

First *IKBKG* Gene Mutation Study in Serbian Incontinentia Pigmenti Patients

Snežana Minić^{1,2}, Dušan Trpinac³, Heinz Gabriel⁴, Martin Gencik⁴, Miljana Obradović³

¹Clinics of Dermatovenerology, Clinical Center of Serbia, Belgrade, Serbia;

²School of Medicine, University of Belgrade, Belgrade, Serbia;

³Institute of Histology and Embryology, School of Medicine, University of Belgrade, Belgrade, Serbia;

⁴Diagenos, Center for Medical Genetics, Osnabrueck, Germany

SUMMARY

Introduction Incontinentia pigmenti (IP) is a rare X-linked dominant genodermatosis. Mutations of the *IKBKG* gene are the only known cause of IP. The presence of other than skin changes is important in the diagnosis of atypical IP cases when skin changes are discrete.

Objective The study was designed to analyze clinical manifestation, family histories and the frequency of *IKBKG* gene mutation in IP patients in Serbia for the first time and to compare them with other reported findings.

Methods Two Serbian unrelated families with eight female subjects were investigated. Blood samples were used for *IKBKG* exon 4-10 deletion testing using modified PCR protocol. For probands pathohistological and ultrastructural analyses of skin biopsies were done.

Results Positive clinical diagnosis according to IP criteria was present in seven cases. In six of them, including probands, positive molecular gene testing for *IKBKG* exon 4-10 deletion was present.

Conclusion This is the first report of genetically confirmed IP in two Serbian families. The IP patients presented a common *IKBKG* exon 4-10 deletion. The frequency and type of *IKBKG* mutation found in investigated IP patients in Serbia were similar to results of other studies. Various clinical features of investigated patients have allowed us to demonstrate that molecular genetic testing which specifically detects the common *IKBKG* mutations, the only known cause of IP, is useful in diagnosing IP especially in mild or atypical cases. The molecular genetic testing of the *IKBKG* mutations may be helpful for rapid confirmation of IP diagnosis, prenatal diagnosis and carrier detection.

Keywords: Incontinentia pigmenti; *IKBKG* gene; *IKBKG* exon 4-10 deletion; X-chromosome; X-chromosome inactivation; phenotype

INTRODUCTION

The X-chromosome holds a unique place in medical genetics since a disproportionately large number of disease conditions have been associated with the X-chromosome because the phenotypic consequence of a recessive mutation is revealed directly in males for any gene that has no active counterpart on the Y-chromosome [1]. Gene expression on one (maternal or paternal) of the female X-chromosomes is silenced early in development by the process of X-chromosome inactivation, and this chromosome remains inactive in somatic tissues thereafter [2]. Because of X-chromosome inactivation, females heterozygous for X-linked genes are mixtures of two types of cells, expressing cellular mosaicism, and show a variable phenotype [3]. Inactivation of one of the two X-chromosomes is random. Skewed X-chromosome inactivation is a marked deviation from a 50:50 ratio [4]. It may occur under genetic influence or under selection that will favor cells in which the normal X is the active X-chromosome [4].

Incontinentia pigmenti (IP; Bloch-Sulzberger syndrome; MIM 308300) is a rare X-linked dominant genodermatosis [5]. The estimated prevalence for IP is 0.2/100,000 [6]. It appears

almost exclusively in females and is usually lethal *in utero* for males [5]. It is a multi-system disorder predominantly affecting ectodermal tissues: skin, hair, nails, teeth, eyes and central nervous system [5]. Criteria for IP proposed by Landy and Donnai [7] are in routine practice since 1993. The presence of other than skin changes is important in atypical IP cases when skin changes are discrete. They can be of great prognostic and diagnostic value because they will be present throughout the patient's whole life, while skin changes usually fade [8]. The prognosis of IP is generally good and depends on extracutaneous manifestations that may also affect patients' quality of life. According to Landy and Donnai's criteria [7], skin lesions as well as multiple male miscarriages were classified as IP major criteria, while dental, hair, nails and retinal anomalies were classified as IP minor criteria. Dental abnormalities were registered in 54.38% of IP patients and comprise dental shape anomalies, hypodontia, and delayed dentition [9]. A typical hair change is scarring alopecia. Ophthalmologic findings occurred in 36.5% IP patients and include retinal anomalies, strabismus, vitreous and lens anomalies, optical nerve atrophy, and microphthalmus [10].

Correspondence to:

Snežana MINIĆ
Clinics of Dermatovenerology
Clinical Center of Serbia
Deligradska 34, 11000 Belgrade
Serbia
dtrpinac@eunet.rs

*IKBK*G (*Inhibitor of Kappa light polypeptide gene enhancer in B-cells, Kinase Gamma*, previously *NEMO*) is the only gene known to be associated with IP [11]. Mutations of the *IKBK*G gene are responsible for IP [5]. The *IKBK*G gene is composed of 10 exons. Located at Xq28, *IKBK*G has a unique genomic organization, as it is part of a segmental duplication or low-copy repeat 1 and 2 (LCR1 and LCR2) containing the gene and its pseudogene copy (*IKBKGP1*). The two LCRs in the *IKBK*G locus are able to recombine producing a pathological recurrent *IKBK*G exon 4-10 deletion [12].

Within cells, the *IKBK*G protein interacts with two enzymes, IKK-alpha and IKK-beta, to activate NF- κ B (Nuclear Factor-kappa-B). The activated factor then moves into the nucleus and binds to DNA. NF- κ B regulates the activity of multiple genes, including genes that control the body's immune responses and inflammatory reactions. It also protects the cell from certain signals that would otherwise undergo apoptosis [13]. Its misregulation is involved in many diseases [14]. However, failure to identify *IKBK*G mutations does not rule out the diagnosis of IP [11]. The phenotypic expression of *IKBK*G mutation is highly variable, even among related patients with the same mutation [5]. Because females with IP have skewed X-chromosome inactivation in which the X-chromosome with the mutant *IKBK*G allele is preferentially inactivated [15] it was thought that this variability was likely to be result of skewed X-chromosome inactivation [16]. It was also suggested that the phenotype of IP might be due to the pleiotropic role of the NF- κ B [12].

OBJECTIVE

This study was designed to analyze clinical manifestation, family histories and identify the existence and frequency of *IKBK*G gene mutation in IP patients in two Serbian families and to compare them with other reported findings.

METHODS

We investigated two Serbian unrelated families with eight subjects, including two probands, all of them females. Pedigrees for both families were made (Figure 1). Probands were first examined by a dermatologist, since they had

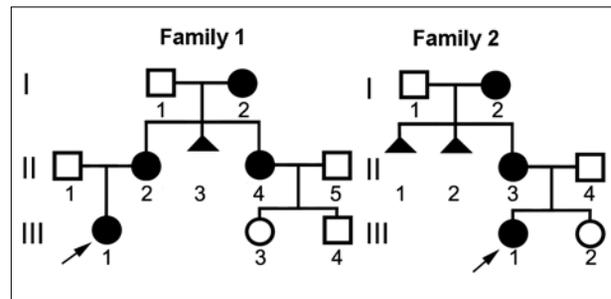


Figure 1. Pedigrees of Families 1 and 2

obvious skin changes, and then sent for additional examinations to stomatologists, ophthalmologists etc. Routine laboratory analyses were done for all patients.

Pathohistological and ultrastructural analysis

Skin biopsies were taken and pathohistological and ultrastructural analysis were done to confirm the diagnosis of IP in both probands. For pathohistological analyses, skin biopsies from affected areas were fixed in formaldehyde and stained with hematoxyline and eosin in a routine manner. For transmission electron microscopy investigation, skin biopsies were fixed in glutaraldehyde, postfixed in osmium tetroxide and embedded in araldite resin in a routine manner [17]. The ultra-thin sections stained with uranyl acetate and lead citrate [17] were analyzed with transmission electron microscopes Philips EM 300 (Philips, Eindhoven, The Netherlands) and LEO 912AB (Carl Zeiss SMT, Oberkochen, Germany).

DNA sampling and genotyping

Blood samples were collected and used to extract DNA using standard protocols. Molecular genetic testing was done at Diagenos, Center for Medical Genetics, Osna-brueck (Germany). For deletion testing a modified PCR protocol according to Smahi et al. 2000 [5] was performed for all patients except III 2 Family 2. For III 2 Family 2 who had no clinical signs of IP all coding exons of *IKBK*G gene were amplified and subsequently sequenced. Obtained sequences were analyzed by comparing to data base entries. Additional deletion testing was done.

Table 1. Facts concerning basic subjects' data, onset and key laboratory and clinical findings

Family subject	Age at onset	Age of patients	IP stage at first exam	<i>IKBK</i> G exon 4-10 deletion positive	Skin pathohistology	Skin ultrastructure	Clinical findings				Miscarriages
							Skin	Eye	Teeth	Hair	
Family 1	III 1	5 days	1980	1, 2, 3*, 4*	+	+	+	-	+	-	-
	II 2	/	1968	3, 4	+	/	+	-	+	-	-
	II 4	/	1964	3, 4	+	/	+	-	+	+	-
	I 2	/	1940	-	+	/	-	-	+	-	1
Family 2	III 1	39 days	1996	1, 2, 3*, 4*	+	+	+	-	+	-	-
	III 2	/	1998	-	-	/	-	-	-	-	-
	II 3	/	1977	-	+	/	-	+	+	-	-
	I 2	/	1952	-	-	/	-	+	+	-	2

* At the age of 14 years

The investigation protocol followed the guidelines of the Declaration of Helsinki and was approved by the Clinical Center of Serbia Ethics Committee. Written informed consent was obtained from all participants or their parental guides.

RESULTS

Basic subjects' data are presented in Table 1. Out of eight subjects, positive clinical diagnosis of IP according to Landy and Donnai's criteria [7] were present in seven cases. Positive molecular gene testing for *IKBKG* mutation was present in six subjects - in both probands and four relatives from two families (Figure 2A). All of them were with positive clinical diagnosis of IP according to Landy and Donnai's criteria [7]. Both families were presented in our previously published articles in context of ocular [18], oral and dental anomalies in IP [19].

Probands had skin (Figure 2B, 2C), dental and oral changes typical for IP while eosinophilia was not registered. Also, they had pathohistological (Figure 2D) and ultrastructural skin findings characteristic for appropriate stage of IP (Figure 2E). Common *IKBKG* exon 4-10 deletion was detected in six of seven clinically diagnosed IP patients and no *IKBKG* exon 4-10 deletion was found in the remaining case. One of the examinees, the sister of proband in Family 2 (III 2), had none of the phenotypical signs of IP. Both probands inherited the *IKBKG* exon 4-10 deletion from their mothers.

In Family 1 three out of four examined patients had typical skin changes. All four tested patients were positive for *IKBKG* exon 4-10 deletion. In Family 2 only proband had typical skin changes and two out of four family members were positive for *IKBKG* exon 4-10 deletion.

DISCUSSION

Although numerous molecular genetic confirmations of IP have been described in the world literature [20], up to date there were not genetically confirmed patients from Serbia. In this study, a genetic analysis of two unrelated Serbian families clinically diagnosed according to Landy and Donnai's criteria [7] with IP was performed.

Skin abnormalities are consistent IP features and usually occur in four stages that evolve sequentially [11]. The pattern of skin changes follows lines of embryonic and fetal skin development known as Blaschko's lines that correspond with cell migration and growth pathways that are established during embryogenesis and represent functional X-chromosome mosaicism [21]. Blaschko's lines are linear on the limbs and circumferential on the trunk [11]. Stage 1, the bullous stage, is characterized by erythema and blistering within the first few weeks of life. Stage 2, is characterized by a hypertrophic rash within the first few months of life. Stage 3, is characterized by hyperpigmentation that occurs along Blaschko's lines. It starts usually as stage 2, begins to resolve and persists into adulthood. The hyperpigmentation usually begins to fade in the teens and early

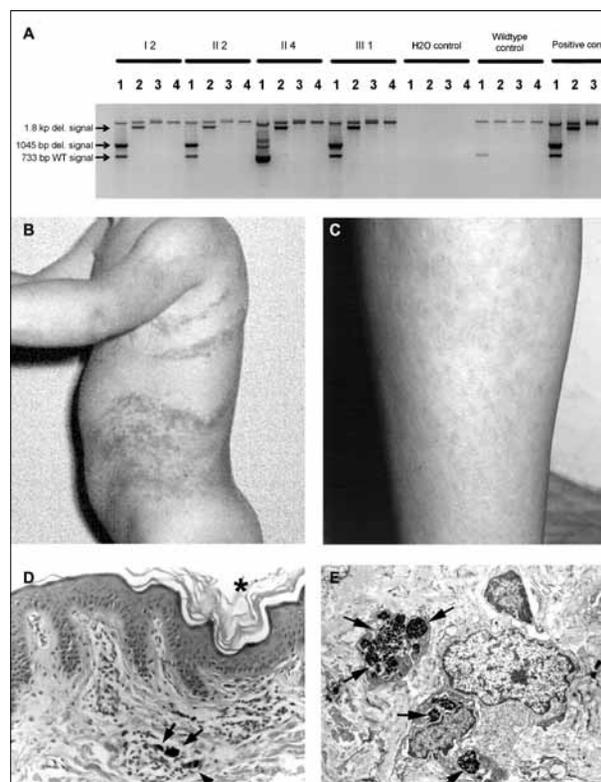


Figure 2. A. Result of deletion testing in the investigated Family 1. A set of deletion spanning PCR primer were used for the detection of the common exon 4-10 deletion. The deletion is characterized by additional PCR product of 1.8 kb and 1045 bp not seen in control samples. **B.** Hyperpigmented stage (stage 3) maculas along Blaschko's lines on the trunk. **C.** Hypopigmented, atrophic, hairless areas on the shin (stage 4). **D.** Histopathological findings in proband 1 (stages 3 and 4). Pigment localized in dermal cells (arrows) and epidermal hyperkeratosis (asterisk) (hematoxyline and eosin, magnification 150 \times). **E.** Ultrastructural appearance of dermis of proband 1 (stages 3 and 4). phagocytosed melanosome clusters (arrows) localized in cytoplasm of dermal cells (magnification 4800 \times)

twenties. It is the reason why IP patients in their thirties may have no skin changes associated with IP. Stage 4, the hypopigmented stage, opposite to stage 3 is characterized by linear hypopigmentation and alopecia. Stage 4 does not occur in all patients. The onset, duration and overlapping of IP stages vary among patients, and not all patients experience all four stages [11]. Besides variable appearance of skin phenotype in IP patients, significant clinical heterogeneity exists with regard to eye, dental, and neurological abnormalities, even within families [22]. These factors are the cause of diagnostic dilemma in atypical or mild IP cases.

In the process of confirming IP diagnosis reliance on the skin biopsy is important. However, one must consider that IP skin changes have clinical course with four different stages with different histological features in each stage [23]. As in IP is not always possible to detect *IKBKG* mutation, in such situations of hidden *IKBKG* mutations, histology can be very helpful for confirmation of IP [24].

Clinical features of IP in seven diagnosed patients were diverse. Both probands inherited common *IKBKG* exon 4-10 deletion from their mothers. They had skin changes typical for IP and previously confirmed IP diagnosis using pathohistology and ultrastructural analyses of skin biopsies because, at that time, *IKBKG* was not discovered as a

causative gene for IP and molecular genetic testing was not available. Six of seven IP affected individuals showed an identical genomic alteration, common *IKBKG* exon 4-10 deletion. Four IP patients with *IKBKG* exon 4-10 deletion showed the classical cutaneous signs of IP. Two patients with *IKBKG* exon 4-10 deletion had no IP skin changes, but had noncutaneous anomalies typical for IP and fulfilled Landy and Donnai's IP criteria [7]. Only one examinee, III 2 Family 2, had no phenotypic signs of IP and was negative for *IKBKG* mutation. Though she did not show phenotypic signs of IP, she was analyzed as at-risk female relative since the *IKBKG* gene mutation had been identified in her family and to discover if she was a carrier of the disease. In this study, no *IKBKG* exon 4-10 deletion was found in the remaining IP case, I 2 Family 2. As failure to identify *IKBKG* mutation does not rule out the diagnosis of IP [11], in this case IP may be attributed to the somatic mosaicism which has been reported in some studies [11, 12, 25].

Most of the studies on IP with molecular genetic confirmation were reported from Europe and North America [12, 20, 25]. A few reports of IP were available from Asia [26, 27, 28] and Australia [29]. A large deletion of *IKBKG* exons 4 to 10 is found in approximately 80% of IP patients [5, 20]. In general, the frequency of *IKBKG* mutation in IP patients was similar in all studies irrespective of the ethnic background [26]. The frequency of *IKBKG* exon 4-10 deletion in Serbian population (6/7) was similar to the results in other ethnic groups [5, 19, 26]. Besides the most frequently found *IKBKG* exon 4-10 deletion [20], a total of 79 different small *IKBKG* mutations (missense, frameshift, nonsense, and splice-site mutations) have been reported [12, 25, 30, 31].

As a consequence of skewed X-chromosome inactivation [16] and consequent mosaicism, and the pleiotropic role of the NF- κ B [12] phenotypical features of IP are variable and it is difficult to diagnose cases with mild manifestations [8]. It is likely that IP in mildly affected patients is often undiagnosed and underrepresented because older patients have poor recall, and their mothers may no longer be alive [29]. Genetic testing is especially helpful in diagnosing IP in such patients. Molecular genetic diagnosis may help to confirm the clinical suspicion of IP and is essential for providing definite genetic counseling and prenatal diagnosis [26]. Carrier testing of at-risk female relatives is possible if the *IKBKG* mutation has been identified in the family. Preimplantation and prenatal genetic diagnosis may be available for families in which the *IKBKG* mutation has been identified [11].

Our study is the first to report genetically confirmed *IKBKG* exon 4-10 deletion in six IP patients from two

families in Serbian population. We investigated IP patients for more than 20 years and registered 9 families with 22 subjects, two of them males [18, 19]. In the present study we analyzed two families willing to cooperate for further investigations, molecular genetic testing, that became available long after they have been diagnosed for IP. The most frequent molecular cause, the *IKBKG* exon 4-10 deletion, is the same as in other populations. Six out of seven IP patients had a common genomic rearrangement involving the deletion of exons 4 to 10 in *IKBKG* and of mutation incidence similar to previously reported [20].

A relatively small number of IP patients were investigated but the variety of their clinical features have allowed us to demonstrate that molecular genetic testing which specifically detects the common *IKBKG* exon 4-10 deletion is useful to confirm the diagnosis in IP patients with typical, and especially with mild or atypical phenotype.

CONCLUSION

This is the first report of genetically confirmed IP patients in Serbian population. Six of seven investigated IP patients presented a common *IKBKG* exon 4-10 deletion. The frequency and type of *IKBKG* mutation found in IP patients in Serbia were similar to the results of other studies irrespective of the ethnic background. Although a relatively small number of patients were investigated, this study indicates that molecular genetic analysis of *IKBKG* is helpful for rapid confirmation of IP diagnosis particularly in mild or atypical cases and in prenatal diagnosis and carrier detection.

ACKNOWLEDGEMENTS

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, grant number 175005.

NOTE

In the period between submission and proof correction, the article: *Minić S, Trpinac D, Obradović M. Incontinentia pigmenti diagnostic criteria update. Clin Genet. 2013 Jun 26. doi: 10.1111/cge.12223* with more accurate criteria than in cited reference 7: *Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger syndrome). J Med Genet. 1993; 30:53-9* was published.

REFERENCES

- Ross MT, Grafham DV, Coffey AJ, Scherer S, McLay K, Muzny D, et al. The DNA sequence of the human X chromosome. *Nature*. 2005; 434:325-37.
- Migeon BR. Why females are mosaics, X-chromosome inactivation, and sex differences in disease. *Genet Med*. 2007; 4:97-105.
- Lyon MF. X-chromosome inactivation and human genetic disease. *Acta Paediatr Suppl*. 2002; 91(s439):107-12.
- Orstavik KH. X chromosome inactivation in clinical practice. *Hum Genet*. 2009; 126:363-73.
- Smahi A, Courtois G, Vabres P, Yamaoka S, Heuertz S, Munnich A, et al. Genomic rearrangement in *NEMO* impairs NF- κ B activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature*. 2000; 405:466-72.
- Orphanet Report Series. Rare Diseases collection. May 2011, No 1. Prevalence of rare diseases: Bibliographic data. Available from: www.orpha.net.

7. Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger syndrome). *J Med Genet.* 1993; 30:53-9.
8. Garcia-Dorado J, de Unamuno P, Fernandez-Lopez E, Salazar Veloz J, Armijo M. Incontinentia pigmenti: XXY male with a family history. *Clin Genet.* 1990; 38:128-38.
9. Minić S, Trpinac D, Gabriel H, Gencik M, Obradović M. Dental and oral anomalies in incontinentia pigmenti: a systematic review. *Clin Oral Invest.* 2013. 17(1):1-8.
10. Minić S, Obradović M, Kovačević I, Trpinac D. Ocular anomalies in Incontinentia pigmenti – literature review and meta-analysis. *Srp Arh Celok Lek.* 2010; 138(7-8):408-13.
11. Scheuerle A, Ursini MV. Incontinentia pigmenti (Bloch-Sulzberger syndrome). [Internet]. University of Washington; Seattle (WA): GeneReviews 2008 Feb [cited 2010 Oct 28]. 22 p. Available from: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=i-p>.
12. Fusco F, Paciolla M, Napolitano F, Pescatore A, D'Addario I, Bal E, et al. Genomic architecture at the Incontinentia Pigmenti locus favours *de novo* pathological alleles through different mechanisms. *Hum Mol Genet.* 2012; 21:1260-71.
13. Genetics Home Reference. Genes. *IKBKG*. [Internet]. National Library of Medicine, Lister Hill National Center for Biomedical Communications. Published: June 25, 2012. Accessed: July 1, 2012. Available from: <http://ghr.nlm.nih.gov/gene/IKBKG>.
14. Courtois G, Gilmore TD. Mutations in the NF-κB signaling pathway: implication for human disease. *Oncogene.* 2006; 25:6831-43.
15. Parrish JE, Scheuerle AE, Lewis RA, Levy ML, Nelson DL. Selection against mutant alleles in blood leukocytes is a consistent feature in incontinentia pigmenti type 2. *Hum Mol Genet.* 1996; 5:1777-83.
16. Fusco F, Bardaro T, Fimiani G, Mercadante V, Miano MG, Falco G, et al. Molecular analysis of the genetic defect in a large cohort of IP patients and identification of novel NEMO mutations interfering with NF-κB activation. *Hum Mol Genet.* 2004; 13:1763-73.
17. Hayat MA. Basic techniques for transmission electron microscopy. Orlando: Academic Press. 1986. p.56-125.
18. Minić S, Gerd EK, Novotny GEK, Stefanović I, Obradović M, Trpinac D. Ophthalmological findings in series of Incontinentia pigmenti patients from Serbia. *Srp Arh Celok Lek.* 2010; 138:150-3.
19. Minić S, Novotny GEK, Trpinac D, Obradović M. Clinical features of incontinentia pigmenti with emphasis on oral and dental abnormalities. *Clin Oral Invest.* 2006; 10:343-7.
20. Aradhya S, Woffendin H, Jakins T, Bardaro T, Esposito T, Smahi A, et al. A recurrent deletion in the ubiquitously expressed *NEMO (IKK-γ)* gene accounts for the vast majority of incontinentia pigmenti mutations. *Hum Mol Genet.* 2001; 10:2171-9.
21. Molho-Pessach V, Schaffer JV. Blaschko lines and other patterns of cutaneous mosaicism. *Clin Dermatol.* 2011; 29:205-25.
22. Thakur S, Puri RD, Kohli S, Saxena R, Verma IC. Utility of molecular studies in incontinentia pigmenti patients. *Indian J Med Res.* 2011; 133:442-5.
23. Freitag S, Rimella A, de Prost Y, Brousse N, Hadj-Rabia S, Bodemer C. Skin biopsy is helpful for the diagnosis of incontinentia pigmenti at late stage (IV): a series of 26 cutaneous biopsies. *J Cutan Pathol.* 2009; 36:966-71.
24. Hadj-Rabia S, Rimella A, Smahi A, Freitag S, Hamel-Teillac D, Bonnefont JP, et al. Clinical and histologic features of incontinentia pigmenti in adults with nuclear factor-κB essential modulator gene mutations. *J Am Acad Dermatol.* 2011; 64:508-15.
25. Fusco F, Pescatore A, Bal E, Ghoul A, Paciolla M, Lioi MB, et al. Alterations of the *IKBKG* locus and diseases: An update and a report of 13 novel mutations. *Hum Mutat.* 2008; 29:595-604.
26. Hsiao PF, Lin SP, Chiang SS, Wu YH, Chen HC, Lin YC. *NEMO* gene mutations in Chinese patients with incontinentia pigmenti. *J Formos Med Assoc.* 2010; 109:192-200.
27. Song MJ, Chae JH, Park EA, Ki CS. The Common NF-κB Essential Modulator (*NEMO*) gene rearrangement in Korean patients with incontinentia pigmenti. *J Korean Med Sci.* 2010; 25:1513-7.
28. Huang J, Kondo H, Uchio E. A case of incontinentia pigmenti in Japan and its genetic examination. *Jpn J Ophthalmol.* 2007; 51:142-5.
29. Phan TA, Wargon O, Turner AM. Incontinentia pigmenti case series: clinical spectrum of incontinentia pigmenti in 53 female patients and their relatives. *Clin Exp Dermatol.* 2005; 30:474-80.
30. Fryssira H, Kakourou T, Valari M, Stefanaki K, Amenta S, Kanavakis E. Incontinentia pigmenti revisited. A novel nonsense mutation of the *IKBKG* gene. *Acta Paediatr.* 2011; 100:128-33.
31. Lee NC, Huang CH, Hwu WL, Chien YH, Chang YY, Chen CH, et al. Pseudogene-derived *IKBKG* gene mutations in incontinentia pigmenti. *Clin Genet.* 2009; 76:417-9.

Прва студија мутације гена *IKBKG* код болесника са инконтиненцијом пигменти у Србији

Снежана Минић^{1,2}, Душан Трпиња³, Хајнц Габијел⁴, Мартин Генцик⁴, Миљана Обрадовић³

¹Клиника за дерматовенерологију, Клинички центар Србије, Београд, Србија;

²Медицински факултет, Универзитет у Београду, Београд, Србија;

³Институт за хистологију и ембриологију „Проф. др Александар Ђ. Костић“, Медицински факултет, Универзитет у Београду, Београд, Србија;

⁴Дијагнос, Центар за медицинску генетику, Оснабрик, Немачка

КРАТАК САДРЖАЈ

Увод Инконтиненција пигменти (ИП) је ретка генодерматоза која се наслеђује доминантно везано за X-хромозом. За појаву ИП одговорне су мутације гена *IKBKG*. У дијагностиковању нетипичних случајева ИП, када су промене коже дискретне, важно је постојање промена на другим органима.

Циљ рада Циљ истраживања је била анализа клиничких манифестација ИП, породичне историје болести, молекуларногенетичко тестирање ради утврђивања постојања и учесталости мутације гена *IKBKG* код болесника са ИП из Србије (први пут) и упоређивање с резултатима других студија.

Методе рада Испитиване су две несродне породице из Србије са осам испитаница. Узорци крви су коришћени за молекуларногенетичко тестирање делеције гена *IKBKG* модификованим *PCR* протоколом. Обављена је патохистолошка и ултраструктурна анализа биопсија коже оба пробанда.

Резултати На основу критеријума за утврђивање ИП, код седам испитаница је била позитивна клиничка дијагноза ИП. Позитивно генетичко тестирање делеције егзона 4–10 гена *IKBKG* је показано код шест болесника.

Закључак Ово је први извештај о ИП код болесника из две породице у Србији којим је дијагноза потврђена и молекуларногенетичким тестирањем. Болесници су имали типичну делецију егзона 4–10 гена *IKBKG*. Учесталост и тип мутације овог гена код испитиваних болесника из Србије слични су резултатима других студија. Различите клиничке слике код испитиваних болесника су омогућиле да покажемо да је молекуларногенетичко тестирање које специфично открива мутације гена *IKBKG*, јединог познатог узрочника ИП, врло корисно за брзо потврђивање дијагнозе, пренаталну дијагнозу и откривање преносилаца гена.

Кључне речи: инконтиненција пигменти; ген *IKBKG*; делеција егзона 4–10 гена *IKBKG*; X-хромозом; инактивација X-хромозома; фенотип