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Association of the *EPHA1* gene polymorphism with idiopathic mild intellectual disability

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Aim. To investigate a possible association of the *EPHA1* gene polymorphism with mild intellectual disability (ID). **Methods.** The group of patients with mild (IQ score between 50 and 70) idiopathic intellectual disability consisted of 65 individuals including 41 (63.1 %) males and 24 (36.9 %) females. The control group consisted of 250 healthy volunteers from different regions of Ukraine. The genotyping was performed using PCR followed by RFLP analysis for rs11768549, rs11767557, rs11771145 and ARMS PCR analysis for novel c.1891G>A *EPHA1* gene mutation. **Results.** The data concerning the *EPHA1* genotypes and allelic variants distribution in ID patients and control group were obtained. Statistical analysis showed a significant association of minor rs11768549-A allele (OR = 3.96, 95 % CI = 1.13–13.89) and wild-type rs11767557-T (OR = 1.99, 95 % CI = 1.18–3.37) and rs11771145-G (OR= 1.55, 95 % CI = 1.02–2.37) alleles with a higher risk of mild ID development (p < 0.05 for all). **Conclusions.** Our results suggest that SNPs (rs11768549, rs11767557, rs11771145) in the *EPHA1* gene are associated with idiopathic mild intellectual disability. Therefore, we propose the *EPHA1*gene as a new candidate gene and the polymorphisms rs11768549, rs11767557, rs11771145 as new markers of genetic susceptibility for intellectual disability.

K e y w o r d s: *EPHA1* gene, intellectual disability, polymorphism, genetic susceptibility.

Introduction

In recent reports we have presented our study on the whole exome sequencing (WES) in two affected siblings with non-syndromic intellectual disability from Ukrainian family and their healthy non-consanguineous parents that identified two missense mutations in the coding region of the *EPHA1* gene (c. 1475 G > A – rs11768549 and novel c.1891G > A) [1–3].

The *EPHA1* gene is located at chromosome 7q34 and contains 18 exons that span a little over 18 kb [4]. The human *EPHA1* gene is transcribed as a single 3.5 kb mRNA [5]. The EPHA1 protein contains 976 amino acids and is approximately 108 kDa [6]. EPHA1 is the first identified member of the erythropoietin-producing hepatocellular (Eph) receptors family [7]. EPHA1 is a receptor tyrosine kinase that plays an important role in developmental processes, including nervous system, where it participates in the forward signaling in receptor-bearing cells and the reverse signaling in ligand-bearing cells by binding to GPI-linked A ephrins, which together facilitate communication between neighboring cell populations and axon guidance [6, 8–12]. Ephrin type-A receptor 1 is highly expressed in the adult brain and in the spinal neural tube during neurulation [13, 14] and seems to be a good disease gene in ID.

The previous studies have shown that EPHA1 regulates the cell morphology and motility through the ILK-RhoA-ROCK pathway [15]. It is therefore important to note that mutations in the genes encoding the regulators and effectors of the Rho GTPases such as *OPHN1*, *PAK3*, *alpha-PIX* (also known as *ARHGEF6* or *Cool-2*), *FMR1* and *MEGAP* have been found to underlie various forms of ID [16, 17]. Interestingly, the defects in Rho signaling pathways have recently also been linked with Alzheimer disease (AD) as well as the *EPHA1* gene SNPs [18, 19]. *EPHA1* was documented to be one of the most strongly associated locus with AD in a few recent genome wide association studies [20–22]. It was shown that the minor C allele at SNP rs11767557 of *EPHA1* was associated with significantly lower odds of being Aβ-positive and protective for late onset AD (LOAD) as well as having the minor A allele in another SNP rs11771145 on *EPHA1* was also associated with lower odds of AD [20–22]. Furthermore, the *EPHA1* gene SNP rs11768549 was associated with the rapid AD progression and the missense mutations in the coding region of the *EPHA1* gene rs202178565 – with LOAD [23, 24].

Intellectual disability is a common neurodevelopmental disorder occurring in 1–3 % of the general population and its burden on the affected individuals, their families and society is enormous. [25]. Still, in ~ 60 % of cases of ID the etiology is unknown because of the extensive clinical and genetic heterogeneity [26]. The causes of intellectual disability vary with the severity of the condition: moderate-to-severe intellectual disability (IQ less than 50) is much more likely to be due to a single pathological cause (genetic or environmental) whereas mild ID (defined as an IQ score between 50 and 70) is rather a complex condition in origin as well as AD [27].

The aim of this study is to evaluate a possible association of the *EPHA1* gene polymorphisms rs11768549, rs11767557, rs11771145 and novel c.1891G > A mutation with mild intellectual disability.

Materials and Methods

DNA-samples were extracted from peripheral blood leucocytes of unrelated volunteers from different regions of Ukraine and ID patients by the standard phenol-chloroform method. Informed consents were obtained from all the individuals participating in our study.

The group of patients with mild (an IQ score between 50 and 70) idiopathic intellectual disability consisted of 65 individuals including 41 (63.1 %) males and 24 (36.9 %) females, where the previous extensive genetic investigations revealed no abnormalities. All patients underwent physical and neurological examination (test used for IQ: WISC III, WISC-R, WISC) and standard G-banding karyotype analysis. DNA tests to determine Fragile X status (*FRAXA, FRAXE, FRAXF* loci) and Prader Willi/Angelman syndromes (PW/AS) were performed to rule out the known genetic causes of ID prior to further investigation. Array-CGH analysis (400K resolution) revealed no pathological rearrangements in all patients.

The control group consisted of 250 individuals including 131 (52.4 %) males and 119 (47.6 %) females. This group may be considered representative for the estimation of DNA polymorphism frequency in autosomal genes [28].

Polymorphic variants c.1475G > A (rs11768549) and c.1891G > A (novel) of *EPHA1* gene were detected as described in our recent work [2].

The presence of *EPHA1* polymorphism rs11767557 was examined by *RsaI* PCR-RFLP (restriction fragment length polymorphism) analysis. Specific oligonucleotides, designed and synthesized in accordance to corresponding sequences of *EPHA1* gene that were used as primers are presented in Table 1. The PCR amplification was performed in a final volume of 25 μl containing 1 × PCR buffer, 1.5 mM MgCl2, 200 μM of each dNTP, 1 μM of each primer, 0.2 units of *Taq*-DNA polymerase and 200 ng of the DNA template. The cycling conditions were as follows: initial denaturation at 95 °C for 5 min, 30 cycles consisting of denaturation at 94 °C for 30 s, annealing at 63 °C for 30 s, extension at 72 °C for 30 s and a final elongation step at 72 °C for 3 min. The amplified fragments were digested with *RsaI*. Digestion was performed in 15 μl reaction volume containing 1 X reaction buffer, 0.5 units of the restriction enzyme and 10 μl of purified PCR product, in-
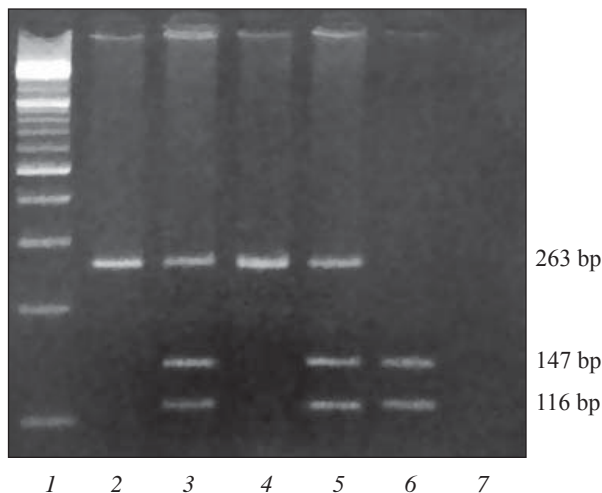
Fig. 1. RFLP analysis of rs11767557 *EPHA1* receptor gene variant (2 % agarose gel electrophoresis): *1* – molecular mass marker (Ladder 100 bp); *2, 4* – individuals with homozygous genotype TT; *3, 5* – individuals with heterozygous genotype TC; *6* – individual with homozygous genotype CC, *7* – negative control

cubated at 37 °C overnight and analyzed using 2 % standard agarose gelelectrophoreses.

The assessment of the *EPHA1* rs11771145 polymorphism was performed by the *DraI* PCR-RFLP analysis using the specific oligonucleotide primers described in Table 1. In the forward primer, the mismatched nucleotides (underlined) were substituted so that amplification of the minor A-allele resulted in the generation of a new *DraI* restriction cutting site. The PCR amplification was performed in a final volume of 25 µl containing 1 × PCR buffer, 1.5 mM MgCl2, 200 µM of each dNTP, 1 µM of each primer, 0.2 units of *Taq*-DNA polymerase and 200 ng of the DNA template. The cycling conditions were as follows: initial denaturation at 95 °C for 5 min, 30 cycles consisting of denaturation at 94 °C for 30 s, annealing at 58 °C for 30 s, extension at 72 °C for 30 s and a final elonga-

tion step at 72 °C for 3 min. The amplified fragments were digested with *DraI*. Digestion was performed in 15 µl reaction volume containing 1 X reaction buffer, 0.5 units of the restriction enzyme and 10 µl of purified PCR product, incubated at 37 °C overnight and analyzed in 2 % standard agarose gels.

The primers were designed using a web-based PRIMER 3.0 program (http://workbench.sdsc.edu). We used the «BLAST» program at http://www.ncbi. nlm.nih.gov/blast to check for the specificity of the primers. Hypothetical RFLP results were tested using NEBcutter V2.0 (http://tools.neb.com/NEBcutter2).

The results were statistically assessed using Arlequin and OpenEpi software and Fisher's 2 by 2 exact test, as well as odd ratio (OR) calculation; $p < 0.05$ was considered to be statistically significant test [29, 30].

Results and Discussion

We did not identify c.1891G>A (p.Gly631Arg) substitution in any of the investigated individuals from the ID patients (n = 65) and control groups (n = 250). It was found only in the members of aforesaid Ukrainian family with ID in two siblings. Furthermore, c.1891G > A substitution was not observed in any of Exome Aggregation Consortium (URL: http://exac.broadinstitute.org), International HapMap Project (URL: http://hapmap. ncbi.nlm.nih.gov/) and 1000 Genomes Project (URL: http://browser.1000genomes.org/) populations. Therefore, we assume that the *EPHA1* gene c.1891G>A (p.Gly631Arg) is the mutation with an extremely low frequency.

Based on the RFLP analysis of rs11768549 (c. 1475G>A and p.Arg492Gln) variant, the individuals were classified into three groups: GG, GA and AA. The genotypes and allele frequencies of the rs11768549 polymorphism are presented in Table 2.

*Table 1.* **Sequences of PCR-RFLP primers used in genotyping reactions**

Substitution	Nucleotide sequence	Amplicon size, bp
rs11767557 T>C	GGGTCTTTCTCTTTAGTATGATGCTCC – forward CAGACGCCAGAAGGGGAAAGA – reverse	263
rs11771145 G>A	TGGATTTGCCTGTTCTTAAACTTTTT – forward CTGAATCCACACACAACCAAGGAA – reverse	122

The T to C transition in the rs11767557 variant, located in *EPHA1-AS1* (*EPHA1 antisense RNA 1*), generates a restriction site for endonuclease *RsaI*. Thereby three different patterns could be observed after the restriction digestion of the PCR-product: a 263 bp band (for genotype TT); a 263 bp, a 147 bp and a 116 bp bands (for genotype TC); a 147 bp and a 116 bp bands (for genotype CC) (Fig. 1).

In the forward primer, designed for the rs11771145 (located in *EPHA1-AS1*) analysis, the mismatched nucleotides (underlined) were substituted so that amplification of the minor A-allele resulted in the generation of a new *DraI* restriction cutting site. Thereby three different patterns could be observed after the restriction digestion: a 122 bp band (for GG genotype); a 122 bp, a 96 bp and a 26 bp (not visible on electrophoregram) bands (for GA genotype); a 96 bp and a 26 bp bands (for AA genotype) (Fig. 2). The genotype and allele frequencies of the rs11767557 and rs11771145 polymorphisms are summarized in Table 2.

All observed genotype distributions showed no deviations from Hardy-Weinberg expectations in the general population of Ukraine and in the ID patients group ($p > 0.05$). A significant linkage disequilibrium (LD) was found between rs11768549 and rs11767557 ($p = 0.00436$), rs11767557 and rs11771145 ($p < 0.0001$).

The SNP analysis showed the significant differences between the ID patients and the controls for the allele frequencies of all (rs11768549, rs11767557, rs11771145) investigated SNPs ($p < 0.05$ for all). We found a signifacant association of minor rs11768549-A (OR = 3.96, 95 % CI = 1.13–13.89) and wild-type rs11767557-T (OR= 1.99, 95 % CI = 1.18–3.37) and rs11771145-G (OR= 1.55, 95 % CI = 1.02–2.37) alleles with a higher risk of mild ID development. Three studied polymorphic variants showed a significant association with mild ID for different genetic models: multiplicative for rs11768549 (A vs G: OR = 3.96, 95 % CI = 1.13 – 13.89, p = 0.02), recessive for rs11767557 (TT vs TC + CC: OR = 0.50, 95 % CI = 0.27–0.9, p = 0.02) and dominant for rs11771145 (GG+AG vs AA: OR= 0.28, 95 % CI = = 0.08 – 0.93, p = 0.03). Genotypes rs11767557-
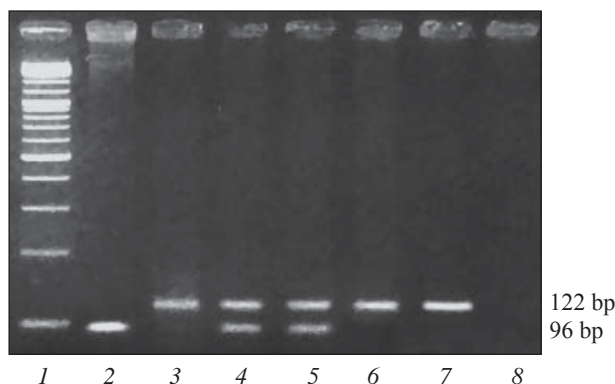
Fig. 2. RFLP analysis of rs11771145 *EPHA1* receptor gene variant (2 % agarose gel electrophoresis): *1* – molecular mass marker (Ladder 100 bp); *2* – individual with homozygous genotype AA; *3, 6, 7* – individuals with heterozygous genotype GA; *4, 5* – individuals with homozygous genotype GG, *8* – negative control

Table 2. **Distribution of genotypes and allele variants in investigated groups**

	Control group, n = 250	ID patients, n = 65
rs11768549 G>A		
Genotype, *n (%)*		
GG	245 (98)	60 (92.3)
GA	5 (2)	5 (7.7)
AA	0	0
Allele, *n (frequency)*		
G	125 (0.99)	495 (0.962)
A	5 (0.01)	5 (0.038)*
rs11767557 T>C		
Genotype, *n (%)*		
TT	141 (56.4)	47 (72.3)
TC	91 (36.4)	17 (26.2)
CC	18 (7.2)	1 (1.5)
TC+CC	109 (43.6)	18 (27.7)*
Allele, *n (frequency)*		
T	373 (0.746)	111 (0.854)
C	127 (0.254)	19 (0.146)*
rs11771145 G>A		
Genotype, *n (%)*		
GG	96 (38.4)	31 (47.7)
GA	117 (46.8)	31 (47.7)
AA	37 (14.8)	3 (4.6)*
GG+AG	213 (85.2)	62 (95.4)*
Allele, *n (frequency)*		
G	309 (0.618)	93 (0.715)
A	191 (0.382)	37 (0.285)*

N o t e s. n – number of individuals; *statistically reliable difference ($p < 0.05$).

TC+CC and rs11771145-AA were associated with significantly lower odds of mild ID developing.

The non-synonymous SNP rs11768549 is located in the coding region (exons 7) of the *EPHA1* receptor gene and results in the mutation of a positive charged Arg492 to an uncharged Gln492 located in the fibronectin type III repeat of the EphA1 ectodomain. This mutation may directly cause the changes in the domain conformational flexibility and might result in the decrease of signal transduction and binding with the ligands or the protein-partners. The SNPs rs11767557 and rs11771145 are located in the *EPHA1 antisense RNA 1* (long non-coding RNA)*,* near the promoter region and may affect the regulation of the *EPHA1* gene expression. Long non-coding RNAs have emerged as key regulators of the gene expression at different levels, including chromatin remodeling, transcriptional control, mRNA stability, mRNA translation, microRNA function, and protein metabolism [31, 32]. Our results suggest that SNPs (rs11768549, rs11767557, rs11771145) in the *EPHA1* gene are associated with idiopathic mild ID. These data can be explained by the changes in the EPHA1 receptor signal transduction efficiency in the rs11768549 minor allele A carriers and/or in the *EPHA1* gene expression levels in individuals with different rs11767557 and rs11771145 genotypes that in turn, may affect the regulation of neurogenesis, axon guidance and synaptic plasticity at least via the EPHA1-ILK-RhoA-ROCK signaling.

Therefore, we propose *EPHA1* as a new candidate gene and the polymorphisms (rs11768549, rs11767557, rs11771145) as new markers of the genetic susceptibility for intellectual disability. Further investigations are necessary to explain the molecular mechanisms of the *EPHA1* involvement in ID pathogenesis.

Acknowledgements

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Асоціація поліморфізму гена *EPHA1* з ідіопатичною легкою інтелектуальною недієздатністю

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Мета. Дослідити можливу асоціацію поліморфізму гена *EPHA1* з легкою інтелектуальною недієздатністю (ІН). **Методи.** Група пацієнтів з легкою (IQ між 50 і 70) ідіопатичною інтелектуальною недієздатністю складалася з 65 індивідів, включаючи 41 (63.1 %) чоловіка і 24 (36.9 %) жінки. Контрольна група складалася з 250 здорових добровольців з різних регіонів України. Генотипування проводили за допомогою ПЛР з подальшим ПДРФ аналізом для rs11768549, rs11767557, rs11771145 та алель-специфічної ПЛР для нової c.1891G>A мутації в гені *EPHA1*. **Результати.** Отримані дані про розподіл генотипів і алельних варіантів гена *EPHA1* в групі пацієнтів з ІН і в контрольній групі. За результатами статистичного аналізу встановлено достовірну асоціацію мінорного rs117685 49- A алеля (OR = 3.96, 95 % CI = 1.13 – 13.89) і алелів дикого типу rs11767557-T (OR = 1.99, 95 % CI = 1.18–3.37) та rs11771145-G (OR = 1.55, 95 % CI = 1.02– 2.37) з більш високим ризиком розвитку легкої ІН (p < 0,05 для всіх). **Висновки.** Наші результати показують, що SNPs (rs11768549, rs11767557, rs11771145) в гені *EPHA1* асоційовані з легкою ідіопатичною інтелектуальною недієздатністю. Тому ми пропонуємо *EPHA1* як новий кандидатний ген, а поліморфізми rs11768549, rs11767557, rs11771145 – як нові маркери генетичної схильності до інтелектуальної недієздатності.

К л ю ч о в і   с л о в а : ген *EPHA1*, інтелектуальна недієздатність, поліморфізм, генетична схильність

Ассоциация полиморфизма гена *EPHA1* с идиопатической легкой интеллектуальной недееспособностью

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Цель. Исследовать возможную ассоциацию полиморфизма гена *EPHA1* с легкой интеллектуальной недееспособностью (ИН). **Методы.** Группа пациентов с легкой (IQ между 50 и 70) идиопатической интеллектуальной недееспособностью состояла из 65 индивидов, включая 41 (63.1 %) мужчину и 24 (36.9 %) женщины. Контрольная группа состояла из 250 здоровых добровольцев из разных регионов Украины. Генотипирование проводили посредством ПЦР с последующим ПДРФ анализом для rs11768549, rs11767557, rs11771145 и аллель- специфической ПЦР для новой c.18 91G>A мутации в гене *EPHA1*. **Результаты.** Были получены данные о распределении генотипов и аллельных вариантов гена *EPHA1* в группе пациентов с ИН и в контрольной группе. Статистический анализ показывает достоверную ассоциацию минорного rs11768549-A аллеля (OR = 3.96, 95 % CI = 1.13 – 13.89) и аллелей дикого типа rs11767557-T (OR = 1.99, 95% CI = 1.18 – 3.37) и rs11771145-G (OR = 1.55, 95 % CI = 1.02– 2.37) с более высоким риском развития легкой ИН (p <0,05 для всех). **Выводы.** Наши результаты показывают, что SNPs (rs11768549, rs11767557, rs11771145) в гене *EPHA1* ассоциированы с легкой идиопатической интеллектуальной недееспособностью. Поэтому мы предлагаем *EPHA1* в качестве нового гена кандидата и полиморфизмы rs11768549, rs11767557, rs11771145 в качестве новых маркеров генетической предрасположенности к интеллектуальной недееспособности.

К л ю ч е в ы е с л о в а: ген *EPHA1*, интеллектуальная недееспособность, полиморфизм, генетическая предрасположенность.