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Molekularna dijagnostika genetičkih bolesti i Europska mreža za kvalitetu molekularne dijagnostike

Jadranka Sertić, Hana Ljubić, Ana Merkler

HAZU, Odbor za primjenjenu genomiku, 16.listopada 2017.
Molekularna genetika – novosti u dijagnostici i terapiji



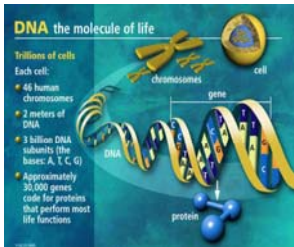
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Molekula života – DNA Humani genom



Molecular Diagnostics



DNA the molecule of life

Trillions of cells
Each cell:
• 46 human chromosomes
• 2 meters of DNA
• 3 billion DNA subunits (the bases: A, T, C, G)
• Approximately 30,000 genes code for proteins that perform most life functions

Francis Collins, 2003.

<https://www.slideshare.net/nirmalajosephine1/biology-form-5-chapter-5-53-a-dna>



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***We now know how God
wrote the book of life***



***But do we know
how to read the book ?***

Bill Clinton 2003.

<https://deista.wordpress.com/2012/03/13/deismo-y-division-deista/>



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**Precizna medicina –
nacionalni prioritet**



President Obama, 2015.

<https://www.nih.gov/allofus-research-program/precision-medicine-initiative-storify-collection>

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100,000 British Genomes

A new initiative lead by the UK's National Health Service aims to sequence the genomes of as many as 100,000 patients, a project that will cost £100 million.

David Cameron, 2012.

<https://citas.in/autores/david-cameron/o=new>

“The UK will sequence 100,000 genomes from patients with cancer or rare disease”

The aims are to:

- *improve diagnosis of patients with rare disease*
- *increase understanding of tumour variants that predict therapeutic response to targeted cancer drugs*
- *accelerate uptake of genomic medicine in the NHS*
- *stimulate and enhance UK industry and investment in genomics*

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DNA sekvenciranje

gel-P₃₂

tisuću bp / dan

kapilarna elektroforeza

milijun bp / dan

**sekvenciranje
sljedeće generacije**

bilijun bp / dan

➤ **Hibridizacijske tehnike**



The screenshot shows the EuroGentest website, titled "Harmonizing genetic testing across Europe". The website features a navigation menu with links to Home, Contact us, Help, Search, Username, Password, Log on, Save, Register, and Forgotten Password. The main content area displays the EuroGentest logo and the text "Harmonizing genetic testing across Europe".

<https://eurogentest.org/>



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Croatia

Legal and regulatory background
In Croatia molecular genetic testing is regulated by national legislation. The legislation covers laboratory medicine in general, however there are no national guidelines or recommendations for MGT. Guidelines from EMQN are recommended.

Licensing, certification, accreditation
A licence is required to operate a MGT laboratory. Certification and accreditation are not mandatory.

Availability of EQA
Participation in EQA is not required by national legislation/guidelines.
There is no national EQA provider for MGT in Croatia.

<https://www.eurogentest.org>





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1991. molekularna dijagnostika u Hrvatskoj

Cistična fibroza – monogenska bolest



Zergollern Lj, Stavljenić-Rukavina A, Barišić I, Sertić J.
F508 deletion in Croatian cystic fibrosis patients.
Acta Med Croat 1992;46:181-184.

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WHO: The Molecular Genetic Epidemiology of Cystic Fibrosis

[Dequeker F, Cuppens H, Dodge J, Estivill X, Goossens M, Pignatti PF, et al. Recommendations for quality improvement in genetic testing for cystic fibrosis. European Concerted Action on Cystic Fibrosis. Eur J Hum Genet.2000;8:2-24.](#)

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WHO - Pojavnost CFTR mutacija

Table 1 Mutations found at a frequency higher than 1% in Europe⁵⁻⁷

Country	Mutations
Albania	ΔF508 (70.0)
Austria	ΔF508 (63.7) G542X (2.1) R1162X (1.9) G512D (1.1)
Belarus	ΔF508 (63.0) N1303K (2.7) G542X (2.1) W1282X (1.7)
Belgium	ΔF508 (71.5) N1303K (2.9) G542X (2.7) W1282X (1.5) S1251N (1.3) 1717-1G-A (1.1)
Belgium	ΔF508 (61.0) N1303K (4.0) G542X (3.6) R347P (2.0) 1677delTA (2.0) R1070Q (1.5)
Croatia	ΔF508 (84.5) N1303K (3.6) G542X (3.3) G512D (1.1)
Cyprus	ΔF508 (46.7) L384P (16.7) 1677delTA (6.7)
Czechia	ΔF508 (71.6) G512D (4.0) N1303K (3.0) G542X (2.2) 1898+1G-A (2.0) Z143delT (1.2) CTRRdel2,321del (0.6)
Denmark	ΔF508 (87.2) 394delTT (1.9) N1303K (1.0)
Estonia	ΔF508 (54.0) 394delTT (13.0)
Finland	ΔF508 (66.2) 394delTT (28.0)
France	ΔF508 (66.8) G542X (1.1) 1717-1G-A (1.6) N1303K (1.4) N1303K (1.2) G542X (1.2) 3849+10delC-T (1.2) CTRRdel2,321del (1.3)
Germany	ΔF508 (73.2) R553X (2.7) R347P (1.3) G512D (1.3) N1303K (1.2) G542X (1.2) 2789+5G-A (1.8) 3849+10delC-T (1.2) CTRRdel2,321del (1.3)
Greece	ΔF508 (52.2) R511+1G-T (4.5) G542X (3.0) N1303K (3.3) Z183delA-G (1.8) 2789+5G-A (1.8) R522X (1.4) R117H (1.2) R344V (1.2) 3272-2delA-G (1.0) R1158R (1.0) G85E (1.0)
Hungary	ΔF508 (54.7) G542X (2.2) N1303K (1.0)
Ireland	ΔF508 (72.7) G512D (6.9) R117H (2.0) G542X (1.0)
Israel	ΔF508 (32.2) W1282X (36.2) G542X (5.6) 3849+10delC-T (4.0) 405+1G-A (3.0) N1303K (3.0) Q1559K-T380K (1.9) S549R (1.1)
Italy	ΔF508 (51.1) G542X (4.8) N1303K (4.0) Z183delA-G (2.7) R1162X (2.4) 1717-1G-A (2.1) W1282X (1.2) R553X (1.2)
Lithuania	ΔF508 (54.2) 3849+10delC-T (12.5) N1303K (8.3) W1282X (4.2)
Lithuania	ΔF508 (26.7) R523K (4.0) N1303K (2.4)
Macedonia	ΔF508 (56.0) G542X (1.3) N1303K (2.6) 621-1G-T (1.9) 3849+10delC-T (1.9) 4577G>C (1.3) V1397E (1.3) S549R (1.4) S549I (1.4) G512D (1.4) 5943I (1.4)
North Africa	ΔF508 (32.0) N1303K (10.2) W1282X (8.2) 711+1G-T (7.5) G542X (4.0) R1162X (2.7) L227R (1.4) S549R (1.4)
Northern Ireland	ΔF508 (88.0) G512D (5.1) R117H (4.1) R560T (2.9) G542X (2.2) 621+1 G-T (2.2) d507 (1.7)
Norway	ΔF508 (66.7) 394delTT (4.2) R117H (3.0) G512D (1.2)
Poland	ΔF508 (2.9) 3849+10delC-T (2.6) G542X (2.5) N1303K (1.7) 1717-1G-A (1.7) R553X (1.0) CTRRdel2,321del (2.0)
Portugal	ΔF508 (52.3) R1066C (3.3) G542X (2.3) R334W (2.0) A561I (2.0) 3272-2delA-G (1.5) N1303K (1.5)
Romania	ΔF508 (77.0) N1303K (1.6) 1677delTA (1.6) Z143delT (1.0) CTRRdel2,321del (7.5)
Russia F	ΔF508 (45.0) W1282X (2.1) 2143delT (2.0) Z184delA (2.0) W1282X (2.0) G542X (1.8) 3849+10delC-T (1.8) CTRRdel2,321del (0.4)
Russia M	ΔF508 (54.3) N1303K (2.8) R523X (2.4) N1303K (3.0) R347P (1.7) CTRRdel2,321del (4.0)
Slovakia	ΔF508 (59.4) G542X (5.4) N1303K (2.3) 1811+1 delA-G (1.5) R1162X (1.3) 712-1G-T (1.1) 1699delA (1.0)
Spain	ΔF508 (54.4) G542X (7.7) 3696delC (1.0) 175delT (2.4) T338I (1.2)
Sweden	ΔF508 (71.3) 394delTT (9.7) 3965delT (4.7) G542X (3.0) 1717-1G-A (2.1) K3120R (2.1)
Switzerland	ΔF508 (40.2) R523X (24.2) 3965delT (14.7) G542X (3.0) 1717-1G-A (2.1)
The Netherlands	ΔF508 (74.4) A455E (5.3) 1717-1G-A (1.5) G542X (1.3) R553X (1.2) R347H (2.8) G542X (2.8) K68N (1.4) 2043delG (1.4) Z183delA-G (1.4) 2789+5G-A (1.4)
Turkey	ΔF508 (48.0) N1303K (6.4) 1677delTA (2.8) E92X (2.8)
Ukraine	ΔF508 (50.0) G542X (1.7)
United Kingdom	ΔF508 (75.3) G512D (3.1)
Yugoslavia	ΔF508 (86.3) G542X (3.3)

Sources: Dethlefsen C., Dörk T., Graham C., Maclell M. Jr., Pacheco P. (Personal communication, January 1999).

Recommendations for quality improvement
in Diagnostic and/or

6

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KBC Zagreb, KZLD-LBL

Molekularna dijagnostika genetičkih bolesti

Genetičke bolesti

Azoospermija (mikrodelecije kromosoma Y - AZF)
Charcot-Marie-Tooth tip CMT1B - (sekvenciranje *MPZ*)
Charcot-Marie-Tooth tip CMTX1 (sekvenciranje *GJB1*)
Cistična fibroza CF (*CFTR*)
Deficit alfa-1-antitripsina (*SERPINA1*)
Friedrichova ataksija FA (*FXN*)
Gilbertov sindrom (*UGT1A1*)
Huntingtonova koreja HD (*HTT*)
Miotonična distrofija tipa 1 MD1 (*DMPK*)
Miotonična distrofija tipa 2 MD2 (*CNBP*)
Mišićna distrofija DMD/BMD (*DMD*)
Monogeni diabetes MODY (sekvenciranje *HNF1A*, *HNF4A* i *GCK*)
Multipla endokrina neoplazija - MEN1 (sekvenciranje *MEN1*)
Multipla endokrina neoplazija - MEN2 (sekvenciranje *RET*)
Nasljedna hemokromatoza (*HFE*)
Nasljedne neuropatije CMT/HNPP (*PMP22*)
Neutropenija (sekvenciranje *ELANE* i *HAX1*)
Shwachman-Diamondov sindrom (sekvenciranje *SBDS*)
Sindrom fragilnog kromosoma X FRAX (*FMR1*)
Spinalna mišićna atrofija SMA (*SMN1*, *SMN2*, *NAIP*)
Spinocerebelarne ataksije SCA tipa 1, 2, 3, 6 i 7 (*ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*)
Wilsonova bolest WB (sekvenciranje *ATP7B*)
X-vezana agamaglobulinemija (sekvenciranje *BTK*)
X-vezani hiper-IgM sindrom (sekvenciranje *CD40LG*)
X-vezani limfoproliferativni sindrom (sekvenciranje *SH2D1A*)

Rizični čimbenici

ACE - angiotenzin-konvertirajući enzim
ADPN - adiponektin
APOB - apolipoprotein B
APOE - apolipoprotein E
GPIa - glikoprotein Ia
HP - haptoglobin
IL-6 - interleukin-6
LPL - lipoprotein-lipaza
MTHFR - metilentetrahidrofolat-reduktaza
PPAR - receptori za aktivator proliferacije peroksosoma

Mitohondrijske bolesti

MELAS (*MT-TL1*)
MERRF (*MT-TK*)
NARP (*MT-ATP6*)

☐ Prof.dr.sc. Jadranka Sertić, spec.med.biokem.
☐ Dr.sc. Hana Ljubić, mag.biol.
☐ Dr.sc. Ana Merkler, mag.ing.bioproc.inž

☐ Domagoj Caban, mag.med.lab.diagn.
☐ Senka Škaro, bacc.med.lab.diagn.
☐ Ana Acman Barišić, bacc.med.lab.diagn.
☐ Karolina Petrović, zdrav.lab. tehničar

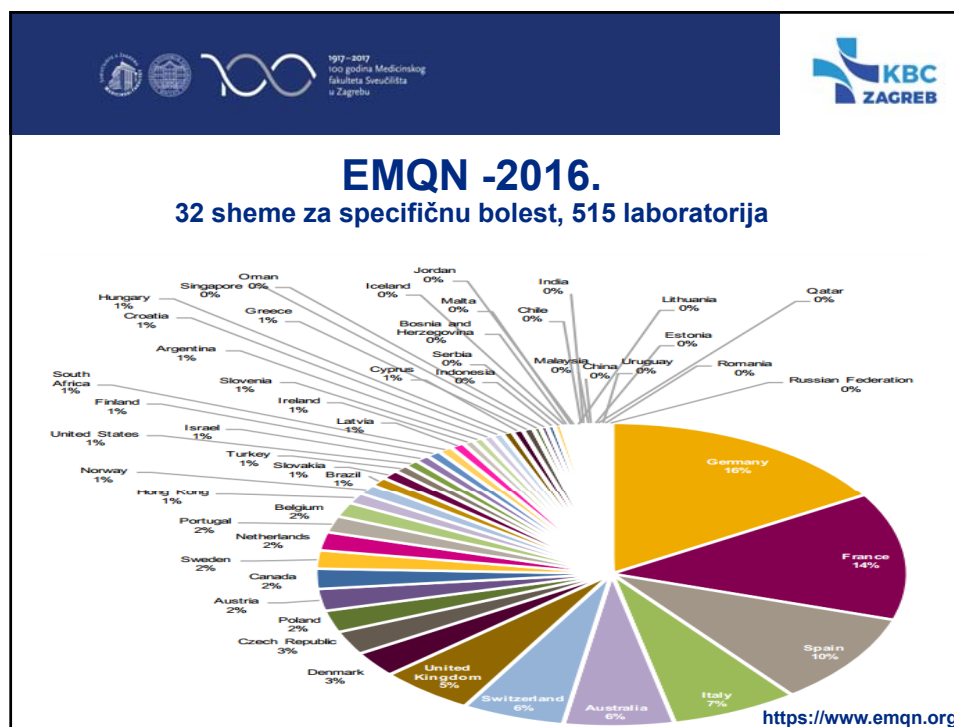
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Molekularna dijagnostika - vanjska procjena kvalitete

The European Molecular Genetics Quality Network

Referenzinstitut für Bioanalytik

<https://www.instand-ev.de/en.html>
<https://www.rfb.bio/cgi/switchLang?lang=en>
<https://www.emqn.org/>



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KBC ZAGREB

CF Network

KBC Zagreb: 1998. -

Country	Number of laboratories that participated in the scheme in			Country	Number of laboratories that participated in the scheme in		
	2014	2015	2016		2014	2015	2016
Australia	11	11	14	The Netherlands	8	8	7
Austria	3	5	4	New Zealand	1	1	2
Belgium	10	8	8	Norway	1	2	2
Croatia	2	2	1	Oman	0	0	1
Cyprus	1	1	1	Poland	6	5	6
Czech Republic	3	3	3	Portugal	2	2	3
Denmark	3	3	3	Serbia	1	1	1
Estonia	1	1	0	Slovakia	1	1	1
Finland	1	0	0	Slovenia	2	2	2
France	33	30	32	South Africa	0	1	2
Germany	47	40	34	Spain	15	15	14
Greece	5	5	4	Sweden	3	3	2
Hungary	4	3	4	Switzerland	15	15	15
Ireland	1	1	1	Tunisia	1	0	0
Israel	0	1	0	Turkey	0	0	3
Italy	26	20	21	Ukraine	1	1	0
Jordan	0	0	1	United Kingdom	2	2	2
Latvia	1	1	1	United States	2	1	2
Lithuania	1	0	0	Uruguay	0	1	1
Macedonia	1	0	1	TOTAL	215	198	199

www.emqn.org/



Ocjenitelji - EMQN za shemu Huntingtonova bolest

Osoba	Država	Funkcija
Peter Bauer	Njemačka	Organizator sheme
Monique Losekoot	Nizozemska	Ocjenitelj
Anniek Corveleyn	Belgija	Ocjenitelj
Sara Seneca	Belgija	Ocjenitelj
Hana Ljubić	Hrvatska	Ocjenitelj

Losekoot M, van Belzen MJ, Seneca S, Bauer P, Stenhouse SA, Barton DE., European Molecular Genetic Quality Network (EMQN).
EMQN/CMGS best practice guidelines for the molecular genetic testing of Huntington disease.
Eur J Hum Genet. 2013;21(5):480-6.



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Ocjenitelji - EMQN za shemu Miotonična distrofija tip 1

Osoba	Država	Funkcija
Morten Duno	Danska	Organizator sheme
Erik Jan Kamsteeg	Nizozemska	Ocjenitelj
Ana Merkler	Hrvatska	Ocjenitelj

Kamsteeg EJ, et al.
Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2.
Eur J Hum Genet. 2012;20(12):1203-8.



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TREAT-NMD
Neuromuscular Network

www.treat-nmd.eu

**Međunarodni registar bolesnika
s neuromuskularnim bolestima**

Hrvatska

DMD 47

BMD 18

SMA 48

Nina Barišić. KBC Zagreb



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Merkler A, Kelecic J, Tjesic-Drinkovic D, Baric I, Vukovic J, Sarnavka V. et al.
Molecular Diagnostics of Severe Congenital Neutropenia and Shwachman-Diamond Syndrome in Seven Croatian Families.
J Clin Immunol. 2014;34 (Suppl 2):363.

Merkler A, Richter D, Kelecic J, Ljubic H, Caban D, Sertic J.
Genetic basis of primary immunodeficiencies in Croatian patients.
Eur J Hum Genet. 2013;21 (Suppl 2): 237.

Nove mutacije utvrđene u genima za primarne imunodeficijencije

BTK
 c.1349+1G>C
 c.831_839+2delAATGTATGAGT
 c.974+4A>G

ELANE
 c.213C>G, p.Cys71Trp

HAX1
 c.737A>C, p.Asp246Ala



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Ljubić H, Kalauz M, Telarović S, Ferenci P, Ostojić R, Noli MC, Lepori MB, Hrštic I,
 Vuković J, Premužić M, Radić D, Grubelić Ravić K, Sertić J, Merkler A, Acman
 Barišić A, Loudianos G, Vucelić B.
ATP7B Gene Mutations in Croatian Patients with Wilson Disease.
Genetic Testing and Molecular Biomarkers. 2016;20:112-7.

Nove mutacije utvrđene u genu ATP7B

c.3079G>A, p.Asp1027Asn
 c.3088G>A, p.Gly1030Ser
 c.4295C>T, p.Ser1432Phe



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Ana Merkler

Genske mutacije u nasljednim demijelinizirajućim polineuropatijama Charcot-Marie-Tooth tipa 1 u stanovništvu Republike Hrvatske.

**Doktorski rad, 2017. Zagreb: Sveučilište u Zagrebu
Prirodoslovno-matematički fakultet.**

Nove mutacije utvrđene u genima za nasljedne neuropatije

PMP22

c.2T>C, p.Met1Thr
c.59_64delTCGTCT, p.Phe20_Val21del

GJB1

c.86T>C, p.Phe29Ser
c.422T>C, p.Phe141Ser
c.529G>A, p.Val177Met



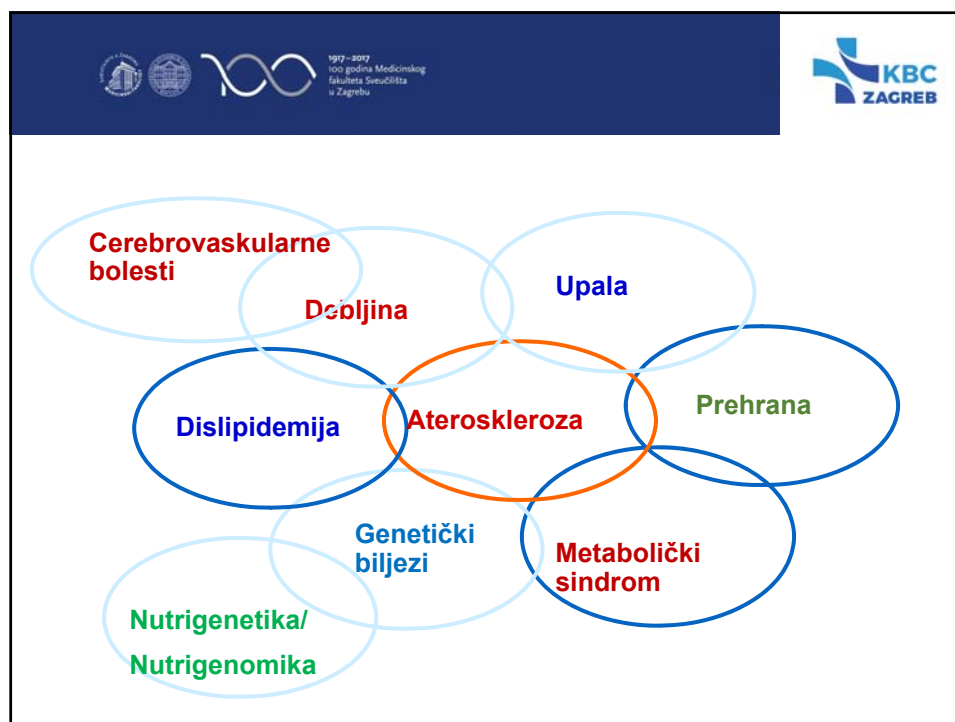
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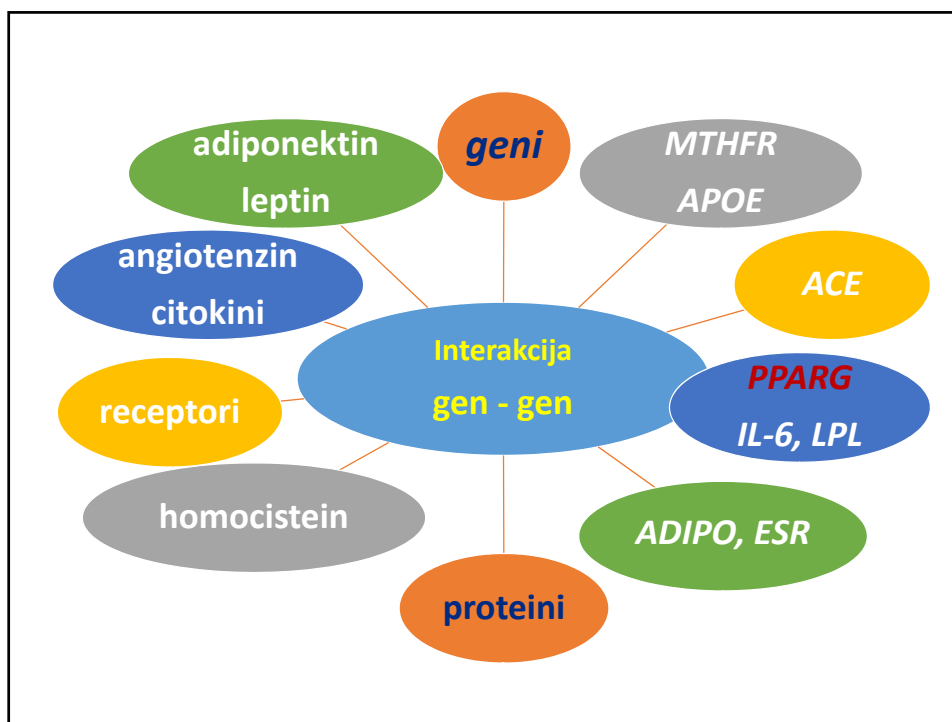


Multifaktorske bolesti / genetička heterogenost

- **Funkcijska genomika i proteomika rizičnih
čimbenika ateroskleroze**
- **Uloga genskih i biokemijskih biljega u razvoju
ateroskleroze i cerebrovaskularnog inzulta**
- **Uloga genskih i biokemijskih biljega u razvoju
monogenetskog dijabetesa**

Ateroskleroza: koncept atero-upale *“počima u djetinjstvu”*





BMC Res Notes, 2009 Oct 5;2:203. doi: 10.1186/1756-0500-2-203.

Variants of ESR1, APOE, LPL and IL-6 loci in young healthy subjects: association with lipid status and obesity.

Sertić J¹, Jurčić L, Ljubić H, Božina T, Lovrić J, Markeljević J, Jelaković B, Merkler M, Reiner Z

Author information

¹ Clinical Institute of Laboratory Diagnosis, Zagreb University Hospital Centre, Zagreb, Croatia. jadranka.sertic@kbc-zagreb.hr

Abstract

FINDINGS: BMI was increased (>25) in 22% of young healthy subjects. Increased cholesterol values (>5.0 mmol/L) were found in 23% of subjects, LDL-C (>3.0 mmol/L) in 23%, triglycerides (>1.7 mmol/L) in 11% of subjects. We found statistically significant differences in subjects' weight ($p = 0.015$), BMI ($p = 0.023$), and waist-hip ratio (WHR) ($p = 0.015$) in regard to their diet type; subjects with Mediterranean diet had the lowest values compared to those on continental and mixed diet. Significant associations were found for: LPL genetic polymorphic variant and abdominal obesity ($p = 0.013$), APO epsilon4 allele and hypercholesterolemia ($p = 0.003$), and ESR1-TA long allele and hypercholesterolemia ($p = 0.011$).

BACKGROUND: Human obesity is a multifactorial syndrome influenced also by genetic factors. Among gene variants found to be involved in body weight regulation and development of obesity, particular attention has been paid to polymorphisms in genes associated with obesity-related metabolic disorders. We explored the association of genetic polymorphisms of: estrogen receptor alpha (ESR1-TA repeats); interleukin-6 (IL-6 G-174C); apolipoprotein E (APO epsilon2, epsilon3, epsilon4); lipoprotein lipase Pvu II (LPL P+/-), with clinical variables: gender, age, body mass index (BMI), diet type and biological variables: triglycerides, cholesterol, HDL-C, LDL-C, CRP, homocysteine, urate, and glucose in 105 healthy young subjects (20-35 yrs) of Croatian origin.

METHODS: Genotyping of IL-6, LPL was performed by PCR-RFLP, of APOE by real-time PCR, and of ESR1 by PCR and capillary electrophoresis. Association analyses were performed of alleles and genotypes with biological variables.

CONCLUSION: ESR-1, LPL, and APO E genetic polymorphic variants could represent predictive genetic risk markers for obesity-related metabolic disorders in young healthy subjects. Mediterranean type of diet is also an important protective factor against abdominal obesity.

PMID: 19804633 PMCID: PMC2765961 DOI: 10.1186/1756-0500-2-203

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Geni i okoliš: redoslijed po važnosti??

"Geni pune revolver, no okoliš povlači okidač."

Elliot P. Joslin,

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Genet Test Mol Biomarkers, 2014 Jan;18(1):32-40. doi: 10.1089/gtmb.2013.0344. Epub 2013 Nov 7.

Interaction of genetic risk factors confers increased risk for metabolic syndrome: the role of peroxisome proliferator-activated receptor γ .

Božina T¹, Sertić J, Lovrić J, Jelaković B, Šimić J, Reiner Ž.

✉ Author information

1 1 Department of Medical Chemistry, Biochemistry and Clinical Chemistry, University of Zagreb School of Medicine, Zagreb, Croatia.

Abstract

AIM: The aim of the study was to estimate the influence of interactions between peroxisome proliferator-activated receptor γ (PPAR γ) and target genes lipoprotein lipase (LPL), interleukin 6 (IL6), angiotensin converting enzyme (ACE), and angiotensin II type 1 receptor (AT1R) on metabolic syndrome (MetSy) and its traits.

METHODS: The study included 527 participants (263 with MetSy and 264 controls). Genotyping of PPAR γ Pro12Ala, LPL PvuII (-/+), IL6 -174G>C, ACE I/D and AT1R 1166A>C was performed using polymerase chain reaction-restriction fragment length polymorphism-based methods.

RESULTS: Interaction between PPAR γ Pro12Ala and LPL Pvu(-/+) improved prediction of MetSy over and above prediction based on a model containing no interactions ($\chi^2=7.22$; df=1; p=0.007). In the group of participants with PPAR γ Pro12Ala or Ala12Ala genotypes, those with the LPL Pvu (-/+) or (+/+) genotype had greater odds for MetSy (odds ratio OR=5.98; 95% confidence interval CI: 1.46-24.47, p=0.013). Interaction between PPAR γ Pro12Ala and IL6 -174G>C improved prediction of high fasting blood glucose ($\chi^2=13.99$; df=1; p<0.001). PPAR γ Ala12 variant was found protective in patients with IL6 -174GG genotype (OR=0.10; 95% CI: 0.02-0.57, p=0.01), while in the case of IL6 -174C allele carriers, for PPAR γ Ala12 carriers, larger odds for high glucose levels compared with Pro12 variant were observed (OR=2.39; 95% CI: 1.11-5.17, p=0.026). Interactions of PPAR γ and ACE were significant for BMI. In the group with ACE DD genotype, those with PPAR γ Pro12Ala or Ala12Ala genotype have greater odds for obesity (OR=9.98; 95% CI: 1.18-84.14, p=0.034).

CONCLUSIONS: PPAR γ gene variants can, in interaction with some of its target genes, modulate physiological processes leading to the development of MetSy.

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PPAR γ and IL-6 -174G>C gene variants in Croatian patients with ischemic stroke.

Bazina A¹, Sertić J², Mišmaš A³, Lovrić T⁴, Poljaković Z⁵, Milčić D⁶.

Author information

- 1 University Hospital Centre Zagreb, Department of Neurology, Neurological Intensive Care Unit, Zagreb, Croatia. Electronic address: antonelabazina@gmail.com.
- 2 University of Zagreb School of Medicine, Zagreb, Croatia; University Hospital Centre Zagreb, Department of Laboratory Diagnosis, Clinical Unit of Molecular Diagnosis, Zagreb, Croatia. Electronic address: jadranka.sertic@kbc-zagreb.hr.
- 3 University Hospital Centre Zagreb, Department of Neurology, Neurological Intensive Care Unit, Zagreb, Croatia. Electronic address: antonija.mismas@gmail.com.
- 4 University of Zagreb School of Medicine, Zagreb, Croatia. Electronic address: tena.lovric@vip.hr.
- 5 University Hospital Centre Zagreb, Department of Neurology, Neurological Intensive Care Unit, Zagreb, Croatia; University of Zagreb School of Medicine, Zagreb, Croatia. Electronic address: zdravka.po@gmail.com.
- 6 University of Zagreb School of Medicine, Zagreb, Croatia; University Hospital Centre Zagreb, Clinic for Cardiovascular Diseases, Zagreb, Croatia. Electronic address: davor.milicic@mef.hr.

Abstract

AIM: Etiology of ischemic stroke (IS) is multifactorial and includes interaction of genetic and environmental factors. Different genes, their polymorphisms, host susceptibility, and inflammation processes play a role in IS development. The aim of this study was to evaluate the effect of PPAR- γ and IL-6 gene variants on IS onset.

MATERIAL AND METHODS: A total of 301 subjects (144 males, 157 females) participated in the study, 114 patients with IS and 187 healthy controls.

RESULTS: Statistically significant predictors of IS were male gender (OR 7.13, 95% CI 2.92–17.39, $p < 0.001$), hypertension (OR 7.82, 95% CI 2.53–24.19, $p < 0.001$), lowered HDL cholesterol (OR 8.20, 95% CI 2.41–27.94, $p = 0.001$), elevated C-reactive protein (OR 5.26, 95% CI 1.92–14.41) and IL-6 -174 GC (OR 2.44 95% CI 1.01–5.91, $p = 0.0048$) genotype. Males, compared to females, had 7 times higher odds for stroke. IL6 -174G/C genotype increased the odds for IS for 2.4 times. PPAR γ was not statistically significantly associated with stroke.

CONCLUSION: We can point to the IL-6 -174G>C polymorphisms as candidate gene marker and risk factor for the prediction of ischemic stroke.

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KBC Zagreb, KZLD-LBL

Molekularna dijagnostika genetičkih bolesti

Genetičke bolesti

Azoospermija (mikrodelecije kromosoma Y - AZF)
Charcot-Marie-Tooth tip CMT1B - (sekvenciranje MP2)
Charcot-Marie-Tooth tip CMT1X (sekvenciranje GJB1)
Cistična fibroza CF (CFTF)
Deficit alfa-1-antitripsina (SERPINA1)
Friedrichova ataksija FA (FXN)
Gilbertov sindrom (UGT1A1)
Huntingtonova koreja HD (HTT)
Miotonična distrofija tipa 1 MD1 (DMPK)
Miotonična distrofija tipa 2 MD2 (CNBP)
Mišićna distrofija DMD/BMD (DMD)
Monogenični dijabetes MODY (sekvenciranje HNF1A, HNF4A i GCK)
Multipla endokrina neoplazija - MEN1 (sekvenciranje MEN1)
Multipla endokrina neoplazija - MEN2 (sekvenciranje RET)
Nasljedna hemokromatoza (HFE)
Nasljedne neuropatije CMT/HNPP (PMP22)
Neutropenija (sekvenciranje ELANE i HAX1)
Shwachman-Diamondov sindrom (sekvenciranje SBD5)
Sindrom fragilnog kromosoma X FRAX (FMR1)
Spinalna mišićna atrofija SMA (SMN1, SMN2, NAIP)
Spinocerebelarne ataksije SCA tipa 1, 2, 3, 6 i 7 (ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7)
Wilsonova bolest WB (sekvenciranje ATP7B)
X-vezana agamaglobulinemija (sekvenciranje BTK)
X-vezani hiper-IgM sindrom (sekvenciranje CD40LG)
X-vezani limfoproliferativni sindrom (sekvenciranje SH2D1A)

Rizični čimbenici

ACE - angiotenzin-konvertirajući enzim
ADPN - adiponektin
APOB - apolipoprotein B
APOE - apolipoprotein E
GPIa - glikoprotein Ia
HP - haptoglobin
IL-6 - interleukin-6
LPL - lipoprotein-lipaza
MTHFR - metilentetrahidrofolat-reduktaza
PPAR - receptori za aktivator proliferacije peroksizoma

Mitohondrijske bolesti

MELAS (MT-TL1)
MERRF (MT-TK)
NARP (MT-ATP6)

Prof.dr.sc. Jadranka Sertić, spec.med.biokem.
Dr.sc. Hana Ljubić, mag.biol.
Dr.sc. Ana Merkler, mag.ing.bioproc.inž

Domagoj Caban, mag.med.lab.diagn.
Senka Škaro, bacc.med.lab.diagn.
Ana Acman Barišić, bacc.med.lab.diagn.
Karolina Petrović, zdrav.lab. tehničar



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Genski biljezi - rizični čimbenici

- ApoE
- ApoB
- MTHFR
- HFE
- ATP7B
- A1AT

- ACE
- UGT
- IL6
-

www.rfb.bio/cgi/switchLang?lang=en



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Molekularna dijagnostika



Medicinska naklada

[https://www.medicinska naklada.hr](https://www.medicinska-naklada.hr)

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Precizna dijagnostika - ciljana terapija

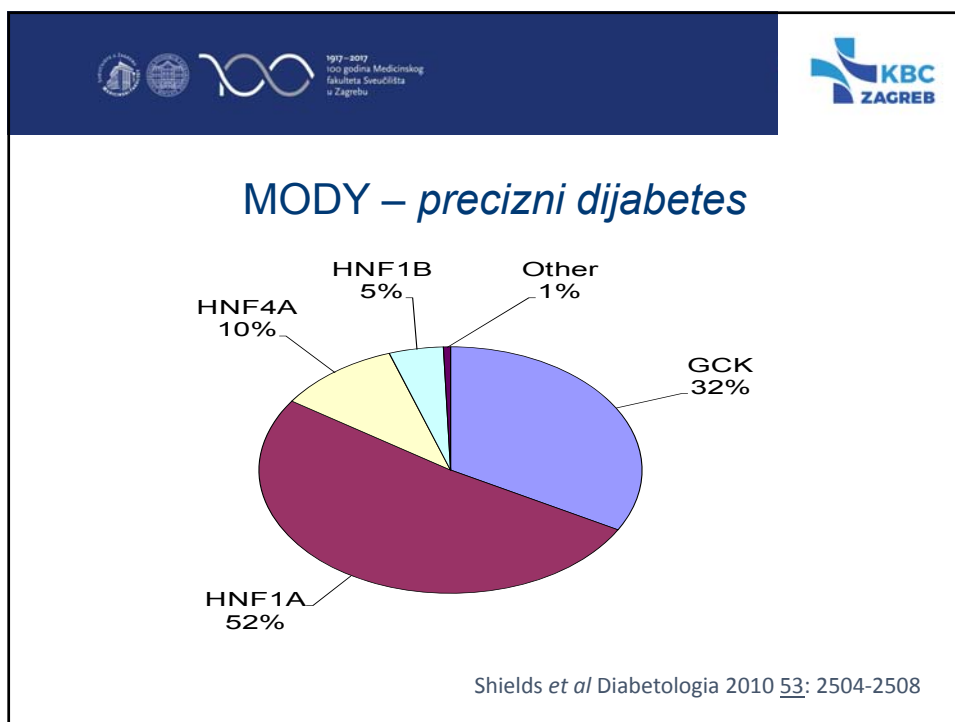
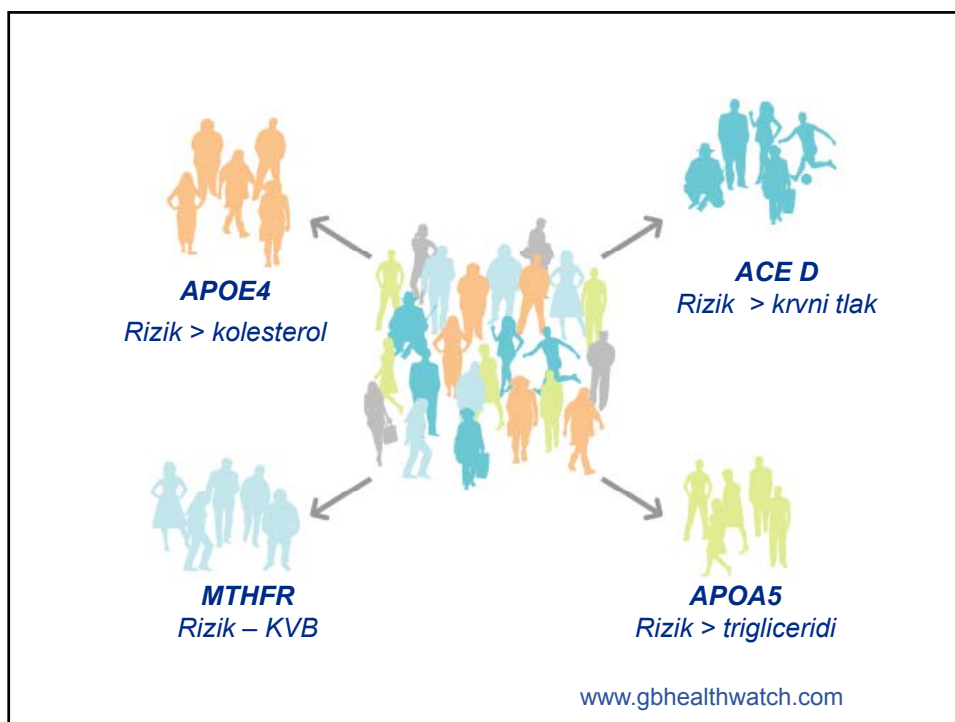
➤ Cistična fibroza – <i>oligonukleotidi</i>
➤ Spinalna mišićna atrofija – <i>oligonukleotidi / neuroprotekcija</i>
➤ Multipla endokrina neoplazija tipa 2 – <i>tireoidektomija</i>
➤ Monogeniski dijabetes (precizni dijabetes) – <i>inzulin/sulfonilurea</i>
➤ MTHFR – folna kiselina
➤ Mikrodelecije kromosoma – <i>IVF</i>

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Nutrigenetika /-omics *personalizirana prehrana*

Interakcija gen – prehrana

- *ApoE*
- *APOA5*
- *ACE*
- *MTHFR*
- *IL-6*



Molekularna genetika – novosti u dijagnostici i terapiji



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Poruke za budućnost

- interdisciplinarnost
- analitička konsolidacija
- neinvazivno uzorkovanje
- pohranjivanje podataka, IT
- edukacija pacijenata
- nanotehnologije



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Hvala za pozornost!

Prof.dr.sc. Jadranka Sertić

Klinički bolnički centar Zagreb
Klinički zavod za laboratorijsku dijagnostiku

Medicinski fakultet Sveučilišta u Zagrebu
Katedra za medicinsku kemiju, biokemiju i kliničku kemiju

jadranka.sertic@kbc-zagreb.hr