MGMT expression: insights into its regulation. 2. Single nucleotide polymorphisms

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High intra- and interindividual variations in the expression levels of the human O6-methylguanine-DNA methyltransferase (MGMT) gene have been observed. This DNA repair enzyme can be a cause of resistance of cancer cells to alkylating chemotherapy. It has been studied the association of single nucleotide polymorphisms (SNPs) of MGMT with the risk for different types of cancer, progression-free survival in patients with cancer treated with alkylating chemotherapy, as well as an effect of SNPs on the MGMT gene expression and activity of the enzyme. SNPs have been suggested to be the factors which influence the levels of interindividual variability of the MGMT expression. Therefore, the aim of this paper was to review the experimental data on SNPs of the human MGMT gene, which are associated with cancer, as well as on location of MGMT-SNPs in regulatory and protein-coding regions of the gene in relation to its regulation. Lots of MGMT SNPs, which could affect the gene expression and result in interindividual MGMT variability or the enzyme resistance to pseudosubstrate inhibitors, have been revealed within the promoter and enhancer regions, the 5'- and 3'-UTRs and introns of the MGMT gene, as well as within the protein-coding region. Many of them may have regulatory effect.

Keywords: O^6-methylguanine-DNA methyltransferase (MGMT), gene regulation, single nucleotide polymorphism (SNP), transcription factor binding site.

Introduction. The expression of the O^6-methylguanine-DNA methyltransferase (MGMT), the DNA repair enzyme responsible for removing alkylation adducts from the O^6-guanine in DNA, and its activity determine cell response to alkylating agents, including anticancer chemotherapy, preventing mutations and cell death. This enzyme can provide resistance of cancer cells to such therapy. The high intra- and interindividual variations in the *MGMT* expression levels have been observed, indicating to a complicated regulation of this gene [1, 2].

It has been suggested that single nucleotide polymorphisms (SNPs) are the factors which influence the levels of interindividual variability of the *MGMT* expression [3, 4]. The association of some *MGMT* polymorphisms with the risk for different types of cancer, as well as the effects of polymorphic variations on the gene expression and activity of this enzyme are discus-

sed in [3]. Many known SNPs of the human *MGMT* gene, which could affect the expression and result in interindividual *MGMT* variability or the resistance of the enzyme to pseudosubstrate inhibitors, have been revealed within the promoter and enhancer regions, the 5'- and 3'-UTRs and introns of the *MGMT* gene, as well as within the protein-coding region [3, 4]. It has been shown that at least two intragenic SNPs have the influence upon an interindividual variation of the MGMT activity in peripheral blood mononuclear cells [5], as well as in normal human lung tissue [6].

Currently, disease- and trait-associated SNPs are rapidly being identified in the genome wide association studies and using related strategies [7]. The majority (~93 %) of these variants lie within non-coding sequences, which are concentrated in regulatory DNA marked by deoxyribonuclease I (DNaseI) hypersensitive sites (DHSs) [8]. Thus, SNPs in functionally important non-coding DNA regions could make a significant
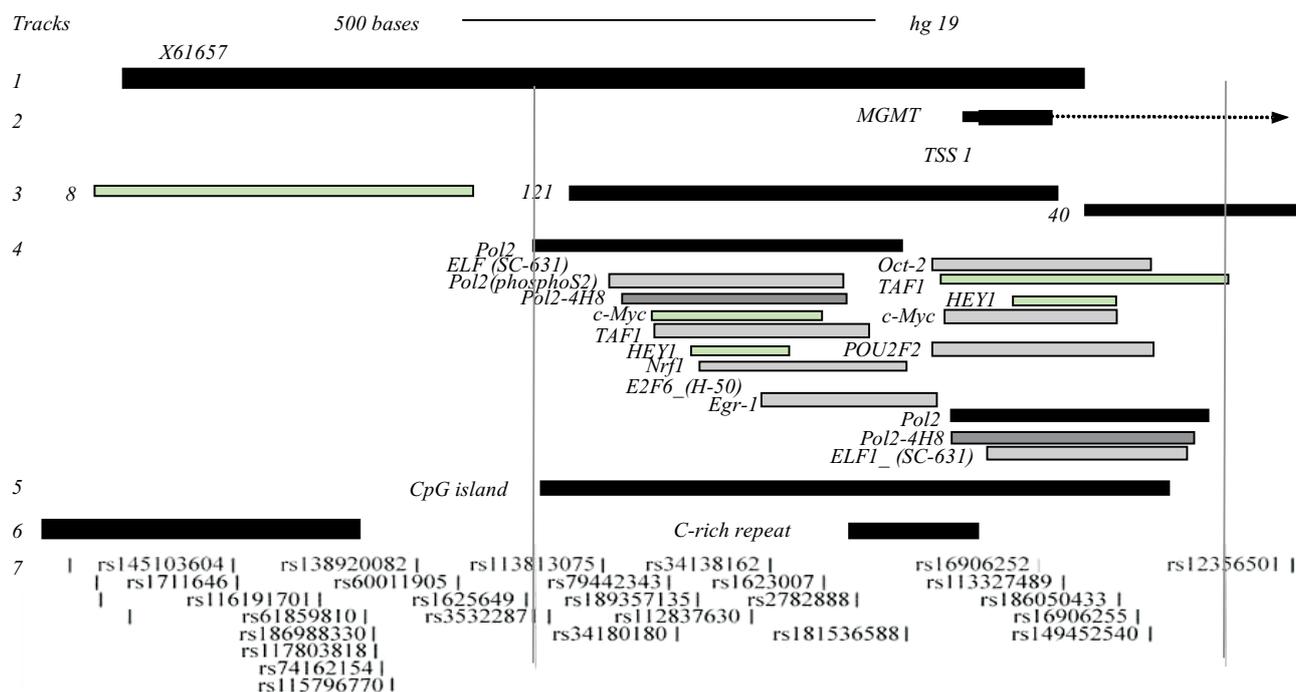
Fig. 1. Single nucleotide polymorphisms (SNPs) from ENCODE [18] within promoter region of the human *MGMT* gene. The open chromatin region of *MGMT* promoter, marked by *DHS* and overlapped with *TF ChIP-seq* binding sites, is separated by straight lines: *1* – the human *MGMT* promoter *X61657* from BLAT search; *2* – *RefSeq* gene and TSS location; *3* – DNaseI hypersensitive regions, marked as gray and dark boxes, darkness of which is proportional to the maximum signal strength observed in any cell line (the number to the left of the box shows how many cell lines are hypersensitive in the region); *4* – the track of *TF ChIP-seq*, which shows regions where TFs bind to DNA as assayed in different cell lines (the darkness of the box is proportional to the maximum signal strength observed in any cell line); *5* – CpG island; *6* – repeating elements (the open chromatin region contains C-rich repeat (Low complexity Family and Class), 156 bps in length at position chr10:131265319-131265474 on plus strand of DNA); *7* – single nucleotide polymorphisms track from dbSNP build 137 which have a minor allele frequency of at least 1 %, mapping only once to reference assembly

contribution to the phenotypic variation and disease susceptibility among individuals [9]. Evaluation of extent and number of SNPs detected within the human *MGMT* gene can be done by looking at the track of all SNPs in the protein-coding and non-coding regions including promoter from the UCSC genome browser (the University of California Santa Cruz, Figure in Supplement). Since disease-associated SNPs systematically perturb the transcription factor (TF) recognition sequences and frequently alter allelic chromatin states, it is suggested the involvement of some SNPs in transcriptional regulatory mechanisms, including modulation of promoter and enhancer elements and enrichment within the expression quantitative trait loci [8]. In particular, SNPs in the regulatory non-coding regions can influence the DNA helical conformations, protein binding, methylation status of CpG dinucleotides, transcript splicing, *etc*.

The aim of this paper is to review the experimental data on SNPs of the human *MGMT* gene, which are as-

sociated with cancer, as well as on location of MGMT-SNPs in regulatory and protein-coding regions of the gene in relation to its regulation. This article is the second part of a thematic series on the regulation of *MGMT* expression.

SNPs in regulatory regions of the human *MGMT* gene. There are several known SNPs in the promoter, enhancer region, and introns of the human *MGMT* gene. They include G135T, G290A, C485A, C575A, G666A, C777A, G795C, A1034G and C1099T (numbered according to the X61657) [5, 10–12]. The X61657 is a genomic clone 1157 base pairs in length which contains the sequence of the 5'-upstream region of the human *MGMT* gene with the promoter activity and the first untranslated exon, taken from the NIH genetic sequence database GenBank [13, 14]. We have aligned X61657 to chromosome 10 by using Nucleotide Blast program (http://blast.ncbi.nlm.nih.gov/Blast.cgi) and BLAT alignment tool [15] (Fig. 1).

Table 1
SNPs from dbSNP build 137 within open chromatin area of the human MGMT gene

SNP ID from dbSNP/137	Position	Strand	Observed	Reference allele	Allele frequencies	UCSC's predicted function relative to *MGMT* gene tracks
rs1625649	chr10:131264931	–	G/T	T	G: 61.53 %; T: 38.47 %	upstream_gene_variant (523 bases)
rs35322871	chr10:131264957	+	–/G	G	Not indicated	upstream_gene_variant (497 bases)
rs113813075	chr10:131265021	+	A/C	C	A: 2.78 %; C: 97.22 %	upstream_gene_variant (433 bases)
rs79442343	chr10:131265102	+	A/G	G	A: 4.39 %; G: 95.61 %	upstream_gene_variant (352 bases)
rs34180180	chr10:131265112	+	A/G	G	A: 3.42 %; G: 96.58 %	upstream_gene_variant (342 bases)
rs189357135	chr10:131265135	+	A/G	G	A: 0.41 %; G: 99.59 %	upstream_gene_variant (319 bases)
rs112837630	chr10:131265201	+	G/T	G	Not indicated	upstream_gene_variant (253 bases)
rs34138162	chr10:131265223	+	A/C	C	A: 5.35 %; C: 94.65 %	upstream_gene_variant (231 bases)
rs1623007	chr10:131265287	–	A/T	T	A: 3.11 %; T: 96.89 %	upstream_gene_variant (167 bases)
rs2782888	chr10:131265328	–	A/C	A	C: 0.091 %; G: 96.98 %; T: 2.93 %	upstream_gene_variant (126 bases)
rs181536588	chr10:131265388	+	A/T	T	A: 10.03 %; T: 89.97 %	upstream_gene_variant (66 bases)
rs16906252	chr10:131265545	–	A/G	G	A: 3.42 %; G: 96.58 %	MGMT (NM_002412): synonymous_variant R (CGC) → R (CGT)
rs113327489	chr10:131265576	+	C/G	G	Not indicated	intron_variant
rs186050433	chr10:131265642	+	C/T	C	C: 99.13 %; T: 0.87 %	intron_variant
rs16906255	chr10:131265665	–	A/C	A	A: 8.02 %; C: 91.98 %	intron_variant
rs149452540	chr10:131265680	+	A/C	C	A: 0.96 %; C: 99.04 %	intron_variant

The changes within the promoter and enhancer regions can affect the gene expression potentially, but it is difficult to check this, because many other factors can influence the *MGMT* expression. In particular, it is suggested that the C575A variant revealed in melanoma patients could influence the gene transcription [10], as it is located closely to the binding site (BS) with the eukaryotic heat shock factor [13]. The C1099T polymorphism located within the enhancer region in the exon 1 [16] has been shown to increase the *MGMT* promoter-enhancer activity in luciferase assay [11].

Since recent numerous studies have identified many disease- and trait-related genetic variants [7], we analysed the human *MGMT* gene non-coding and coding regions for SNP enrichment. The Fig. 1 presents a track that contains the information about SNPs located within an open chromatin area marked by DHS and overlapped with TF ChIP-seq BSs [17, 18]. They include rs1625649; rs35322871; rs113813075; rs79442343; rs34180180; rs189357135; rs112837630; rs34138162; rs1623007; rs2782888; rs181536588; rs16906252; rs113327489; rs186050433; rs16906255; rs149452540 (Table 1). The location and data on SNPs were taken from the UCSC Genome Browser, the SNP database (dbSNP, build 137) at NCBI [17] and the SNPedia resource, which is focused on the medical, phenotypic and genealogical associations of SNPs [19].

Some of the revealed SNPs are associated with cancer. In particular, the TT genotype of rs1625649 located 523 bases upstream the transcription start site (TSS) of *MGMT* was found to correlate with a worse progression-free survival in patients with metastatic colorectal cancer treated with oxaliplatin-based chemotherapy than the combined GG + GT genotypes [20]. The coding-synonimous polymorphism R (CGC) → R (CGT) in NM_002412 (rs16906252, Table 1) was found to have
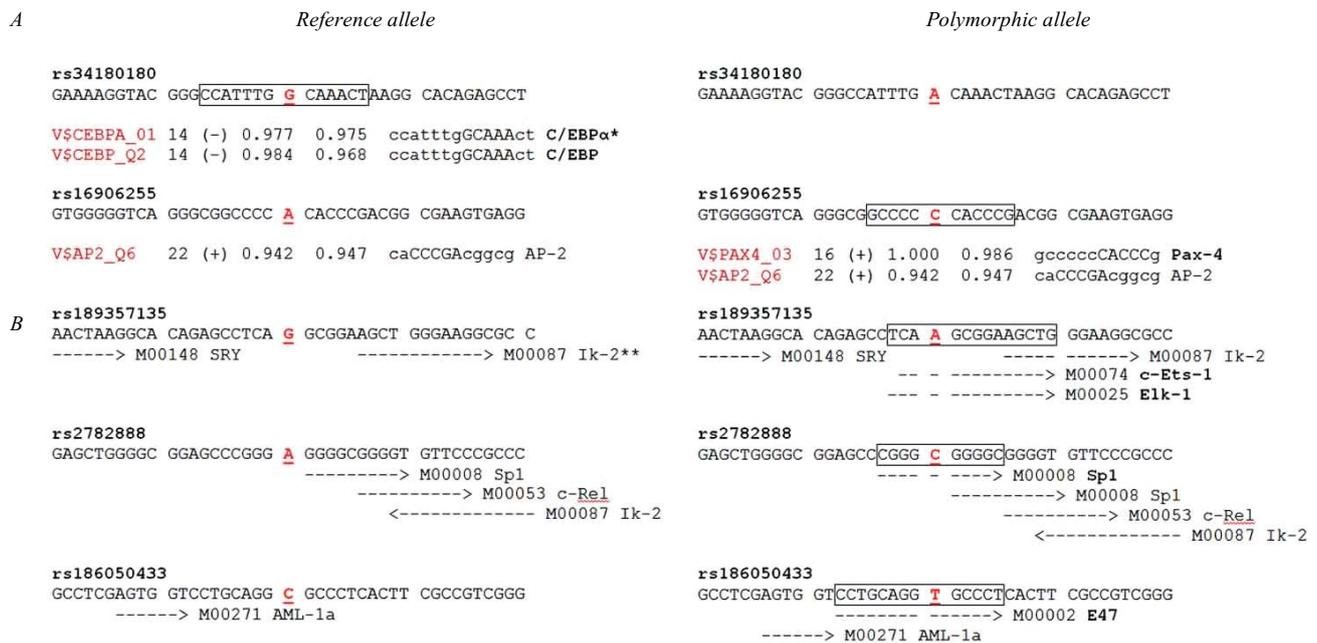
A   *Reference allele*   *Polymorphic allele*

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rs34180180                                           rs34180180
GAAAAGGTAC GGGCCATTTG G CAAACTAAGG CACAGAGCCT         GAAAAGGTAC GGGCCATTTG A CAAACTAAGG CACAGAGCCT

V$CEBPA_01  14 (-) 0.977  0.975  ccatttgGCAAAct C/EBPα*
V$CEBP_Q2   14 (-) 0.984  0.968  ccatttgGCAAAct C/EBP

rs16906255                                           rs16906255
GTGGGGGTCA GGGCGGCCCC A CACCCGACGG CGAAGTGAGG         GTGGGGGTCA GGGCGGCCCC C CACCCGACGG CGAAGTGAGG

V$AP2_Q6    22 (+) 0.942  0.947  caCCCGAcggcg AP-2     V$PAX4_03   16 (+) 1.000  0.986  gcccccCACCCg Pax-4
                                                     V$AP2_Q6    22 (+) 0.942  0.947  caCCCGAcggcg AP-2
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B
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rs189357135                                          rs189357135
AACTAAGGCA CAGAGCCTCA G GCGGAAGCT GGGAAGGCGC C        AACTAAGGCA CAGAGCCTCA A GCGGAAGCTG GGAAGGCGCC
------> M00148 SRY         -----------> M00087 Ik-2** ------> M00148 SRY       -----  ------> M00087 Ik-2
                                                               -- - ---------> M00074 c-Ets-1
                                                               --- - ---------> M00025 Elk-1

rs2782888                                            rs2782888
GAGCTGGGGC GGAGCCCGGG A GGGGCGGGGT GTTCCCGCCC         GAGCTGGGGC GGAGCCCGGG C GGGGCGGGGT GTTCCCGCCC
          ---------> M00008 Sp1                                 ---- - ---------> M00008 Sp1
              ----------> M00053 c-Rel                              ----------> M00008 Sp1
                  <------------ M00087 Ik-2                            ----------> M00053 c-Rel
                                                                         <------------ M00087 Ik-2

rs186050433                                          rs186050433
GCCTCGAGTG GTCCTGCAGG C GCCCTCACTT CGCCGTCGGG         GCCTCGAGTG GTCCTGCAGG T GCCCTCACTT CGCCGTCGGG
         ------> M00271 AML-1a                                 --------- ------> M00002 E47
                                                               ------> M00271 AML-1a
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Fig. 2. Examples of effect of polymorphic allele upon change of recognition motif for TF. Bioinformatic analysis has been done by using Match (*A*) and TFSEARCH (*B*) programs. Notes: *matrix identifier, position (strand), core match, matrix match, sequence (always the plus strand is shown), factor name; **TFMATRIX entries with High-scoring

a strong association with the promoter methylation (silencing) in colorectal cancer [21, 22]. Also, it has been shown, that polymorphism C485A in promoter was associated with increased risk of lung cancer in a Korean population, despite this SNP did not have an effect on the promoter activity [12].

Many other SNPs have been also found in introns (Suppl. Fig.). It has been shown that the A allele of the rs7087131 variant of the *MGMT* gene (chr10:131474474, plus DNA strand; ref. allele G) was associated with a decreased risk of esophageal squamous cell carcinoma [23], while rs12268840 (chr10:131325299, in intron 1, plus DNA strand) – with increased risks of adenocarcinoma of the esophagus [24].

We discussed in our previous paper [25] that promoter of the human *MGMT* gene from GenBank (X61657) contained TSS, which is located within the CpG island (CGI), DHS and exon 1 of the gene (Fig. 1). The overlapping of CGI and DHS marks the open chromatin region and the location of active cis-regulatory elements. The ENCODE studies of different cell lines have demonstrated by using ChIP-seq (chromatin immunoprecipitation with antibodies specific to the TF followed by sequencing of the precipitated DNA), that

the MGMT promoter can be targeted by several TFs in open chromatin region including c-Myc, E2F6, Egr-1, ELF1, HEY1, Nrf1, Oct-2, Pol2, POU2F2, TAF1 (Fig. 1, Table 2). TFBSs form two clusters located close to each other. It has been identified a 59 bp enhancer within the second cluster, which produced increased transcriptional activity in a reporter gene assay and was required for efficient promoter function [16]. This enhancer sequence is located at the first exon/intron at position +144 to +202 with respect to the TSS of the *MGMT* promoter X61657 [16]. This sequence overlaps with BSs for c-Myc, Oct-2, Pol2, POU2F2, TAF1 revealed in different cell types (Fig. 1).

Since SNPs can perturb TF recognition sites, we have analyzed the DNA sequences around polymorphic nucleotides ± 20 bases for any changes (Fig. 2) using Match, which utilizes a library of positional weight matrices from TRANSFAC® Public 6.0 (http://www.gene-regulation.com/pub/programs.html#match), as well TFSEARCH program (http://www.cbrc.jp/research/db/TFSEARCH.html). It has been revealed using Match, that polymorphic A allele of rs34180180 caused disappearance of BS for C/EBP (CCAAT/enhancer binding factor), and polymorphic C allele of rs16906255 for-

Table 2
Transcription Factor ChIP-seq from ENCODE [18]: binding sites within open chromatin area of the human MGMT promoter

Factor	Position	Genomic Size	Cluster Score (out of 1000)
Pol2	chr10:131264940-131265389	450	1000
Pol2 (phos-phoS2)	chr10:131265030-131265313	284	351
Pol2-4H8	chr10:131265045-131265320	276	487
Pol2	chr10:131265442-131265759	318	918
Pol2-4H8	chr10:131265444-131265734	291	395
ELF1_(SC-631)	chr10:131265006-131265281	276	157
ELF1_(SC-631)	chr10:131265483-131265729	247	367
Oct-2	chr10:131265419-131265686	268	294
HEY1	chr10:131265510-131265642	133	242
HEY1	chr10:131265128-131265249	122	243
POU2F2	chr10:131265419-131265686	268	293
c-Myc	chr10:131265081-131265290	210	236
c-Myc	chr10:131265434-131265643	210	334
TAF1	chr10:131265086-131265349	264	311
TAF1	chr10:131265429-131265771	343	259
Nrf1	chr10:131265139-131265388	250	291
E2F6_(H-50)	chr10:131265205-131265404	200	84
Egr-1	chr10:131265216-131265431	216	376

med BS for Pax-4 (member of the paired box family of TFs). Polymorphic A allele of rs189357135 has been shown by using TFSEARCH to create two new BSs for c-Ets-1 and Elk-1 (TCF) TFs, C allele of rs 2782888 – for SP1, and T allele of rs186050433 – for E47 TF. Thus, this short prediction analysis has shown a possible implication of SNPs in the change of recognition sequences for TFs within the human *MGMT* promoter. Also, SNPs can change the methylation pattern of CGI of promoter and gene body, in particular due to the forming new or destruction of existing CpG dinucleotides in DNA.

For example, in an open chromatin region of the given gene there are three SNPs (rs79442343, rs113327489, rs186050433), a reference allele of which forms CpG dinucleotide (Table 1). The rs2782888 SNP forms such dinucleotide, increasing a total number of CpG dinucleotides within CGI, methylation of which can potentially be attractive to binding with methyl-CpG binding proteins which in turn recruit histone deacetylase complexes and cause the chromatin condensation [26].

Also, we have classified SNPs revealed from the open chromatin area of the human MGMT promoter by using Regulome database [27] to identify a putative regulatory potential and a functional role of variants (Table 3). According to this database, only three of the analyzed SNPs (rs112837630, rs2782888, rs16906255) belong to the group of variants, which likely affect TF binding, since these SNPs are located within TF binding motif and DNase hypersensitive site [27]. However, the Fig. 1 shows higher amount of such SNPs, which are located within an open chromatin area and may affect TF binding. This difference is probably caused by the fact that RegulomeDB contains data from the old built 132 of dbSNP.

SNPs in the protein-coding region of the human MGMT gene. SNPs in the protein-coding region of the *MGMT* gene were also found out in populations of healthy donors and patients with different types of cancers. For instance, SNP at codon L53L (silent coding effect) in exon 3 was detected in melanoma patients and healthy Swedish individuals [10, 28] and those from the UK [5], L84F (missense) in exon 3 – in melanoma patients and healthy individuals in Sweden [10, 28], lung patients and healthy controls from Poland [11] and in Caucasian population [29], as well as from the UK [5], I143V (rs2308321, missense) in exon 5 – in Swedish [10, 28], Polish [11], English [5] and Caucasian [29] populations. SNP at codon G160R (missense) in exon 5 was detected in young patients with adult type cancers and in the control group [30]. K178R (rs2308327, missense) in exon 5 was identified in melanoma patients and healthy individuals in Sweden [10, 28], in lung cancer patients and healthy donors from Poland [11] and the UK [5]. A silent SNP A197A in exon 5 was found in melanoma patients and healthy Swedish individuals [10].

Frequent in the human population polymorphic variants L84F, I143V and K178R are shown to have the same DNA repair efficiency as the wild-type MGMT enzyme, but they are more resistant to the pseudosub-

Table 3
Summary of analysis of SNPs located within the human MGMT promoter by using Regulome DB [27] within open chromatin area of the human MGMT promoter

dbSNP ID	Category	Other resources
rs1625649	4*	UCSC | ENSEMBL | dbSNP
rs35322871	4	UCSC | ENSEMBL | dbSNP
rs113813075	4	UCSC | ENSEMBL | dbSNP
rs79442343	4	UCSC | ENSEMBL | dbSNP
rs34180180	4	UCSC | ENSEMBL | dbSNP
rs112837630	2b**	UCSC | ENSEMBL | dbSNP
rs34138162	3a***	UCSC | ENSEMBL | dbSNP
rs1623007	4	UCSC | ENSEMBL | dbSNP
rs2782888	2b	UCSC | ENSEMBL | dbSNP
rs16906252	4	UCSC | ENSEMBL | dbSNP
rs113327489	4	UCSC | ENSEMBL | dbSNP
rs16906255	2b	UCSC | ENSEMBL | dbSNP

Category Description: * (4) – Minimal TF binding evidence + DNase peak; ** (2b) – Likely to affect TF binding + any motif + DNase footprint + DNase peak; *** (3a) – Less likely to affect TF binding + any motif + DNase peak.

strate inhibitors, such as O^6-benzylguanine and O^6-(4-bromothenyl) guanine, or PaTrin-2 [3, 4]. In particular, it has been revealed that I143V and I143V/K178R variants have no effect upon the DNA repair activity compared with the wild-type *MGMT* [28]. Despite I143V is located closely to the C145 residue at the active site of *MGMT*, this variant has been shown to have no effect on the activity of the enzyme, but it was more resistant to inactivation by the PaTrin-2 [5]. A higher sensitivity of proteins to inactivation by PaTrin-2 has been also observed for variants I143-K178 and I143-R178 comparable with the V143-K178 and V143-R178 alleles [5].

SNPs L84F and I143V showed a statistically significantly increased risk of lung cancer in Caucasian population, especially in smoking women with non-small cell lung cancer [29], and of adenocarcinoma of the esophagus [24]. In another study, distributions of L53L and L84F polymorphisms did not significantly differ between the lung cancer patients and healthy controls [12]. I143V and K178R have been recently shown to corre-late with an increased risk of temozolomide-induced myelosuppression [31]. It has been shown that K178R is associated with increased risks of adenocarcinoma of the esophagus [24], lung cancer risk [32], and with colorectal cancer risk [33]. The association of MGMT polymorphisms with a risk for lung, breast, colorectal and endometrial cancer is reviewed in [3].

Conclusions. Many SNPs have been identified within the human MGMT gene coding and non-coding regions, in particular within the promoter region, 5'- and 3'-UTRs and introns. Some SNPs, which are detected in the open chromatin area of promoter region and marked by DHS, overlap with experimentally revealed in different cell lines TF BSs. Consequently, they can perturb these recognition sites, change methylation pattern, due to forming new or destruction of existing CpG dinucleotides in DNA, and as a result, such SNPs may affect the gene expression. The association of *MGMT* SNPs with the risk for different types of cancer, progression-free survival in patients with cancer treated with alkylating chemotherapy, as well as an effect of SNPs on the gene expression, activity of this enzyme and its resistance to pseudosubstrate inhibitors were discussed. Thus, SNPs can be the factors which influence the levels of interindividual variability of the *MGMT* expression.

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Експресія гена *MGMT*: розуміння її регуляції.
2. Однонуклеотидні поліморфізми

Резюме

Відомо, що в рівнях експресії гена O^6-метилгуанін-ДНК метилтрансфераза (MGMT) людини існують значні внутрішньо- та міжіндивідуальну варіації . Цей репаративний фермент може спричиняти стійкість ракових клітин до алкілувальної хіміотерапії. Вивчено асоціації однонуклеотидних поліморфізмі (ОНП) MGMT з ризиком багатьох типів раку, виживанням пацієнтів без прогресування захворювання після алкілувальної хіміотерапії, а також вплив ОНП на експресію гена MGMT та активність даного фермента. Припускають, що ОНП є факторами, які чинять вплив на рівні міжіндивідуальної варіації експресії MGMT. В огляді розглянуто експериментальні дані щодо ОНП гена MGMT людини, асоційованих з раком, а також стосовно локалізації ОНП MGMT у регуляторних і білок-кодуючій ділянках гена, залучених до його регуляції. Значну кількість ОНП MGMT з потенційною здатністю впливати на експресію гена та спричиняти міжіндивідуальні варіації MGMT або на стійкість фермента до

псевдосубстратних інгібіторів виявлено у промоторній та ен-
хансерній областях, 5'- і 3'-нетрансльованих ділянках та інтро-
нах гена MGMT, а також у білок-кодуючій ділянці. Багато з них
можуть слугувати регуляторними факторами.

*Ключові слова: О⁶-метилгуанін-ДНК метилтрансфераза
(MGMT), регуляція експресії гена, однонуклеотидні поліморфізми
(ОНП), сайт зв'язування з транскрипційним фактором.*

А. П. Яцышина, О. В. Пидпала, Л. Л. Лукаш

Экспрессия гена *MGMT*: понимание ее регуляции.
2. Однонуклеотидные полиморфизмы

Резюме

*Известно, что существуют значительные внутри- и межинди-
видуальные вариации уровней экспрессии гена О⁶-метилгуанин-
ДНК метилтрансфераза (MGMT) человека. Этот фермент ре-
парации ДНК может быть причиной устойчивости раковых
клеток к алкилирующей химиотерапии. Изучены ассоциации одно-
нуклеотидных полиморфизмов (ОНП) MGMT с риском для раз-
личных типов рака, выживаемостью пациентов без прогресси-
рования заболевания после алкилирующей химиотерапии, а также
влияние ОНП на экспрессию гена MGMT и активность этого фер-
мента. Высказано предположение, что ОНП являются фактора-
ми, влияющими на межиндивидульные уровни вариабельности
экспрессии MGMT. В обзоре рассмотрены экспериментальные
данные относительно ОНП гена MGMT человека, ассоцииро-
ванных с раком, а также по локализации ОНП MGMT в регулятор-
ных и белок-кодирующих участках гена, причастных к регулиро-
ванию. Большое количество ОНП MGMT с потенциальной спо-
собностью влиять на экспрессию гена и приводить к межинди-
дуальной вариабельности MGMT или на стойкость фермента к
псевдосубстратным ингибиторам выявлено в промоторной и эн-
хансерной областях, 5'- и 3'-нетранслируемых участках и интро-
нах гена MGMT, а также в белок-кодирующем участке. Многие
из них могут служить регуляторными факторами.*

*Ключевые слова: О⁶-метилгуанин-ДНК метилтрансфераза
(MGMT), регуляция експресии гена, однонуклеотидный полимор-
физм (ОНП), сайт связывания с транскрипционным фактором.*

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