UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
DOCTORAL SCHOOL

DOCTORAL THESIS
SUMMARY

PROMOTER:
PROF. UNIV. DR. FRANCISC MIXICH

PhD CANDIDATE :
IOANA STREAȚĂ

CRAIOVA
2016

UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
DOCTORAL SCHOOL

MOLECULAR ASSESSMENT IN GLOBAL DEVELOPMENTAL DELAY AND INTELLECTUAL DISABILITY

PROMOTER:
PROF. UNIV. DR. FRANCISC MIXICH

PhD CANDIDATE :
IOANA STREAȚĂ

CRAIOVA
2016

TABLE OF CONTENTS

INTRODUCTION

Genetic diagnosis is unknown for 60% of patients with global development delay and intellectual deficiency. This is due to the limited resolution of conventional cytogenetic techniques that fail to identify submicroscopic chromosomal abnormalities (less than 5-10 Mb) associated with numerous well defined syndromes, thus requiring the use of more advanced techniques such as FISH (fluorescence in situ hybridization) PCR techniques, Real Time PCR or array CGH.

Establishing the genetic etiology of syndromes characterized through global developmental delay and intellectual deficiency has a major economic and social impact. Thus, it can be explained the pathogenesis and details about recurrence, clinical management and prognosis can be offered.

This project aims to contribute to the development of Medical Genetics in Oltenia by ensuring the access of patients with global development delay and intellectual impairment to molecular diagnostics and appropriate genetic counseling.

The specific objectives of this project are:

1. To identify genetic changes such as CNVs (copy number variations - segments of DNA with different sizes, from a few kb (kilobases) to Mb (megabase), present in a varying number of copies compared to a reference genome) involved in the etiology of the genetic pathologies characterized through global development delay and intellectual deficiency, and establish their frequency in the studied population.
2. Identification and clinical and genetic characterization of the subjects with global development
3. Increasing the access of patients with genetic pathology to modern molecular diagnostic techniques by signing and strengthening partnerships between the Regional Center for Medical Genetics Dolj of Emergency County Hospital Craiova, University of Medicine and Pharmacy of Craiova and social welfare institutions from Oltenia.
4. To develop the current DNA biobank of Human Genomics Laboratory that could be used in future medical research.
5. To build a database with persons affected by a genetic pathology in Oltenia that can be the starting point for the next genetic epidemiology investigations.

Key words: intellectual deficiency; global developmental delay; microdeletion; microduplication; aCGH

I. BACKGROUND

Chapter I, entitled **"Global Development Disorder. Intellectual deficiency "** presents the incidence and etiology of global development disorders and intellectual deficiency and the steps that have to be followed in order to establish the etiologic diagnosis of these pathologies.

Chapter II., entitled **" Genetic assessment of global developmental disorders and intellectual disability"** describes the main genetic changes responsible for global developmental delay and intellectual deficiency and the molecular techniques available to identify them.

In **chapter III.**, entitled **" array CGH in genetic diagnosis of developmental disorders and intellectual deficiency"** is described the impact of introducing aCGH method in the tools used to establish the genetic causes of global developmental disorders and intellectual deficiency.

II. PERSONAL CONTRIBUTIONS

Chapter IV. Rationale, Aim and Outline

This project aimed to identify the genetic substrate of disorders characterized through global developmental delay and intellectual deficiency in patients assessed in the Human Genomics Laboratory (LGU-UMFCV) of the Regional Center for Medical Genetics Dolj (CRGM Dolj).

Chapter V. Materials and methods

For this study we tested through aCGH technology 36 patients diagnosed with global developmental delay and / or intellectual deficiency of unknown etiology within the Regional Center for Medical Genetics Dolj. The biological sample used to obtain the genomic DNA was peripheral venous blood collected on EDTA.

Testing was performed using microarray slides provided by Roche NimbleGen with 720,000 (3x720K) or 135,000 (12x135K) probes (Roche NimbleGen, Madison, WI, USA) or Agilent with 180,000 (4x180K) and 60000 (8x60K) probes (Agilent Technologies Inc. ., US). Data analysis was performed with Nexus 6.1 (Nexus BioDiscovery, El Segundo, CA) or Agilent Cytogenomics 3.0 (Agilent Technologies Inc., US) software.

Chapter VI. Results

The study group consisted of 36 patients with developmental delay and / or intellectual deficiency associated with other clinical signs and symptoms such as abnormal behavior, neurological disorders, growth abnormalities, birth defects, dysmorphic features, metabolic or endocrine problems, skin lesions or abnormal skeletal development (Table 6.1).

After performing genetic analysis through aCGH, the results were normal for 10 patients, for other 6 was possible to accurately determine the genetic etiology, while for 20 patients we did not find any genotype-phenotype corellation (Figure 6.1).

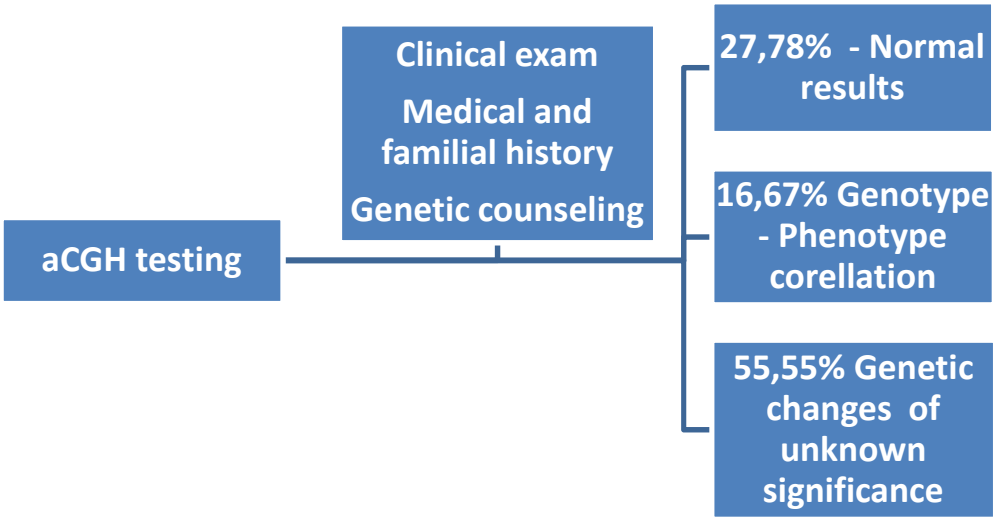

Figure 6.1 aCGH results of patients included in the study group

aCGH analysis of the 36 patients included in the study group managed to identify 54 CNVs in 26 of them. Through careful analysis of the literature and trying to correlate the results with patient phenotype, we classified these CNVs into four groups:

- Pathogenic (Table 6.2);
- Potentially pathogenic (Table 6.3);
- variants of unknown clinical significance;
- CNVs unrelated with rhe phenotype of the patient.

Clinical features of patients assessed through aCGH			Affected patients
Developmental delay			30/36
ID	Mild (IQ 50-69, mental age 9-12 years)		10/36
	Moderate (IQ 35-49, mental age 6-9 years)		10/36
	Severe (IQ 20-34, mental age 3-6 years)		14/36
	Profound(IQ <20, mental age <3 years)		2/36
Specific developmental disorder	Language disorder		20/36
	Learning disorder		10/36
	Mathematical calculation learning disorder		15/36
	Neuromotor disorder		36/36
Neurodevelopmental disorder	Autistic spectrum disorders		3/36
	ADHD		4/36
	Stereotypes		7/36
	Sleep disorders		3/36
	Feeding dificulties		5/36
	Psychosis		1/36
	Behavioral disturbances		15/36
Neurologic signs	Impaired sight		3/36
	Impaired hearing		2/36
	Abnormal involuntary movements		5/36
	Cerebral lesions		1/36
	Cerebral palsy		5/36
Growth disorders	At birth	small for gestational age (<10th percentile)	1/36
		large for gestational age (> 90th percentile)	1/36
	Actual	Dwarfism (height <5th percentile)	1/36
		Macrocephaly (> 95th percentile)	2/36
		Microcephaly (<5th percentile)	3/36
Congenital anomalies	Cardiac defects (Atrial/ ventricular septal defect)		3/36
	Renal and urogenital malformations		1/36
	Cleft lip/palate		1/36
	Micrognathia		1/36
	Limb abnormalities (short/long limbs)		2/36
Cranio-facial dysmorphism			30/36
Metabolism and endocrine disorders			5/36
Skin lesions			1/36
Abnormalities of hair, nails and teeth			5/36
Skeletal abnormalities (eg scoliosis)			5/36
Other anomalies			25/36

Table 6.1 Clinical assessment of the subjects enrolled in the study group

Pacient	Sex	Age	Locus / Inheritance	Size [Mb]	MIM/Genes	aCGH platform
Pacient 2	F	34	Dup 3q29	1,65 Mb	611936	Roche NimbleGen
Pacient 11	M	5	Del 7q11.23	1,35Mb	194050	Roche NimbleGen
Pacient 19	M	4	Dup Xq28	0,17 Mb		Agilent
			Dup Xq27.1-q27.3	6,451 Mb		
Pacient 20	M	24	Del 2q33.1-q33.2	1,596 Mb		Agilent
			Del 14q21.3-q22.1	1,928 Mb		
Pacient 21	M	4	Dup 3q26.1	4,521 Mb		Agilent
Pacient 23	M	4	Dup 14q12	3,949 Mb	613454	Agilent

Tabel 6.2 Pathogenic CNVs

Pacient	Sex	Age	Locus/Inheritance	Size [Mb]	MIM/Genes	aCGH platform
Pacient 1	F	8	Dup 6q27	0,255 Mb		Roche NimbleGen
Pacient 4	F	14	Dup 5p15.33	0,127 Mb		Roche NimbleGen
Pacient 5	M	11	Del 1q44	0,150 Mb		Roche NimbleGen
			Dup Xq28	0,117 Mb		
Pacient 6	M	10	Del 2q37.3	0,443 Mb		Roche NimbleGen
Pacient 8	M	15	Dup 17p12	1,010 Mb		
Pacient 12	M	5	Del 6p25.3	0,231 Mb		Agilent
			Del 8p23.1	0,925 Mb		
			Del 10q11.22	0,706 Mb		
Pacient 13	M	9	Dup 19p13.3	2,488 Mb		Roche NimbleGen
Pacient 14	M	10	Del 2q37.3	0,488 Mb		Roche NimbleGen
			Dup 21q22.12	0,369 Mb		
Pacient 15	F	8	Del 5q13.2	0,167		Roche NimbleGen
Pacient 22	M	40	Del2p16.3	61 kb		Agilent
Pacient 24	M	3	Del6p25.3	0,435 Mb		Agilent
			Del8p23.1	0,583 Mb		
Pacient 25	M	5	Del8p23.1	0,91 Mb		Agilent
			Del10q11.22	0,706 Mb		

Tabel 6.3 Likely pathogenic CNVs

Chapter VII. Discussions

Introduction of microarray technology among the tests used to detect the genetic substrate of global development disorder, cranio-facial dysmorphism and intellectual disability allowed detection of small changes in the genetic material - CNVs - and the precise location of the breakpoints[1,2]. This allowed the identification and description of numerous microdeletion and microduplication syndromes located in different chromosomal segments [2,3].

Use of aCGH method in this study allowed precise molecular characterization and better genotype-phenotype correlations of the identified CNVs. Our study group consisted of subjects diagnosed with global developmental disorder and / or intellectual deficiency, and in a significant percentage of cases it was possible to identify changes with certain pathogenicity located in different regions of the genome.

To determine the pathogenicity of the CNVs identified in the tested patients, we considered their type (deletion or duplication) and size, the genes contained in the affected area, the familial history of the patients and available data from the literature and international databases. Based on these criteria, the CNVs identified among the patients included in the study group were classified as pathogenic CNVs (Table 6.2), potentially pathogenic (Table 6.3), with uncertain clinical significance / unknown and CNVs unrelated with the phenotype of the patient.

CNVs were identified in 26 of 36 tested patients (72%). Regarding the identification of changes with certain pathogenicity for global developmental disorders and / or intellectual deficiency , this was possible for six of the assessed patients, which means a detection rate of approximately 17%, value that correlates with the data available in the literature. [4-6]. Within this group are five CNVs responsible for microdeletion / microduplication syndromes well known or recently identified and described.

In one of the cases examined (patient 2) we identified a microduplication in the 3q29 region. 3q29 microduplication syndrome (OMIM 611 936) was recently described by Lisi et al and is characterized by a variable phenotype that includes intellectual deficiency, developmental and speech delay, chronic esophagitis with Candida, dysmorphic features kidney, heart or palate malformations.[7-9]. This microduplication may occur de novo or can be inherited from one of the parents [7].

Comparing this case with the previously published cases, we observed that our patient has a 3q29 duplication that contains the critical region described in the literature. [7-11]. In this region are located 29 genes, including PAK2, DLG1, BDH1, FBXO45, TFRC, ZDHHC19, PIGX and RNF168.

Previous studies have shown that PAK2, DLG1, FBXO45, BDH1 and ZDHHC19 genes play an important role in the development of the central and peripheral nervous system and neuro-synaptic maturation [12,13]. In addition to these two roles, and DLG1 and PAK2 are autosomal homologous of DLG3 and PAK3 genes involved in the ethiopatogenicity of X-linked intellectual deficiency [14-16].

This is a typical case of 3q29 microduplication with severe clinical features. This case proves the importance of high resolution genetic testing in cases with severe intellectual deficiency associated with brain abnormalities and recurrent fungal infections.

In other patient with global developmental disorder , facial dysmorphism, neuromotor disorder and history of recurrent respiratory infections, we detected the presence of two duplications located on the long arm of chromosome X: arrXq27.1-q27.3 (139 283 418 -145 734 190) x3, respectively arrXq28 (153002622-153172603) x3.

In the case of our patient, the genes located in the Xq28 region affected by the duplication are: ABCD1, L1CAM, AVPR2, IDH3G, PLXNB3 and PDZD. This duplication is very close to the area where MECP2 gene is located . MECP2 mutations are responsible for 80% of Rett syndrome cases among girls and syndromic or non-syndromic intellectual deficiency associated with treatment-resistant seizures and recurrent infections responsible for premature death in male patients.[20,21].

In the literature are reported cases of X-linked intellectual deficiency associated with axial hypotonia and limb spasticity characterised through duplications of L1CAM and MECP2 genes involved in the development and functioning of the central nervous system [22]. La nivelul regiunii duplicate în cazul pacientului nostru sunt localizate șase gene, printre care și gena L1CAM, fapt care ar putea explica parțial etiopatogeneza întârzierii în dezvoltare și a tulburării neuromotorii caracterizate prin spasticitate severă a membrelor. In our case, the duplicated region contains six genes, including L1CAM, which could partly explain the ethiopatogenesis of the developmental delay and the neuromuscular disorder characterized through severe limb spasticity.

aCGH can detected genetic changes with a resolution that can not be achieved by the use of conventional techniques. Thus, it was possible to identify new genetic syndromes and elucidating the molecular mechanisms underlying the clinical syndromes that are characterized and recognized. This has greatly contributed to changing the diagnosis of many inherited and acquired genetic diseases, such as global developmental disorders, intellectual deficiency, birth defects or cancer. Thus, aCGH became the first-line diagnostic testing for these pathologies. The data obtained in this study correlate well with so far existing data and supports the utility and necessity of implementing aCGH testing for genetic diagnosis as a first option for people with global developmental disorders and / or intellectual deficiency in Romania.

Chapter VIII. Conclusions and outlook

Our study allowed identification of pathogenic or potentially pathogenic genetic changes in patients with complex phenotype, thus showing the importance of aCGH technology in clarifying the molecular substrate involved in such cases.

Thus it was possible to characterize the molecular substrate of global developmental disorders and / or intellectual deficiency in six of the patients included in this study:

- We identified the first case of 3q29 microduplication syndrome in Romania in a 34 years old patient with severe psychomotor delay, learning disabilities, behavior disorders (psychosis), impaired speech, dysphagia, recurrent fungal infections and progressive brain atrophy.

- Genetic confirmation of clinically diagnosed Williams-Beuren syndrome through identifying the presence of microdeletions in the 7q11.23 region and characterisation of the genes content: ELN, LIMK1, FZDS, WBSCR22, WBSCR27, WBSCR28, STX1A, CLDN3, CLDN4, LAT2, ABHD11 and EIF4H .

- Identification of two pathogenic duplications on the long arm of chromosome X: Xq27.1 Xq28-q27.3 in a patient with global developmental delay, severe axial hypotonia, limbs spasticity, dysmorphic features, and recurrent respiratory infections.

- Detection of 2q33.1 - q33.2 and 14q21.3 - q22.2 microdeletions in a patient with moderate intellectual deficiency, cardiac defect and dysmorphic features.

- Establishing a possible genotype-phenotype corellation in a patient with global developmental delay, dwarfism and cranio-facial dysmorphism, where aCGH evaluation identified a 4, 52 Mb microduplication in 3q26.1 region.

- Identification of a new case of 14q12 microduplication syndrome (FOXG1 gene is contained in the affected region) in a patient with global development delay, history of afebrile seizures, microcephaly and dysmorphic features.

În vederea confirmării sau infirmării acestor rezultate urmează să fie efectuate suplimentar testări moleculare țintite atât a pacienților, cât și a părinților acestora pentru stabilirea cu exactitate a genelor a căror funcție și structură au fost afectate de rearanjamentul genetic identificat și a mecanismului de producere al acestuia (de novo sau moștenit). In 12 patients we identified the presence of potentially pathogenic CNVs. To confirm these results we will perform additional molecular testing of both patients and their parents in order to determine the genes whose function and structure were affected by the identified genetic rearrangements and if they were de novo or inherited.

Also, through this study more families received a definitive diagnosis and the recurrence risk of changes identified through aCGH.

Following this study we aim to consult the literature and international databases to identify new candidate genes for the analyzed pathologies and the new emerging syndromes with low penetrance. It also intends to re-evaluate the changes identified in our group to offer our patients a clinically appropriate and fair management.

Bibliography

1. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, et al. (2010) Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 86: 749-764.
2. Nevado J, Mergener R, Palomares-Bralo M, Souza KR, Vallespin E, et al. (2014) New microdeletion and microduplication syndromes: A comprehensive review. Genet Mol Biol 37: 210-219.
3. Watson CT, Marques-Bonet T, Sharp AJ, Mefford HC (2014) The genetics of microdeletion and microduplication syndromes: an update. Annu Rev Genomics Hum Genet 15: 215-244.
4. Jaillard S, Drunat S, Bendavid C, Aboura A, Etcheverry A, et al. (2010) Identification of gene copy number variations in patients with mental retardation using array-CGH: Novel syndromes in a large French series. Eur J Med Genet 53: 66-75.
5. Ahn JW, Bint S, Bergbaum A, Mann K, Hall RP, et al. (2013) Array CGH as a first line diagnostic test in place of karyotyping for postnatal referrals - results from four years' clinical application for over 8,700 patients. Mol Cytogenet 6: 16.
6. Park SJ, Jung EH, Ryu RS, Kang HW, Ko JM, et al. (2011) Clinical implementation of whole-genome array CGH as a first-tier test in 5080 pre and postnatal cases. Mol Cytogenet 4: 12.
7. Lisi EC, Hamosh A, Doheny KF, Squibb E, Jackson B, et al. (2008) 3q29 interstitial microduplication: a new syndrome in a three-generation family. Am J Med Genet A 146a: 601-609.
8. Willatt L, Cox J, Barber J, Cabanas ED, Collins A, et al. (2005) 3q29 microdeletion syndrome: clinical and molecular characterization of a new syndrome. Am J Hum Genet 77: 154-160.
9. Ballif BC, Theisen A, Coppinger J, Gowans GC, Hersh JH, et al. (2008) Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication. Mol Cytogenet 1: 8.
10. Goobie S, Knijnenburg J, Fitzpatrick D, Sharkey FH, Lionel AC, et al. (2008) Molecular and clinical characterization of de novo and familial cases with microduplication 3q29: guidelines for copy number variation case reporting. Cytogenet Genome Res 123: 65-78.
11. Aleixandre Blanquer F, Manchon Trives I, Fornies Arnau MJ, Alcaraz Mas LA, Pico Alfonso N, et al. (2011) [3q29 microduplication syndrome]. An Pediatr (Barc) 75: 409-412.
12. Chung FZ, Sahasrabuddhe AA, Ma K, Chen X, Basrur V, et al. (2014) Fbxo45 inhibits calcium-sensitive proteolysis of N-cadherin and promotes neuronal differentiation. J Biol Chem 289: 28448-28459.
13. Phee H, Au-Yeung BB, Pryshchep O, O'Hagan KL, Fairbairn SG, et al. (2014) Pak2 is required for actin cytoskeleton remodeling, TCR signaling, and normal thymocyte development and maturation. Elife 3: e02270.
14. Fernandez-Jaen A, Castellanos Mdel C, Fernandez-Perrone AL, Fernandez-Mayoralas DM, de la Vega AG, et al. (2014) Cerebral palsy, epilepsy, and severe intellectual disability in a patient with 3q29 microduplication syndrome. Am J Med Genet A 164a: 2043-2047.
15. Dubos A, Combeau G, Bernardinelli Y, Barnier JV, Hartley O, et al. (2012) Alteration of synaptic network dynamics by the intellectual disability protein PAK3. J Neurosci 32: 519-527.
16. Tarpey P, Parnau J, Blow M, Woffendin H, Bignell G, et al. (2004) Mutations in the DLG3 gene cause nonsyndromic X-linked mental retardation. Am J Hum Genet 75: 318-324.
17. Li T, Guan J, Huang Z, Hu X, Zheng X (2014) RNF168-mediated H2A neddylation antagonizes ubiquitylation of H2A and regulates DNA damage repair. J Cell Sci 127: 2238-2248.
18. Moens LN, Falk-Sorqvist E, Asplund AC, Bernatowska E, Smith CI, et al. (2014) Diagnostics of primary immunodeficiency diseases: a sequencing capture approach. PLoS One 9: e114901.
19. Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Conley ME, et al. (2014) Primary immunodeficiency diseases: an update on the classification from the international union of immunological societies expert committee for primary immunodeficiency. Front Immunol 5: 162.
20. Friez MJ, Jones JR, Clarkson K, Lubs H, Abuelo D, et al. (2006) Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and adjacent region in Xq28. Pediatrics 118: e1687-1695.
21. Yamamoto T, Shimojima K, Shimada S, Yokochi K, Yoshitomi S, et al. (2014) Clinical impacts of genomic copy number gains at Xq28. Human Genome Variation 1.
22. Van Esch H, Bauters M, Ignatius J, Jansen M, Raynaud M, et al. (2005) Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. Am J Hum Genet 77: 442-453.

CURRICULUM VITAE

Personal Information:
Name: Streață Ioana
Date and place of birth: 25.12.1987, Craiova, Dolj
Nationality: română
E-mail: ioana.streata@yahoo.com

Education:
- 2002-2006, Colegiul Național "Nicolae Titulescu", Craiova
- 2006-2012, Faculty of Medicine, University of Medicine and Pharmacy from Craiova

Work Experience:
01.2013 - present – Medical Geneticist in training – Emergency County Hospital Craiova

Scientific Activity:
- 10.2012 – present – PhD student, University of Medicine and Pharmacy of Craiova - Faculty of Medicine, Department of Cellular and Molecular Biology.
- 04.2013 – present – Research assistent, member in the research team of the FP7 project – TANDEM (Concurrent Tuberculosis and Diabetes Mellitus; unravelling the causal link, and improving care).

Courses:
• "Molecular Cytogenetics Course", „Victor Babeş" Institute, Bucharest, May– September 2013.
• Next Generation Leaders in Biology of Ageing, Intensive Programme for Master and PhD students, Rimini, Italy, June 2014
• "Clinical Dismorphology" Course, Nowgen Center, University of Manchester, UK, 1st – 3rd April 2014
• Flow-Citometry Course, University of Medicine and Pharmacy from Iaşi, Romania, 23rd – 28th September 2013
• 29th Course in Medical Genetics, Bertinoro, Italia, 8 – 12 May, 2016 –ESHG fellowship

Publications:

- Prenatal and postnatal findings in a 10.6 Mb interstitial deletion at 10p11.22-p12.31. Sosoi S, Streata I, Tudorache S, Burada F, Siminel M, Cernea N, Ioana M, Iliescu DG, Mixich F. J Hum Genet. 2015 Apr; 60(4):183-5.
- Streata, I., Burada, F., Sosoi, S., Iliescu, D. G., Ioana, M., Cara, M., ... & Tudorache, S. (2013). Microarray-Based Prenatal Diagnosis in Developing Countries. *Global Journal of Human Genetics & Gene Therapy*, *1*(1), 8-11.
- Burada, F., Ciurea, M. E., Nicoli, R., Streata, I., Vilcea, I. D., Rogoveanu, I., & Ioana, M. (2015). ATG16L1 T300A Polymorphism is Correlated with Gastric Cancer Susceptibility. *Pathology & Oncology Research*, 1-6.
- Nicoli, E. R., Dumitrescu, Th., Uscatu, C. D., Popescu, F. D., Streata, I., Serban Sosoi, S.,& Lungulescu, D. (2014). Determination of autophagy gene ATG16L1 polymorphism in human colorectal cancer. *Rom J Morphol Embryol*, *55*(1), 57-62
- Cucu, M. G., Riza, A. L., Cimpoeru, A. L., Streață, I., Sosoi, S. S., Ciontea, M. S., ... & Mixich, F. Implication of TLR2 polymorphism in pulmonary tuberculosis.
- Stefan, E., Streata, I., Gherghina, F., Cimpoeru, A., Cucu, M., Petrescu, F., ... & Burada, F. (2013). IL-1B-511C> T polymorphism is not correlated with osteoarthritis susceptibility. *Annals of the Romanian Society for Cell Biology*, *18*(1), 182.
- Nicoli, E. R., Ivanov, P., Cucu, M. G., Al Eisa, N., Dumitrescu, T., Serban Sosoi,S., Cimpoeru, A., Streata, I., & Popescu, F. (2013). Experimental animal models for intestinal inflammation. Current Health science journal vol. 39, suppl. 5, 12-15.
- Ivanov P., Nicoli E-R., Lungulescu D., Streață I., Cucu M. G., Dumitrescu T., Smarandache C. & Popescu F. (2013). Pharmacogenetics of chemotherapic agents in colorectal cancer, Current Health Science Journal.
- Cimpoeru A., Streață I., Cucu M., Nicoli E. R., Șerban -Șoșoi S., Marchian S., Verdeș D. & Cruce M. (2013). Polymorphisms in Cytokines and Toll-Like Receptor Genes and Susceptibility to Tuberculosis. Current Health Science Journal.
- C.D. Uscatu, Elena-Raluca Nicoli, T. Dumitrescu, Ioana Streață, Simona Serban-Sosoi, M. Cucu, A. Barbalan, I. Munteanu, Amelia Dobrescu, F. Mixich (2014). Autophagy and colorectal cancer, Current Health science journal vol. 40, suppl. 1, 13-19
- M. Georgescu, D. Enescu-Bieru, D. Georgescu, C. Bogdan, V. Sfredel, I.(O.) Streata, V. Nestianu, M. Iancau (2011). Using the edge frequency index of the cerebral frequencies spectrum in evaluating the development of skills; CLIN NEUROPHYSIOL 01/2011; 122. DOI:10.1016/S1388-2457(11)60579-8

Trainings:

- Stagiu de pregătire în Genetică Clinică și Imunogenetică - Department of Human Genetics, Radboud University Medical Nijmegen Center, Nijmegen, The Netherlands, 15 Iunie – 15 Septembrie 2015, Coordonatori: Wendy van Zelst-Stams, M.D., Coordinator of Clinical Genetics Department, Alexander Hoischen, PhD, Assistant Professor Developmental Genomics & Genomic Disorders, M. G. Netea, M. D. Professor of Experimental Medicine
- Stagiu de cercetare în Imunologie– Department of Immunology, Max Planck Institute for Infection Biology, Berlin, Germania, 7 January -8 Mai 2015, Coordonatori: Stefan H.E. Kaufmann, Professor for Microbiology and Immunology - Charité University Clinics Berlin, Managing Director Department of Immunology, Max Planck Institute for Infection Biology, Dr. Anca Dorhoi, Minerva Group Leader, Max Planck Institute for Infection Biology Department of Immunology