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P04.042.C Association of one-carbon metabolism-related genes and ichthyosis vulgaris manifestation in Eastern Ukraine

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Introduction: The prevalence of ichthyosis vulgaris (IV) in Eastern Ukraine is 1:2557. The dermatosis is caused by *FLG* mutations R501X and 2282del4, but their penetrance in heterozygotes is incomplete. The purpose of the study was to analyze the effects of one-carbon metabolism-related genes on the IV clinical manifestation in *FLG* mutation carriers.

Materials and methods: The *MTHFR* C677T (rs1801133), *MTHFR* A1298C (rs1801131), *MTR* A2756G (rs1805087) and *MTRR* A66G (rs1801394) SNPs were analyzed by PCR-RFLP in 31 IV patients, 7 their non-IV first-degree relatives with *FLG* mutations and 150 healthy controls. Statistical analysis was performed using chi-square test and OR.

Results: In 2282del4/wt IV individuals, the distributions of wild-type, heterozygous and variant homozygous genotypes were: rs1801133 — 0.29:0.71:0.00; rs1801131 — 0.53:0.47:0.00; rs1805087 — 0.70:0.24:0.06; rs1801394 — 0.23:0.53:0.24. In this group the *MTR* 2756AA genotype and *MTR* 66GG genotype frequencies were 1.4-1.6 higher than in IV patients with the other *FLG* genotypes, the *MTR* 2756AA genotype frequency was 1.6 times higher than in healthy controls ($p < 0.01$). The association between IV and one-carbon metabolism-related genes was evaluated for single- and multilocus disease models. The strongest genotype-phenotype relationships were found for the genotypes: *MTHFR* 677CT — OR = 3.60 (95% CI 1.21−10.71, $p = 0.032$), *MTHFR* 677CT/*MTHFR* 1298AA +AC — OR = 4.39 (95% CI 1.47−13.14, $p = 0.008$), *MTHFR* 677CT/*MTHFR* 1298AA/*MTRR* 66AG — OR = 7.64 (95% CI 2.34−24.94, $p = 0.001$), *MTHFR* 677CT/*MTHFR* 1298AA/*MTR* 2756AA/*MTRR* 66AG — OR = 11.23 (95% CI 2.51−50.21, $p = 0.002$).

Conclusion: SNPs in one-carbon metabolism-related genes can be considered as modifiers of *FLG* 2282del4 mutation in IV clinical manifestation.

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P04.044.D Incontinentia pigmenti and favism due to a large genomic deletion including *IKBKG* and *G6PD*

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Incontinentia pigmenti (IP) is a genodermatosis in four stages including blistering, wart-like rash, swirling macular hyperpigmentation and linear hypopigmentation, and also affects hair, teeth, nails, eyes and brain. IP is caused by mutations in the *IKBKG* (*NEMO*) gene and inherited in an X-linked dominant manner with high penetrance. Affected females show a highly variable phenotype. IP is usually prenatally lethal in males. About 65% of females with IP have a recurrent ~11.7-kb deletion spanning exons 4 to 10 and ~8.6% have point mutations. Only seven other deletions were described to date.

Here we describe a 24-year-old female patient with typical skin lesions since birth. She showed neither neurological nor other symptoms of IP and suffered two miscarriages. Furthermore, the patient had intolerance of fava beans and some drugs, indicating X-linked dominant *G6PD* associated favism. Her mother and her sister were also affected of IP and favism.

Neither long-range (gap) PCR for detection of the recurrent exon 4 to 10 deletion, nor sequence analysis detected a pathogenic mutation. MLPA revealed a heterozygous deletion spanning the whole *IKBKG* gene as well as the 5′ adjacent entire *G6PD* gene. NC_000023.10:g.(153,744,322_153,759,773)_(153,793,401_153,798,250)del. This deletion is to our knowledge of yet undescribed extent. The only two patients with large *IKBKG* deletions involving the whole *G6PD* gene described so far by Fusco et al. did not show any clinical manifestations of *G6PD* deficiency in contrast to the patients described here.

In summary, this is the first description of a contiguous gene syndrome including Incontinentia pigmenti and favism.

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P04.045.B The importance of extracutaneous organ involvement for the clinical severity and prognosis observed in incontinentia pigmenti caused by *IKBKG* mutations

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Incontinentia pigmenti (IP) is a rare X-linked skin disease caused by mutations of the *IKBKG* gene, which is required for activation of the nuclear factor-kappa B signaling pathway. Multiple systems can be affected with highly variable phenotypic expressivity. We aimed to clarify the clinical characteristics observed in molecularly-confirmed Korean IP patients. Medical records of 25 females confirmed as IP by molecular genetic analysis were retrospectively reviewed. A phenotypic score of extracutaneous manifestations was calculated to assess the disease severity. The *IKBKG* gene partial deletion or intragenic mutations were investigated by a long-range PCR, multiplex ligation-dependent probe amplification, and direct sequencing methods. Among 25 individuals, 18 (72%) were sporadic cases. All patients showed typical skin manifestations at inborn or during the neonatal period. Extracutaneous findings were noted in 17 (68%) cases; ocular manifestations (28%), neurological abnormalities (28%), hair abnormalities (20%), dental anomalies (12%), nail dystrophy (8%). The common *IKBKG* exon 4-10 deletion was observed in 20 (80%) patients. In addition, 5 intragenic sequence variants were identified, including 3 novel ones. The phenotype scores were highly variable from abnormal skin pigmentation only to one or more extracutaneous features, even though there was no meaningful significant difference for each clinical characteristic between the groups with sequence variants and common large deletion. Heterogeneity of