice), astfel, 500 de pacienți vor beneficia de testare genetică (analize de citogenetica clasică si moleculara, secventiere de nouă generatie).

Pe baza rezultatelor obținute ne propunem sa fundamentam utilitatea unui Plan Național de testare genetică comprehensivă pentru toate categoriile de pacienți care pot beneficia de aceste investigații pentru stabilirea diagnosticului de certitudine, a managementului pacientului inclusiv personalizarea terapiei și a opțiunilor reproductive pentru nașterea unui copil sănătos.

Alte obiective importante ale proiectului sunt realizarea unei aplicații pentru managementul de caz virtual pentru pacienții cu boli genetice și rare si operationalizarea și acreditarea Centrului Național de Coordonare pentru bolile rare, conform legislației europene (National Coordination Hub) pentru transfer de

bune practici din European Reference Network (ERN) în sistemul național de sănătate.

Ultrasound examination and prenatal genetics. Where do we meet, where do we part ways?

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Many clinical ethics and counseling dilemmas have emerged as a result of advanced prenatal ultrasound (US) diagnosis worldwide. In Romania also, obstetricians are increasingly involved in performing high quality anomaly scans throughout pregnancy, applying genetic screening programs and practicing invasive procedures. These allowed an unprecedented performance in the prenatal structural and chromosomal anomalies diagnosis. We face a wider range of diagnosable diseases, symptoms either never reported before or rarely described in the prenatal life. Yet, establishing prenatally the neonatal and childhood outcome accurately - became ever more challenging.

We currently discuss all difficult cases in multidisciplinary teams, geneticians having the most important inputs. Yet, we face every now and then cases in which we agree to disagree and cases in which the best collaborative estimates of prognosis turn out to be wrong. The postnatal symptoms/evolution may be less severe or more severe than anticipated based on the prenatal assessment. We present a case series which requested a complex work-up program and benefited of a long-term follow-up, highlighting the prenatal US features and correlations with the non-invasive prenatal testing, conventional karyotyping and/or results on molecular genetics. We emphasize the useful and the worthless so-called “minor US markers”, that triggered particularly challenging counselling sessions.

Based on our case series, we may state that counsellors should be thoughtful above all else. They should be specifically, continuously trained in this rapidly developing field.

Also, we show that the parental psychological impact has an extremely large spectrum, couples facing same anomalies having completely different responses.

Keywords: ultrasound, prenatal genetics, congenital structural anomaly, counseling.

Is conventional karyotyping still required as a routine test for prenatal diagnosis? LGU-UMF Craiova/ CRGM DOLJ experience

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Conventional karyotype analysis has gradually lost its leading role among genetic tests while molecular methods (e.g., aCGH, NGS) became increasingly more used in clinical prenatal diagnosis. Despite the better diagnostic yield of molecular methods, conventional karyotyping remains one of the most used genetic methods in prenatal diagnosis in many laboratories.

In this retrospective study, we investigated the incidence and type of chromosomal abnormalities in high-risk pregnancies using conventional karyotyping. A total of total of 1052 amniotic fluid samples were referred to LGU UMF Craiova/CRGM Dolj, between 2014 - 2022.

The major indications for prenatal cytogenetic testing were the abnormal results of combined or triple test and fetal anomalies detected using ultrasound examination. Abnormal karyotypes were detected in 53 of 1052 cases (5%).

Pure aneuploidies accounted for 2.56% of all samples (27 cases) and structural rearrangements were observed in 1.8% (19 cases), the most detected ones being reciprocal translocations and deletions. Mosaicism was found in 7 cases (0.66%). The most common abnormality was trisomy 21 (free and homogeneous -23, mosaic - 1 and unbalanced Robertsonian translocation - 1). Conventional cytogenetic analysis remains an important prenatal diagnosis tool.

Diagnostic difficulties in sexual differentiation disorders with prenatal onset - case report

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Introduction:Differences/disorders of sex development (DSD) can be detected at different ages, including prenatally. Recent implementation of prenatal genetic testing (including cell-free DNA) may affect frequency and impact of prenatal diagnosis of DSD.

46,XY disorders of sex development (DSD) is characterized by incomplete masculinization genitalia, with gonadal dysplasia and with/without the presence of Müllerian structures. The incidence of 46,XY DSD is about 1/6000. At least 30 genes related to 46,XY DSD have been found.

Case presentation: We report the case of a 29-year-old pregnant woman who performed a non-invasive prenatal blood test at 11 weeks of pregnancy, and the result was normal - a male child without autosomal aneuploidy. The patient had 2 spontaneous abortions in the past, for which she and her husband performed karyotype with G bands. The patient's karyotype showed an inversion on chromosome 9-46,XX,inv(9)(p11;q13), and the husband's karyotype was normal 46,XY. In this context, at 18 weeks, amniocentesis was performed and fetal genetic tests were performed. The fetal karyotype showed the presence of the inversion on chromosome 9 inherited from the mother.

The ultrasounds performed in the 21st and 23rd weeks of pregnancy showed female genital organs. After several genetic counseling sessions, the parents decided to terminate the pregnancy. Blood was collected from the umbilical cord and WES(Whole exome sequencing) testing was performed to elucidate the etiology of DSD. The potentially pathogenic variant, c.226C>T p.(Arg76Cys) in the SRY gene was identified. This variant was not found in the father.

The particularities of the case: pure gonadal dysgenesis - de novo mutation and the first case in Romania diagnosed in the prenatal period.

Keywords: disorders of sex development, SRY gene, fetal karyotype

Newborn screening for spinal muscular atrophy in Romania: a pilot project

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Spinal muscular atrophy (SMA), the most common neurodegenerative disease in childhood, with a natural history marked by an early death or a lifetime of progressive disability, benefits now in Romania from an approved treatment. Clinicians' practice and extended studies emphasize the need for a presymptomatic diagnosis.

This objective can be achieved by newborn screening (NBS), already available in most European countries, as a national, regional or as a pilot programme.

We started a NBS pilot project for SMA, in collaboration with four maternities in Bucharest, using the same initial procedure as for phenylketonuria and congenital hypothyroidism, respective neonatal heel prick on filter paper.

We choose an IVD-CE kit (SALSA MC002 SMA Newborn Screen, MRC Holland) and a method (Melt Assay) easy to apply in a standard molecular biology laboratory. Spot blood samples were screened for homozygous deletion of SMN1 gene exon 7. Ambiguous and positive results are verified with multiplex PCR. Every stage of NBS, preparing, analytical and post- analytical, is carefully evaluated in terms of feasibility and pitfalls, in order to be further applied at a national level for a rapid access to life-saving treatment for Romanian SMA patients.

Prenatal screening - combined test and NIPT- and diagnosis for fetal aneuploidies - CRGM Dolj update

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Background/Objectives: Prenatal screening, either by combined test or by NIPT, followed by prenatal diagnosis of frequent aneuploidies is a must in the correct pregnancy management.

Methods: We are reporting on 864 pregnant women at risk, referred to CRGM-Dolj between 2020-2022. They had been screened either by the combined test or NIPT. During the same period, 483 amniotic fluid samples and paired maternal blood were processed for potential aneuploidies by QF-PCR, followed by karyotyping. DNA from amniotic fluid samples was extracted using the Invitrogen DNA Extraction Kit and blood samples by the Promega Wizard® Genomic DNA Purification Kit. For detection we used Devyser Compact v3 QF-PCR kit and capillary migration was done a Thermo Fisher 3730xl DNA Analyzer. Data analysis uses GeneMarker V2.2.0 by Soft Genetics.

Results: The overlap between screening cases managed by our centre and risk case tested in CRGM DJ is 57 cases. The rest of the cases had been referred from private practices. Out of the 483 cases tested QF-PCR identified 14 aneuploidies: 11 cases of trisomy 21, 2 cases of monosomy X and 1 case of Klinefelter syndrome. Genetic confirmation was mostly achieved though G banded karyotyping.

Conclusion: Our dataset reports similar frequencies by comparison to literature reports. The Regional Centre of Medical Genetics Dolj is making all efforts to implement an efficient patient flow for managing high risk pregnancies. Screening using the combined test or NIPT and molecular prenatal diagnosis of aneuploidies and cytogenetic testing are offered, supported by National Health Programmes and The National Insurance House.

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Rare partial Xq chromosome deletion in an infertile patient

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Background: Turner syndrome (TS) is a genetic disorder characterized by the complete or partial loss of the X chromosome or by structural X and/or Y chromosomal anomalies. The incidence is aprox. 1/2500-3000 women. It is estimated that about half of the patients with TS have a 45,X karyotype. The other cases may present different cytogenetic variants, including Xq isochromosome (the most common structural rearrangement involving the X chromosome), ring X chromosome, Xp or Xq deletions or Y chromosome abnormalities. Clinical case presentation: We present a case of a 37 y.o. female patient with infertility, referred to our medical genetics laboratory for genetic testing (whole blood karyotyping) Genetic testing result: The result of the analysis identified the 45,X,del(X)(q22) karyotype formula (ISCN 2020), indicative for TS, in all analyzed cells. Conclusions: In conclusion, the detected deletion is the cause of the patient's phenotype. Genetic counselling is adviced for a clear explination of the result and for future possible reproductive options.

Key words: Turner syndrome, Xq deletion, whole blood karyotype

Diagnostic pathway and current screening options for aromatic L-amino acid decarboxylase deficiency

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Aromatic L-amino acid decarboxylase (AADC) deficiencyis a very rare, inherited disorder of neurotransmitter synthesis, caused by mutations in the Dopa

Decarboxylase(DDC) gene. The clinical manifestations–hypotonia and delayed motor development with structural normal MRI, accompanied by autonomic orbehavioural symptoms – usually guide the clinician to more frequent cerebral palsy,epilepsy, autism, mitochondrial diseases, but considering this rare diseasecould help improve the patients' care and management.

To approach AADC deficiency diagnosis, at least two of the three core diagnostic tests – single gene or genetic testing panel, plasma enzyme assay and cerebrospinal fluid metabolite panel - should be positive. Additional screening tests could be important tools, as high levels of 3-O-methyldopa (3-OMD) on dried blood spot or plasma, or increased vanillactic acid and ratio vanillactic acid/vanillylmandelic acid in urine. 3-OMD measurement could be a part of high-throughput newbornblood sample screening by mass-spectrometry.

GENETICS OF SPEECH AND LANGUAGE

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Disorders of speech and language are very common at any age, especially in preschool age children. This presentation proposes a survey of what is currently known about the complex interaction between genetics and speech (language).

Normal language development implies: phonology, semantics and syntax. Children learn to speak in their native language without specific instructions. There is great variation in normal language development. Receptive language development usually begins at 31 weeks. Expressive language development begins in the first weeks of life.

The clinical manifestation may appear as primary disorder (in the absence of more generalized cognitive or motor dysfunction) or as comorbid condition. The most common speech-language disorders are briefly presented.

Strong familial aggregation and twin studies demonstrate the contribution of genetic factors to susceptibility to speech and language disorders. Nonetheless, it is generally thought that the genetic mechanisms underlying susceptibility to speech and language disorders are multifactorial in nature.

Current molecular genetic techniques are increasingly used to identify genetic factors that may be involved in susceptibility to these disorders. A number of candidate genes have been identified but, so far," language genes" have not yet been established. FOXP2 is one of the only genes we know that has a clear connection to language.

The authors speculate that polyglots may represent the reverse of speech disorders through a particular genetic constellation.

In conclusion, the investigation of genetic factors may help understand the complex relationships between speech and language disorders and related developmental conditions.

Key words: speech, language, susceptibility, FOXP2 gene, polyglots

The utility of aCGH in the diagnosis of patients with syndromic intellectual disability - data from a small Romanian cohort

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Introduction. Intellectual disability (ID) is defined as a significantly reduced ability to understand new or complex information, to learn and apply new skills (impaired intelligence), and to cope independently (impaired social functioning). Various causes could lead to intellectual disability, including genetic abnormalities such as CNVs (copy number variations).

The aim of our study is to present the results of aCGH (array comparative genomic hybridization) testing from a small Romanian cohort of patients with intellectual disability.

Materials and Methods. The clinical inclusion criteria were the presence of ID/DD and the absence of epilepsy; most of the patient were syndromic. Purified

genomic DNA from peripheral blood was examined for copy number variations (CNVs) using Agilent Cytogenomics 4x180K/8x60K or OGT Cytosure 8x60K ISCA design oligonucleotide microarrays. Copy number data was analyzed with Agilent Cytogenomics and OGT Cytosure Interpret software, respectively.

Results. From a total of 374 patients with syndromic ID tested through aCGH, 83 had at least one CNV predicted as pathogenic or likely, resulting in a diagnostic yield of 22.19%. The group of patients was clinically heterogeneous, as were the identified microdeletions and microduplications.

Conclusions. This study confirms the importance of aCGH testing in the diagnostis of patients with syndromic ID. Although the results are heterogeneous, we hope the data could contribute to a better understanding of the underlying mechanisms of CNVs-determined ID.

Investigation of neurodevelopmental disorders within the Medical Genetics Laboratory of "Victor Babes" National Institute of Pathology, Bucharest

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Neurodevelopmental disorders represent one of the common medical problems in the departments of Pediatric Neurology and Psychiatry, with a significant impact on the quality of life of children and their families. Genetic anomalies have been identified in up to 10% of patients with autism spectrum disorder (ASD) to 40% in global developmental disorders.

The Medical Genetics Laboratory of "Victor Babes" Institute in partnership with Obregia Hospital has a collaboration of over 20 years in the field of neurodevelopmental disorders, in national and international research projects. We currently have 2 ongoing research projects that address ASD and cerebral heterotopias, respectively. 304 children with ASD and 24 children with heterotopias were included in these studies in which arrayCGH, MLPA,PCR and sequencing studies were performed. The results obtained so far identified

pathological/possibly pathological anomalies in 36 patients, and a number of variants with uncertain significance in over 80 children.

The results obtained within these projects demonstrates the usefulness of genetic testing in patients with neurodevelopmental disorders, both for elucidating their etiology, and for establishing a disease management plan and providing an appropriate genetic councelling. The collaboration with other genetics centers in the country is very useful to share the clinical and genetic aspects of cases with rare anomalies or of uncertain significance.

Cauze genetice ale hipostaturii

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Hipostatura este definită ca talie sub 2DS față de media populației de aceeași vârstă, sex și stadiu pubertar. La pacienții cu hipostatură fenotipul clinic adesea nu este sugestiv pentru o anumita cauză. Factorii genetici conduc la afectarea anumitor căi patogenetice în principal prin intermediul factorilor externi cartilajului de creștere, a celor intriseci cartilajului de creștere și a proceselor celulare fundamentale. Factorii externi cartilajului de creștere sunt reprezentați de: factori endocrini ai axului GH-IGF1 și factori paracrini cartilajului de creștere. Factorii intrinseci cartilajului de creștere sunt: factori ai matricii extracelulare ai cartilajului de creștere și căi de semnalizare intracelulară. Hipostatura poate fi și consecința afectării proceselor fundamentale celulare: anomalii cromozomiale numerice si structurale, CNVuri, anomalii ale metilării, afectarea reparării ADN-ului.

Obiectiv: Identificarea cauzelor genetice ale hipostaturii la pacienți care s-au prezentat in Centrul Regional de Genetica Medicala Cluj-Napoca in perioada 2010-2022.

Metoda. Analizele genetice efectuate au fost: analiza citogenetica clasica (cariotip), analizele FISH și MLPA pentru gena SHOX, analiza cromozomială prin microarray, MS-MLPA pentru regiunea 11p15.5, testarea genetică a genelor FGFR3, PTPN11, secvențierea unui panel de gene și secvențierea exomului.

Rezultate și discuții. 617 pacienți au fost analizați, iar dintre aceștia, la 76 (12.3%) s-a identificat o cauza genetica a hipostaturii. Randamentul diagnostic cel mai mare a fost dat de testarea FGFR3, de 49%, de secvențierea panel de gene/exom, de 45%, de analiza analiza cariotipului, de 21.76% (cu diagnosticul sindromului Turner, cel mai frecvent). Aceste teste s-au efectuat fie pentru boli cu un fenotip clinic foarte specific, ceea ce a permis astfel o rata mare de diagnostic la aplicarea unui test genetic țintit, fie pentru pacienți cu hipostatură fără o cauză evidentă, la care secvențierea extinsa, în absența unei ipoteze clare, a fost de ajutor, conducând astfel la o rata mare de diagnostic.

Concluzii. Deși hipostatura reprezintă cea mai frecventa patologie evaluată de endocrinologul pediatru, foarte puțini dintre acești copii primesc un diagnostic etiologic. O abordare incluzând testarea genetica, efectuată după un anumit algoritm de evaluare, va permite stabilirea unui diagnostic optim si alegerea terapiei adecvate, inclusiv a celei personalizate translaționale.

From phenotype to genotype – current and future perspectives in genetic epilepsies

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The genetic etiology of epilepsy has been an intensely studied and debated topic over the last two decades. The progress of genetic diagnosis techniques have brought a shift in the paradigm and there are currently over 900 genes involved.

We present a case series of epilepsy or epileptic/ developemental encephalopathies which were managed at the Pediatric Neurology Department/ Center of expertise in rare pediatric neurology diseases in Dr. Victor Gomoiu Clinical Hospital in Bucharest. Both genotype-phenotype correlations and the complementarity of the diagnosis methods have led to a positive diagnosis in the aforementioned cases.

We highlight the importance of genetic testing via several methods when facing a genetic etiology suspicion in an epilepsy/epileptic encephalopathy case. Also, precocious phenotype identification may lead to a fast diagnosis in some patients.

Keywords: genetic, epilepsy, encephalopathy, genetic diagnosis, genes

Evolution of phenotypes in pediatric patients diagnosed with spinal muscular atrophy as part of a therapeutic paradigm shift

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Spinal muscular atrophy is a rare neuromuscular genetic disease caused by deletion of the SMN1 gene from chromosome 5 that causes a typical clinical picture with significant muscle weakness, skeletal deformities, respiratory failure. The most severe form of the disease is type I SMA, which until the first approved treatment was available on the market was one of the most common causes of infant mortality.

At this point, given that with the help of treatment variants and the application of standards of care children reach milestones that go beyond the classical phenotypes of SMA, we wonder if the current classification is up-to-date with the clinical reality.

We present a series of cases diagnosed with SMA, treated with Nusinersen and monitored in a multidisciplinary manner in the Neurology department at the Rare Diseases Expertise Center, Dr Victor Gomoiu Children's Hospital in Bucharest.

We emphasize the importance of the multidisciplinary team in the management of children diagnosed with SMA so that they can reach their maximum potential and their best quality of life.

Key words: spinal muscular atrophy, evolving phenotypes, standards of care, multidisciplinary team

Biological therapy in X-linked hypophosphatemia

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Introduction. X-linked hypophosphatemia (XLH) is a monogenic disorder with X-linked inheritance. It is caused by mutations present in the Phosphate Regulating Endopeptidase Homolog X-Linked (PHEX) gene responsible for the degradation of the bone-derived hormone fibroblast growth factor 23 (FGF23) into inactive fragments. The inactivation of the gene prevents the degradation of FGF23, causing increased levels of FGF23, which leads to decreased tubular reabsorbtion of phosphorus.

Clinical aspects are growth delay, limb deformities, bone pain, osteomalacia, dental anomalies, enthesopathy. Laboratory evaluation show hypophosphatemia, elevated alkaline phosphatase (ALP), normal serum calcium levels, parathormone (PTH) may be normal or increased FGF23 greatly increased. Conventional treatment consists of administration of oral phosphate and calcitriol. Biological therapy with Burosumab, a monoclonal antibody that binds to FGF23, reducing its activity, was approved in 2018.

Methods. We described case of two siblings, diagnosed with XLH, monitored by the Genetic Department of the County Emergency Clinical Hospital since 2019. The clinical picture, laboratory investigations and radiological aspects are suggestive for XLH. DNA analysis performed on the two siblings revealed a nonsense mutation in exone 5 of the PHEX gene: c.565C>T (p.Gln189Ter).

Results. At the age of 13 ½ and 7, the two children started treatment with Burosumab in therapeutic doses, and were monitored clinically and biochemically at regular intervals, according to the protocol established by the Endocrinology Commission of the Romanian Health Ministry.

Conclusions. The first of results of the Burosumab treatment in the two siblings are extremely encouraging and suggest a favorable long-term evolution under this treatment.

Keywords: fibroblast growth factor 23, PHEX gene, Burosumab

The Importance of Extensive Molecular Testing in Rare Genetic Disorders

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Rare diseases affect more than 300 million worldwide, often causing chronic illness, disability, and premature death. Traditional diagnostic techniques rely mostly on fundamental approaches, coupling clinical experience from prior rare disease presentations with the medical literature.

Many patients remain undiagnosed for years and many even die without an accurate diagnosis. In recent years, gene panels, microarrays, and exome sequencing have helped to identify the molecular cause of such rare and undiagnosed diseases and therefore allowed diagnoses for 25–35% of undiagnosed patients, often with actionable findings.

We shortly present a series of 3 case reports of rare genetic disorders each diagnosed using exome sequencing: a 6-year-old boy with autist spectrum disorders with ODLURO syndrome, a 14-year-old adolescent boy with Kartagener syndrome and a 10-year-old girl with Primary Ciliopathy. In the past two decades, gene panels, microarrays, and exome sequencing have identified the underlying causal mutations for many rare disease patients.

As for many undiagnosed cases, we share examples where these technologies played a significant role in deciphering the causative mutation in undiagnosed patients.

MLPA Genetic Testing: available kits and positive cases, an update at CRGM Dolj

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Introduction: The Multiplex Ligation-dependent Probe Amplification technique, or MLPA, is a multi-target PCR based method able to simultaneously detect structural abnormalities for up to 50 different genomic DNA or RNA sequences, in a single PCR-based reaction. MLPA is a quick and reliable technique to identify inherited or acquired DNA copy number changes, as well as to investigate the methylation status of DNA sequences.

Material and Method: At CRGM Dolj we investigate samples coming from patients with known genetic conditions in their families or with clinical features that point towards a genetic disorder. We processed more than 1150 samples from different types of tissue. The investigations were performed using the SALSA MLPA probemixes and SALSA MLPA Reagent kits.

Results: The detection rate for genetic disorders in postnatal diagnosis was 17.7%. Among the diseases diagnosed in our center we name: Williams-Beuren Syndrome, Fragile X Syndrome, Neurofibromatosis Type I, 1p36.32->1p36.33 deletion, Duchenne Muscular Dystrophy, Spinal Muscular Atrophy, Charcot–Marie–Tooth disease, DiGeorge Syndrome, 22q11 duplication, Down Syndrome, 15q13.3 microdeletion/ microduplication syndrome, 16p11.2 deletion syndrome, GRIN2B-Related Neurodevelopmental Disorder.

MLPA is a fast and robust molecular analysis technique that can be used to detect a wide variety of structural abnormalities in genomic DNA. The results, however, should always be confirmed through other methods and not all deletions and duplications detected by MLPA are pathogenic, one needing to consult the latest scientific literature when interpreting them.

There are also limitations regarding this technique, namely regarding the inability to determine single nucleotide polymorphisms or mosaicisms.

Key words: DNA, Ligation, Probe.

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Clinical case: hemyzygous CYBB gene variant in an infant with recurrent family affected males

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Introduction: X-linked chronic granulomatous disease (CGD) is a inborn error of immunity (IEI) associating recurrent and persisting infections, granulomatous colitis, fever, osteomyelitis, inflammatory bowel disease in the first years of life. It is caused by hemizygous mutation in the CYBB gene on chromosome Xp21 or homozygous mutations in NCF1 on 7q11.23, NCF2 on 1q25.3, NCF4 on 22q12.3, CYBA on 16q24.2, CYBC1 on 17q25.3.

Method: We collected data about history, physical exam and laboratory investigations, includingmolecular genetic tests on a 3 years old boy. The diagnostic was established by Phagoburst test and confirmed by 207 genes NGS Primary Immunodeficiency Panel.

Results: We present the case of a proband with a hemyzygous CYBB gene mutation associated with X-linked recessive CGD. This sequence change is known to replace glycine with arginine at codon 20 of the CYBB protein. This variant is not present in population databases, but this missense variant has been observed in individuals with X-linked CGD. The patient comes from a family with many affected males in mother's family line, with fatal evolution. Unfortunately, his younger brother is also affected.

Conclusions: Full diagnosis (genetics included) is paramount in CGD. Males are more likely to have the disease. Genetic counseling along with early diagnosis and treatment are needed in CGD to avoid suffering and life loses. Prenatal diagnosis, even though more easily accessible nowadays, is sometimes ignored or even rejected.

Genetic diagnosis of Dravet syndrome using next generation, capillary sequencing and multiplex-ligation dependent probe amplification - Romanian showcase

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Background/Objectives: Dravet syndrome (DS), associated with intractable seizures and developmental delay, is one of the most studied genetic epilepsies.

De novo variants in SCN1A gene, encoding for the voltage-gated Na+ channel alpha subunit Nav1.1, are the most frequent causes of DS.

Methods: We are reporting 36 patients with DS presumptive diagnosis, referred to CRGM-Dolj between 2017-2020. Testing options include multiplex-ligation dependent probe amplification (MLPA) Probemix P137 SCN1A MRC Holland and in-house capillary sequencing on a Thermo Fisher 3730xl DNA Analyzer, and next generation sequencing (NGS) panel Illumina TruSight One on Illumina NextSeq550 IVD. Data analysis uses Coffalyser.Net, Mutation Surveyor, and our bioinformatic pipeline based on nf-core/sarek v2.7.1(GATKv4.1.7.0) and Ensembl VEP v104.3.

Results: MLPA identified a mutation in SCN1A for 1 case. Genetic confirmation was mostly achieved though NGS, identifying SCN1A variants for 7 subjects and, for an additional 8 patients, variants in other genes that could explain the clinical phenotype of infantile-onset epileptic encephalopathy. Capillary sequencing was offered to identify the de-novo status of the identified

variants in the extended family and was accepted for a few of the parents. Mosaicism was not evaluated, although we intend to include testing options in the future.

Conclusion: Comprehensive clinical phenotyping is crucial for interpreting results. Genetic postnatal assessment of patients with DS/severe epileptic encephalopathy can be a powerful diagnostic tool for clinicians, with implications in the management and counseling of patients and their families.

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Clinical case of CHARGE syndrome genetically diagnosed -varia

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Introduction: CHARGE is a complex genetic syndrome, an abbreviation for several of the common features: coloboma, heart defect, choanal atresia, growth and developmental delay, genital abnormalities and ear malformations.

Material and method: We describe the case of a girl, who was refferded for genetic counseling for the first time at the age of 11 months, with global developmental delay, facial dysmorphism: hypotelorism, deformed and posteriorly rotated ears, flattened nasal root, plagiocephaly, hypocalcemia, laryngomalacia, hearing loss, atrial septal defect type ostium secundum, strabismus, astigmatism, ocular asymmetry. The molecular karyotype was performed with a normal result: arr(1-22, X x 2) (ISCN 2020), Whole Exome Sequencing testing was recommended, with a focus on genes involved in developmental delay, facial dysmorphism and deafness.

Results and discussion: Sequencing identified a variant with pathogenic clinical significance (class 5) in heterozygosity, in the CHD7 gene: c.7803C>G, p.(Tyr2601*), with autosomal dominant transmission, known to be involved in CHARGE syndrome and hypogonadotropic hypogonadism and a variant of uncertain clinical significance (VUS) (class 3), in heterozygosity, in the COCH gene: c.341T>A, p.(Leu114His) with autosomal dominant transmission , which may be involved in deafness. The discovered variants explain the patient's phenotype and offer the possibility of making the genetic diagnosis of CHARGE syndrome. The patient returns to the consultation for the reinterpretation of WES test results at the age of 1 year and 5 months, in the meantime she underwent a surgical

intervention for the atrial septal defect, an intervention for the insertion of a cochlear implant and uses hearing aid, wears glasses with corrective lenses for hypermetropia and strabismus.

Conclusions: To find out the type of mutations (inherited or de novo), testing of parents and sisters was recommended. The identification of gene variants involved in CHARGE syndrome has important consequences for the genotype-phenotype correlation as well as for the counseling of patients and their families.

Clinical case of two siblings – complex immunological manifestations of a new DADA2 variant

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Introduction: Deficiency of ADA2 (DADA2 disease) develops a rare recessively inherited systemic autoinflammation, characterized by vasculitis, cytopenias, recurrent fevers and high risk of ischemic stroke. The clinical spectrum is broad, and the manifestations vary within family members with the same genotype.

Method: Patients undergo physical exam, symptoms history and biochemical investigations, including molecular genetic tests. In these clinical cases a NGS primary immunodeficiency panel of 429 genes, along with an assay for the ADA2 enzyme activity were performed.

Case report: We present the case of a 14 years old girl and her younger brother with the same DADA2 heterozygous pathogenic variant found in the immunodeficiency test panel (p.F80S fs*23 – cytogenetic location 22q11.1). The activity of ADA2 enzyme was decreased in both cases. In contrast, clinical manifestations and some biochemical findings appear contradicting. Multiple additional variants of uncertain significance were also detected.

Conclusions: Genetic diagnosis is important when considering initiating a preventive treatment against immunological syndromes, especially the ones that associate important complications such as brain damage. Further follow up test methods, such as magnetic resonance imaging or computed tomography scans may be considered. There are more and more genetic discoveries in the field of inborn errors of immunity, such as immunodeficiencies and autoimmunity pathologies. Yet until now there is no cure available for DADA2 pathogenic

variants. The treatment focuses on stabilizing the symptoms and varies from patient to patient, which is challenging for the clinician and for the patient and family.

Epidemiological analysis and genotype-phenotype correlation in patients with phenylketonuria from a region in north-western Romania

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Background/ Objectives: Phenylketonuria (PKU) is the most common inborn error of amino-acid metabolism, caused by mutations in the phenylalanine hydroxylase (PAH) gene. The objective of this study was to analyze the epidemiological status of PKU in a region from the north-western of Romania.

Material and Method: The study group consist of 10 patients with phenylketonuria diagnosed between 1981 - 2021 and included in the database of the Regional Medical Genetics Center Bihor. The clinical and metabolic data were completed with molecular tests (Library preparation kit: TruSight Inherited Diseases; Illumina Rapid Capture. Sequencing Kit: NextSeq 500/550 High Output Kit v2.5, 150 Cycles. Sequencing platform: Illumina NextSeq550 IVD) performed on each patient included in the study.

Results: The prevalence of phenylketonuria in Bihor between 2011 - 2020 is 1:12.167 newborns. Most patients (72%) have a classic form of disease (cPKU), 20% of them have a milder phenotype (mild PKU) and 8% are with mild hyperphenylalaninemia (HPA). The most common variant identified in the study group was p. Arg408Trp (c.1222C>T), affecting 55.10% of the alleles.

Conclusions. The prevalence of phenylketonuria in the north-western region of Romania is decreasing and is currently below the estimated national average. In the north-western region of Romania, the vast majority of PKU cases had a severe metabolic phenotype (cPKU).

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POSTERE

A NOVEL VARIANT (C.1291C>T)(P.GLN431*) IN FAM 20C GENE DESCRIBED IN A RAINE SYNDROME CASE

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Raine syndrome is a congenital disorder, caused by a mutation in FAM20C gene. Most of the patients diagnosed with this disorder die in the first months of life, but there are also described non-lethal cases of Raine syndrome. Characteristic for this syndrome is typical facial dysmorphism and generalized osteosclerosis, and in some of the cases intracranial calcification, hearing loss and seizures were also described.

We report a case of a 4-days-old patient at the time of examination, born with a characteristic facial dysmorphism, short neck, narrow chest and curved tibia. The parents, affirmative gipsy and non-consanguineous, had a previous male child born with the same phenotype who died at 4-months-old. Computer tomography scan of the face and brain has shown choanal atresia. Transfontanelar ultrasound showed hypoplasia of the frontal and temporal lobes, corpus callosum dysgenesis and multiple areas of intracranial hyperechogenicity. The X-Ray of the chest revealed generalized increased bone density. A skeletal disorders gene panel was performed that identified two variants in the FAM20C gene: a pathogenic variant (c.1291C>T)(p.Gln431*) and a likely pathogenic variant (c.1135G>A)(p.Gly379Arg) which confirmed the clinical diagnosis. The parents were also tested and each was found to carry one of the variants.

The particularity of this case is that the detected variant (c.1291C>T)(p.Gln431*) has not been reported in the literature. Also, our case is one of the few compound-heterozygous mutation in FAM20C gene described so far in a non-consanguineous marriage.

Phenotypic and Genotypic Spectrum of SWI/SNF-Related Intellectual Disability Disorders (SSRIDDs) - case series of 5 patients

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INSMC Alessandrescu-Rusescu

Intellectual developmental disorder (IDD) is one of the most common causes of disability. Generally it's very difficult to identify phenotypic features that would allow differential diagnosis between monogenic and microstructural chromosomal rearrangements in IDD based on only clinical examination, but whole exome/whole genome sequencing should be an efficient diagnostic method.

SWI/SNF complexes regulate gene expression by a process known as chromatin remodelling and have extensive roles in the development of cell lineages. SWI/SNF complex-associated genes cause a spectrum of disorders that ranges from syndromic intellectual disability to Coffin-Siris syndrome (CSS) to Nicolaides-Baraitser syndrome (NCBRS), the clinical picture being defined by Intellectual disability, speech delay, behavioural problems, ectodermal, and skeletal features, as well as similar abnormal facial features.

We summarize the clinical presentation of 5 unrelated patients presenting the SSRIDD spectrum, discuss overlapping and distinctive features, and delineate the mutational landscapes of the associated genes confirmed by molecular genetic testing using NGS technologies.

Only in two of five individuals from all group presented with very suggestive of Coffin-Siris syndrome showing characteristic major features of this condition: global developmental delay, dysmorphic features and hypoplastic fifth fingernails; the rest of the cases presented with an unspecific phenotype, but suggestive for a genetic condition.

Many individuals who present with multiple congenital anomalies and developmental delay should include use of a multigene panel or more comprehensive genomic testing to detect the cause of this form of intellectual disability. Probably due to the large clinical spectrum of these patients many of them remain under-recognized for the SSRIDD spectrum.

When genetics meet psychiatry: perspectives on hyperammonemia caused by adult-onset OTC, an urea cycle defect

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The urea cycle is the body's primary tool for the disposal of excess nitrogen, and dysfunction in urea production results in hyperammonemia (HA). The main complication of HA in all age groups can cause cumulative neurocognitive damage and even death. Ornithine transcarbamylase (OTC) deficiency is a genetic disorder involving mutation in OTC gene located on the X chromosome. This makes the expression of the gene defect most common in males, but heterozygous females can also be affected, presenting serious morbidity. Most males present early in the neonatal period with more devastating outcomes than female. Females often have partially functioning mitochondria due to uneven distribution of the mutant gene secondary to lyonization (X-chromosome-inactivation). There are several exogenic factors that might trigger HA episodes, but symptomatic females may not even present until adulthood, when they are in a metabolic challenge, such as: intense catabolism in a severe illness, fasting, high protein intake, medication etc. The OTC patient (adult-onset female after a psychotic event in the context of a hyper-catabolic state) was admitted in gastroenterology for evaluation and treatment. In adults with OTC defect, the specific long-term management includes: restriction in protein intake (0,83 g proteins/kg bw/day), L-citrulline 100-200 mg/kg bw/day, and a chronic administration of an ammonia scavenger, preferably orally (glycerol phenylbutyrate - 1.1 g/ml). Biological evaluations include monthly measurement for ammonia (that should be < 80 µmol/L), of glutamine (that should be < 1000 µmol/L) and in every 6 months the patients should undergo regular blood tests and an abdominal ultrasounds.

Genetic counseiling for a case with robertsonian translocation (13;15)

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Introduction: Robertsonian translocation is defined as the fusion of the long arms of two non-homologous acrocentric chromosomes (13, 14, 15, 21 and 22) and is the most common structural chromosomal abnormality.

Material and method: A 29-year-old patient is reffered for a genetic counseiling, for the interpretation of the constitutional karyotype analysis and preconceptional genetic advice.

According to peripheral blood karyotype result 45,XY,der(13;15)(q10;q10), cytogenetic analysis revealed an abnormal male karyotype with 45 chromosomes, having a derivative chromosome resulting from Robertsonian translocation between chromosomes 13 and 15 The proband's spermogram revealed cryptozoospermia: result <2 mil./ml (reference interval >=15).

Results and discussion: Carriers of a Robertsonian translocation are phenotypically apparently normal, but may present with infertility, the formation of pregnancies with abnormal embryos and respectively early pregnancy loss, spontaneous abortions, fetal deaths or the birth of a child with unbalanced chromosomal abnormalities.. According to studies pattern of gamete segregation in heterozygous carriers of Robertsonian translocation 13q;15q (most of whom presented with infertility), the fraction of spermatozoa with viable disomy is between 7% and 23%, with an average of 17%. It was recommended: the pre-implantation genetic diagnosis of the embryos, or the prenatal diagnosis of the pregnancy in progress, with the performance of the chorionic villus biopsy starting from the 12-week term and the performance of the classic and molecular karyotype.

Conclusions: The risk of recurrence is high in families where one parent is a carrier of the translocation. For this reason, in order to offer appropriate genetic counseling, karyotyping of parents and first-degree relatives is necessary.

A very rare KCNMA1 – linked channelopathy. A case report

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KCNMA1 – linked channelopathy is a genetic disorder characterised by the presence of a mutation in the KCNMA1 gene, associated with various clinical manifestations of movement disorders, seizures, global developmental delay, and intellectual disability. Because of its rareness and the diversity of the clinical features, this condition does not yet have a diagnostic criteria, or therapeutic approach. The KCNMA1 gene codes for a large-conductance voltage – and Ca2+ - activated K+ channel, also called the BK ("Big K") channel, which differs from other K+ channels in that it can be activated by both intracellular Ca(2+) ions and by membrane depolarization.

We report the case of a pediatric patient which was referred to our clinic for genetic counseling by the pediatric endocrinologist for the following clinical picture: a 12 y.o. girl with global developmental delay, autism spectrum disorder, speech delay and precocious puberty. We recommended to start genetic testing in steps as follows: first constitutional karyotype, molecular karyotype and then WES. The constitutional chromosome analysis yielded a normal result, 46,XX, a normal female karyotype. The molecular karyotype – an array 180K yielded a VUS CNV, that did not explain the patient's phenotype. The WES returned a positive result, a likely pathogenic gene variant in KCNMA1

Our patient was finally diagnosed through WES testing which found a rare likely pathogenic variant in KCNMA1 gene. Rare diaseases should have a multidisciplinary management team, with a pediatrician, endocrinologist, medical geneticist, neurologist and psychiatrist.

Genome Alterations In Breast Cancer

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The malignant phenotype, defined by intratumoral heterogeneity, results from the genetic instability of the neoplastic cell combined with the dynamics of evolution and cell differentiation hierarchies in tumor cell populations.

The HER2 gene, HER2/NEU, synthesises a protein acting as a receptor at the cell level, essential for cell growth. The HER2 receptor is a tyrosine-protein kinase receptor; member of the EGFR family. HER2 multiplication status can be determined from all invasive tumors, using the in situ hybridisation technique. High levels of HER2 gene amplification or protein expression have an unfavourable prognosis. The use of anti-HER2 monoclonal antibodies has been shown to reduce recurrence and mortality rates, in HER2-positive patients.

The biomarkers, used in the therapeutic decision of early breast cancer, are determined by genomic tests. The first generation test analyses the expression of 21 genes by PCR from a breast tissue specimen. Depending on its predictive score and the patient's age, follow risk groups, useful in distinguishing between utility and benefit of a neoadjuvant chemotherapy vs. hormone therapy. The 2nd generation prognostic genetic tests, analyses the activity of 12 genes related to the likelihood of recurrence within 5 - 10 years of diagnosis. A strong family history of breast cancer is linked to the presence of an abnormal gene associated with a high risk of breast neoplasia: BRCA1 or BRCA2.

The identification of elements of molecular biology is important for prognosis and therapy. It leads to the hope of a curable future for breast neoplasia. It allows development of new targeted therapies, increasing overall- and disease-free survival.

Key words: breast, cancer, HER2 gene, BRCA1 , BRCA2

Next-Generation Sequencing testing in genetic evaluation of monogenic dilated cardiomyopathy patients

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Background: Dilated cardiomyopathy (DCM) is a rare heterogenous disease, translated into a response of myocardium to diverse genetic and environmental insults. Inherited DCM may occur in 25-50% of patients, which is why it is also present in children. More than 40 genes have been identified as responsible for causing DCM, yet TTN, the gene encoding the sarcomere protein titin, have been related most frequently. Next-Generation Sequencing (NGS) have recently become the routine genetic diagnosis testing for DCM patients. We aimed to show the contributions different genes in the etiology of DCM.

Methods: We included 20 patients with DCM where a significant variant was identifyed. The sequencing used Illumina TruSight Cardio Sequencing Panel (174 genes) at Genomic Medicine Center Timisoara.

Results: The patients' age ranged between 4 months to 66 years. Variants in TTN, MYH7, RBM20, LMNA genes were identifyed using NGS: TTN - four pathogenic, three likely pathogenic, three variants of unkown significance (VUS); MYH7 - one pathogenic, two likely pathogenic, five VUS; RBM20 - one pathogenic, one VUS; LMNA - one pathogenic variant. Variants in TTN gene were most often identifyed (10 cases out of 20). Two of the patients (age 13, 16y) who presented variants in MYH7 and TTN gene, have had heart transplantation. NGS have established twelve positive diagnosis.

Conclusion: Even in small DCM cohorts, the genetic variation can be observed. The most important conclusion is that even if the clinical context might be similar, the genetic classification is accurate, leading to improved clinical approaches.

Keywords: DCM, NGS.

The influence of different single nucleotide polymorphisms on acute myeloid leukemia

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UMFST George Emil Palade

This study aimed to identify associations between certain single nucleotide polymorphisms (SNPs) and acute myeloid leukemia (AML) susceptibility, prognosis, and treatment.

In different studies, we analyzed 18 SNPs by several molecular techniques.

The SNPs were selected taking into account the role of the genes: DNA replication, DNA repair genes, cell cycle control genes, cytokines genes, and tumor suppressor genes. The following SNPs were associated with AML susceptibility: XPC Ala499Val; TP53 rs1042522; MDM4 rs4245739; TGF-β1 rs1800470; IFN-γ rs2430561 and one haplotype for three SNPs of MCM7 gene. Regarding the overall survival, we found as negative predictors the following SNPs: TERT rs2853669; TP53 rs1042522, IL-10 rs1800896, and TNF-α rs1800629.

Several clinical/ paraclinical negative predictor factors for AML overall survival were also found, such as leukocytosis, thrombocytopenia, high LDH level, high percentage of blasts in bone marrow, low ECOG performance score, unfavorable cytogenetic or molecular scores, etc.

Our results demonstrated the utility of simultaneous investigation of SNPs for AML patients. Moreover, the SNPs results must be interpreted by taking into account the somatic mutations, the clinical and paraclinical data, prognostic scores, patients' overall survival, their treatment, etc.

Genetic aspects of Charcot–Marie–Tooth disease

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Hereditary motor and sensory neuropathy or Charcot–Marie–Tooth (CMT) disease is the most prevalent group of genetic neuromuscular disorders. The features include symmetric, slowly progressive distal muscle weakness and wasting, decreased reflexes, pes cavus, hammer toes, and vibratory sensory loss. Electrodiagnostic tests are valuable diagnostic tools for CMT. There are over 100 genes associated with CMT, reflecting the heterogeneity of this disorder. The majority of the mutations are inherited dominantly, but some are inherited recessively. Prognosis, management, and family planning require an accurate genetic diagnosis; also genotype could represent inclusion criteria for some clinical trials (e. g. gene-based therapy).

We summarize the classification of CMT, molecular aspects, and clinical overlap with other neuromuscular disorders. The theory is illustrated with cases from our experience, underlying the suggestive aspects for specific diagnoses.

In conclusion, clinical phenotype, inheritance pattern, and neurophysiological findings could guide genetic testing in some cases.

Utility of comprehensive molecular testing of patients with acute myeloid leukemia

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Acute myeloid leukemia (AML) is a hematological malignant disease. Recently, significant molecular progress was made in the pathogenesis, diagnostic methods, risk stratifications, prognosis, and personalized therapy of AML patients. Considering these, the genetic testing protocol must be as complex as possible. The objective of this study was to evaluate the utility of multiple molecular investigation techniques in patients with AML and to achieve a genetic testing protocol tailored to the infrastructure of Romanian laboratories.

We performed targeted molecular analysis of FLT3, NPM1, and DNMT3A mutations; Multiplex Ligation-dependent Probe amplification (MLPA) using different kits, Ligation-dependent reverse transcription polymerase chain reaction (LD-RT PCR) for the identification of fusion genes, and Next generation sequencing (NGS) with a specific panel.The FLT3-ITD and D835 mutations were identified in 18.6% of patients, DNMT3 R882 in 11.5% of patients, and NPM1 mutation in 16.4% of patients. Using the MLPA technique we identified copy number variations in 35% of patients. The LD-RT PCR technique identified gene fusions in 10% of patients.

All of these techniques, cytogenetics analysis, MLPA, LD-RT PCR, and capillary electrophoresis with variant allele ratio determination for FLT3-ITD and NPM1, allow us to identify genetic abnormalities in more than 50% of AML cases. These percentages can be higher if the NGS technique is used. The NGS technique with an AML-specific panel used for our patients identified an average of 22 variants/patient. This study demonstrated the usefulness of comprehensive testing of patients with AML for personalized therapy.

The 15q11-q13 region: large structural variations and imprinting defects in correlation with clinical phenotype.

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Introduction: Chromosome 15q11q13 abnormalities are known causes for distinct disorders, the main three being Prader-Willi syndrome, Angelman syndrome, and 15q12-q13 duplication syndrome.

Objectives: Clinical characterization of patients with 15q11q13 abnormalities, identifying genotype-phenotype correlations.

Methods: We analyzed 17 confirmed cases of 15q11q13 abnormalities recorded from 2015 to 2022 at Cluj-Napoca Emergency Clinical Hospital for Children.

Results: Out of the 17 cases, 12 were Prader-Willi syndrome, 3 Angelman syndrome, one 15q12-q13 duplication syndrome. There was also a case of 15q11.1q11.2 deletion. Copy number variation was present in 13 cases. Abnormal methylation by itself was recorded in 4 cases. Mean age at diagnosis was 5.5 years, with a median of 2.3 years. Half of all patients were diagnosed before the age of 1.

Consistent findings were intellectual disability, craniofacial dysmorphism (varying degrees), and epilepsy in Angelman syndrome patients. Macrocrania was only recorded in the patient with a 15q11.1q11.2 deletion. This patient also had a second chromosomal anomaly, an Xq11.4 deletion that could, in part, explain their symptoms. One of the Angelman syndrome patients, despite presenting mosaicism, had a severe phenotype.

Conclusions: Early diagnosis is important, as it allows for quicker implementation of therapeutic strategies, with maximum long-term benefits. Identifying the pathogenic mechanism is important, as it affects recurrence risk. Some patients may have multiple chromosomal abnormalities. Cases with 15q11q13 abnormalities are complex, and require a multidisciplinary therapeutic approach.

Maple syrup urine disease (MSUD): a systematic review of newborn screening studies and their diagnostic methods

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Introduction. MSUD is a rare inborn error of metabolism caused by mutations in the genes coding for the branched-chain alpha-keto acid dehydrogenase multi-enzyme-complex, involved in the degradation of leucine, isoleucine and valine. In untreated classic MSUD patients these accumulate, often leading to death. If diagnosed, MSUD can be managed following a restricted diet in these amino acids, by thiamine supplementation (in responsive forms) or by liver transplantation - with better outcome. Thus, newborn screening is a worthwhile investment for the early identification of these patients.

Methods. We conducted a systematic literature review until August 2022. A narrow search was performed on PubMed for papers on newborn screening which included MSUD and calculated its incidence.

Results. The search returned 184 studies which were then further selected based on their title and abstract. Thirty-one studies were reviewed, of which sixteen met the inclusion criteria. Calculated incidence varies widely, from 1 in 620,170 (Japan) to 1 in 22,150 (South Korea). The most used diagnostic methods nowadays are tandem mass spectrometry (replacing the old Guthrie-bacterial-inhibition-assay) or DNA sequencing tests. Besides, a rapid plasma two-dimensional-chromatography-method applied in our laboratory (Duran, Wadman et al. 1994) in patients suspected for aminoacidopathies is available for diagnosing MSUD.

Conclusions. MSUD is a rare but not irrelevant disease, the prognosis being 'satisfactory' with prompt and strict therapy. While its incidence seems to be geographically heterogeneous, this might be due to its rarity and the screened populations' sizes, making screening studies on larger populations a necessary future step.

ATP Synthase Deficiency due to TMEM70 Mutation: molecular analysis, clinical manifestations, laboratory characteristics and treatment in a targeted literature review

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Introduction. Partial deficiencies in oxidative phosphorylation system (OXPHOS) are an important cause of a large and diverse group of multisystem disorders. TMEM70 mutation leads to a nuclear-encoded ATP synthase deficiency, resulting in a syndrome characterized by a neonatal mitochondrial disorder with muscular hypotonia, cardiomyopathy, variable central nervous system involvement, accompanied by severe lactic acidosis, 3- methylglutaconic aciduria (3-MGA) and hyperammonemia. This is a panethnic disease, frequently in the Roma population, with variable outcome and depends mainly on the adequate management of metabolic crises in the neonatal period.

Methods. Retrospective clinical data, metabolic profiles and therapy methods of about 62 patients, from European countries, also, Japan, Turkey, Israel, Russia with confirmed TMEM70 mutations, were collected and included in a targeted literature review.

Results. An increasing number of affected individuals, many from consanguineous parents of Roma ethnic background, have been reported, due to a founder allele effect in this population, since its first description in 2008 by Cízková et al. The disease outcome is severe, and more than half of affected individuals die in early childhood. The three most common clinical features associated with these mutations are hypertrophic cardiomyopathy, 3-MGA, and hypotonia. Anaplerotic therapy is recommended for patients with the TMEM70 defect and especially during metabolic crises, although clinical trials for this are still lacking.

Conclusions. Certainly, this comprehensive analysis will help to diagnose and provide therapy in future cases, as well as to supply important information regarding the prognosis and optimal management of metabolic crises, often found in these patients.

Co-occurrence of two chromosomal aberrations, one pediatric phenotype

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Introduction: Cat eye syndrome(CES) is a rare developmental disorder caused by the presence of a small supernumerary chromosome (sSMC) derived from the proximal part of chromosome 22. This disorder manifests a multitude of clinical manifestations that sometimes include coloboma of the iris, anal atresia and preauricular tags/pits. 2q13 microdeletion syndrome is a very rare chromosomal anomaly with a variable outcome and unspecific phenotype with heart or kidney anomaly or hernia, unusual facial features, developmental delay and behavioural characteristics.

Materials and methods: We present the case of a male newborn from a twin pregnancy showing postnatal failure to thrive, facial particularities (short phrenulum, microgathism, open anterior fontanella, right ear with preauricular pit), single palmar crease of the right hand, cryptorchidism, umbilical hernia, axial hypotonia, cardiac murmur. We applied combined analyses of karyotype and FISH(fluorescence in situ hybridization) for testing of our index patient and his parents. Subsequent genetic testing using aCGH was performed for the proband.

Results: Conventional karyotype identified a mosaic sSMC. Based on sSMC frequencies, FISH testing for chromosome 15 was applied and incomplete hybridisation of probes was observed. Subsequent aCGH identified a loss of genetic material in 2q13 region (110 kb) and a gain at 22q11.1-q11.21 region (4.91 Mb). FISH probes for chromosome 22 confirmed the origin of the sSMC. Parental karyotypes were normal.

Conclusions: sSMCs are usually identified using G-banding, which is still the basic step in multiple abnormalities syndromes diagnosis. Karyotyping also reveals the mosaic status, and molecular cytogenetic techniques must be applied to identify the origin of the sSMC. Our case highlights the role of combined molecular genetic testing in the process of differential diagnosis and the implications of this approach for genetic counselling.

Clinical heterogeneity in spinal muscular atrophy types 2 and 3

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Spinal muscular atrophy (SMA) is a progressive neurodegenerative disease characterized by degeneration of the anterior horn cells in the spinal cord and motor nuclei in the lower brainstem. The most common form is caused by mutations in SMN1 gene.

We aimed to describe sporadic cases of SMA types 2 and 3, which were characterized by variable levels of muscle weakness and atrophy. Three girls, mean age 7 years, were hospitalized for functional rehabilitation in Medical Rehabilitation Clinical Hospital Baile Felix, Romania.

Patients presented with a broad spectrum of clinical abnormalities, ranging from severe neuromotor deficits, hypotonia and use of the wheelchair to being able to sit, stand and walk short distances without support. Two cases with type 2 SMA had developmental delay, the onset being at 8 and 10 months, respectively. Their clinical phenotype also included severe dorso-lumbar scoliosis, joint contractures of different severities, absent deep tendon reflexes, inconstant support and control of the head in one patient; one was able to raise the lower limbs off the bed and move them horizontally. The third case, with SMA type 3, reached all major motor milestones and independent walking. The onset was at about 2 years. She presented with muscle weakness, hypotonia, gait deficit, difficult tiptoes walk, mobility limitation, polymyoclonus, fatigue, frequent falls, involuntary tremors in her fingers. She was able to climb stairs with support, but did not run and jump.

Clinical heterogeneity of SMA was revealed by the age of onset and complexity of symptoms in the presented cases.

TCF7L2, CASC8 and GREM1 Polymorphism in Patients with Colorectal Cancer and Diabetes Mellitus

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The aim of the study was to explore the association of the TCF7L2 rs7903146, CASC8 rs 6983267 and GREM1 rs16969681 polymorphism in patients with type 2 diabetes mellitus and colorectal cancer. Real time PCR was used to determine the genotypes of TCF7L2 rs7903146, CASC8 rs 6983267 and GREM1 rs16969681in patients with CRC and T2DM and patients without T2DM and CRC. Hardy Weinberg equilibrium was determined in the control group for genotypes distribution of every polymorphism. The association between disease status and the genetic variants were tested by Pearson's Chi-square test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used in calculating the corresponding χ^2 distribution test. People carrying TT genotype of rs7903146, rs6983267 and rs1696981 had a significant association with T2DM and CRC. Moreover, the people with TT genotype of rs1696981 had a greater risk for T2DM and CRC (OR=7, CI 0.397-23.347).TCF7L2 rs7903146, CASC8 rs 6983267 and GREM1 rs16969681 maybe a risk factor for association of T2DM with CRC.

NARP/LS overlap in the clinical presentation associated with mitochondrial DNA mutations

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Introduction. Mitochondrial disorders are heterogeneous genetic conditions caused by a wide spectrum of mutations in genes encoded by either

the nuclear or the mitochondrial genome. Leigh syndrome (LS) and NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa) are both severe mitochondrial diseases; sometimes the clinical presentation of the disorders can overlap.

Material and methods. We report cases of two patients manifested with recurrent seizures, muscle weakness, psychomotor retardation, feeding difficulties; meanwhile, additional symptoms include exercise intolerance and partial atrophy of the optic nerve in the case of the patient with NARP, in addition to tremor, ataxia and abnormal ECG in the LS patient.

Results. The Nijmegen Mitochondrial Disease Criteria Scale revealed a score equal to 8 in both patients, which indicates a definite mitochondrial disorder. Biochemical tests determined elevated lactate in blood, hyperalaninemia and hyperaminoaciduria.Neuroimaging findings consisted of pathological foci in the bilateral basal nuclei in the case of NARP, and a symmetrical distribution of lesions along thalamus, mesencephalon, brainstem, medullary tegmentum and cerebellar hemispheres and medulla oblongata, in a pattern that is characteristic of LS.

Genetic analysis revealed the m.3243A>G mutation (MT-TL1 gene) in the case of LS patient and the m.8993T>G mutation (MT-ATP6 gene) in the case of the patient with NARP.

Conclusion. Our experience suggested that early onset in the presence of complete health, the polymorphism of clinical manifestations, such as a central nervous system lesion, muscle weakness, impaired psychomotor development, and seizures in a child should prompt the clinician to consider LS or NARP syndromes.

Carnitine palmitoyltransferase II (CPT II) deficiency, 11 Years Until Diagnosis

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Introduction: Carnitine palmitoyltransferase II (CPT II) deficiency is a condition in which long chain fatty acid cannot be processed in the mitochondria, a multistep process that breaks down (metabolizes) fats and converts them into energy. Fatty acids are a major source of energy for the heart and muscles, particularly during fasting periods. There are three main types of CPT II deficiency:

a lethal neonatal form, a severe infantile hepatocardiomuscular form, and a myopathic form

Case presentatin: We present a case of a 16 year old patient, who was referred to the genetic department because she experienced muscular pain after exercising, more pronounced in the evening. She has been having these symptoms since she was five years old, worsening in the last 2 years. About 1 ½ years ago, after an intense workout she presented: hyperchromic urine, elevated urea, creatinine and muscle enzimes (CK, LDH, AST, ALT). At presentation in our service, main etiologies were investigated: infectious myositis, inflammatory myopathy, metabolic myopathy, muscle glycogenosis, mitochondrial disease, disorders of fatty acid oxidation, disorders of purine cycle. An autoimmune disease was rulled out, cardiolipin antibodies IgM were negative. A specific antibodies panel for IgG myositis was also negative. Mitochondrial disease was less probable, lactic acid was normal. In a muscle glycogenose symptoms typically occur at the start of an intense exercise, but may improve after a short rest Testing for Pompe disease was considered, but it was also negative. The acylcarnitines isoforms profile revealed low C0 (Carnitine, free) and slightly elevated C16 and C18:1-carnitine, so fatty acids beta oxidation disorder was suspected.

A gene panel for fatty acid oxidation defects was ordered. The result revealed a homozygous pathogenic variant in CPT2 c.338C>T (p.Ser113Leu), which is associated with autosomal recessive carnitine palmitoyltransferase II (CPT2) deficiency. The patient is also a carrier for heterozygous, pathogenic variant in ACADM gene c.244dup(p.Trp82Leufs*23) associated with medium-chain acyl-coenzyme A dehydrogenase deficiency. The sister of the proband was also tested for these variants and she is a carrier only for the CPT2 pathogenic variant .

Conclusions: This diagnostic was important for this girl because she received a personalized diet with fat exclusion, small quantities of olive oil and more carbohydrates. She was counseled to avoid triggers like intense exercise, long fasting, cold, stress, lack of sleep. The necessary steps have been taken to receive treatment with triheptanoin (Dojolvi™, a synthetic medium-chain triglyceride).

In June 2020, triheptanoin received its first regulatory approval, in the USA, for use as a source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD).

After three month of treatment with triheptanoin, the evolution of our patient is favorable, the level of C0 (Carnitine, free) is normal and the amount of C16 and C18:1-carnitine has decreased since the first evaluation.

In our case recurrent attacks of muscle weakness and myoglobinuria precipitated by prolonged exercise in an apparent healthy girl could have pointed towards a defect of the fatty acid oxidation pathway.

The particularity of this case is the association of a homozygous pathogenic variant in CPT2 gene and a heterozygous pathogenic variant in ACADM gene (it could have some influence in an altered pathway of fatty acids beta oxidation, even in heterozygous state in a recessive disorder) .