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БІОЛОГІЧНА СЕКЦІЯ – "THE IMPORTANCE OF G. GAMOW'S IDEAS FOR BIOLOGY OF THE 21ST CENTURY" XXII МІЖНАРОДНОЇ ГАМОВСЬКОЇ КОНФЕРЕНЦІЇ, ЩО ВІДБУВАЛАСЯ У СЕРПНІ 2022 р. В ОДЕСЬКОМУ НАЦІОНАЛЬНОМУ УНІВЕРСИТЕТІ ІМЕНІ І.І. МЕЧНИКОВА

25.08.2022 відбулася робота Біологічної секції щорічної Міжнародної Гамовської конференції у режимі он-лайн на платформі Zoom. Традиційно Біологічна секція проходить під назвою "The Importance of G. Gamow's Ideas for Biology of the 21st Century".

У роботі секції брали участь відомі науковці, що ведуть дослідження в області молекулярної біології та генетики з провідних наукових установ України, Канади, США, Великої Британії і Німеччини, також брали участь аспіранти та студенти (загалом 52 учасники). Було представлено 13 усних доповідей, серед них доповіді – «Генетичні ресурси рослин для підвищення стресостійкості – на прикладі зернових культур» – проф., д.б.н. Бьорнера А. (Інститут генетики рослин і досліджень культурних рослин імені Лейбніца, Гатерслебен, Німеччина); «Дослідження загальногеномних асоціації для виявлення локусів та генів-кандидатів, що впливають на вміст білка в зерні пшениці м'якої» – проф., д.б.н. Мішевої С. (Інститут фізіології рослин і генетики Болгарської академії наук, Софія, Болгарія); «Дослідження молекулярної еволюції та таксономічне застосування 5S рДНК при аналізі роду *Aconitum*» – проф., д.б.н. Волкова Р.А. (Чернівецький національний університет імені Юрія Федьковича, Чернівці, Україна); «Подолання селекційних бар'єрів для пшениці» – проф. Гріффітса С. і докт. Вінген Л.У. (Центр Джона Іннеса, Норвіч, Велика Британія); «Оцінка сучасного стану популяцій *Gentiana lutea* L. Українських Карпат: Еколого-генетичні підходи» – доц., к.б.н. Прокоп'як М.З. (Тернопільський національний педагогічний університет імені Володимира Гнатюка, Тернопіль, Україна); «Часова динаміка спектрів фонового світіння *Photobacterium phosphoreum*» – проф., д.б.н. Мартинюка В.С. (Київський національний університет імені Тараса Шевченка, Київ, Україна.); «Нові мутації *STARD8* і *STARD9,* виявлені в 46,XY пацієнтів з гонадальним дисгенезом, підтримують ці гени як гени-кандидати, що обумовлюють ПРС (порушення розвитку статі)» – Сірохи Д. А. і проф., д.б.н. Лівщиць Л.А. (Інститут молекулярної біології і генетики НАН України, Київ, Україна); «*MYD88* і *CXCR4*, два гени, які відіграють вирішальну роль у макроглобулінемії Вальденстрема» – д.б.н. Мончака Ю. (зав. відділу молекулярної генетики, Центр охорони здоров'я університету Макгілла,

Університет Макгілла та Монреальський університет, Канада); «Джордж Гамов і генетичний код ДНК» – проф., д. ф. н. Сегре Г. (Університет Пенсільванії, США).

Серед підготовлених доповідей вважаємо необхідним відмітити високу якість та актуальність виконаних на сучасному рівні досліджень молодих науковців: «Біоінформатичний аналіз нуклеотидних послідовностей локусів *Gli-1 Triticum aestivum* L.» – аспірантки Попович Ю. А. (ОНУ імені І. І. Мечникова, Одеса, Україна); «Скринінг продуцентів тіопептидних антибіотиків за допомогою репортерної системи на основі промотору гена *tipA*» – аспіранта Тістечка С. І. (Львівський національний університет імені Івана Франка, Україна); «Довгі та короткі варіанти 5S рДНК у геномах видів *Apis*» – аспірантки Рошки Н. М. (Чернівецький національний університет імені Юрія Федьковича, Чернівці, Україна).

Як позитивну рису роботи біологічної секції було відмічено багатоплановість охопленої тематики, що має генетичне підґрунтя, та перспективність досліджень, що виконуються на стику наук.

Учасники Біологічної секції звернули увагу, що Г. А. Гамов зробив внесок у розвиток саме молекулярної біології, поставивши питання про розшифрування генетичного коду, тому необхідно у назву щорічної Гамівської конференції, яку організовують астрономи і фізики ОНУ, додати – «Molecular biology», щоб назва конференції охоплювала всі напрямки досліджень, в розвиток яких зробив внесок Г. А. Гамов: «Astronomy and Beyond: Astrophysics, Cosmology and Gravitation, Astroparticle physics, Rradioastronomy, Astrobiology and Molecular biology».

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Börner A.
Leibniz Institute of Plant Genetics and Crop Plant Research (IPK), Gatersleben, Germany, e-mail: boerner@ipk-gatersleben.de

PLANT GENETIC RESOURCES FOR IMPROVING STRESS TOLERANCE – EXAMPLES FOR CEREALS

Plant genetic resources for food and agriculture (PGRFA) play a major role for global food security. The most significant and widespread mean of conserving PGRFA is *ex situ* conservation. World-wide 7.4 million accessions are stored in about 1,750 *ex situ* genebanks. Plant *ex situ* genebank collections comprise seed genebanks, field genebanks as well as *in vitro* and cryo collections. Species whose seed can be dried, without damage, down to low moisture contents can be conserved in specially designed cold stores. Such “orthodox” seeds can be expected to maintain a high level of vigour and viability for decades. Field genebanks, *in vitro* and cryo

storage are used primarily for species which are either vegetatively propagated or which have non-orthodox seeds that cannot be dried and stored for long periods. With a total inventory of 150,000 accessions from 3,212 plant species and 776 genera, the 'Federal *ex situ* Genebank of Germany' in Gatersleben holds one of the most comprehensive collections worldwide. It comprises wild and primitive forms, landraces as well as old and more recent cultivars of mainly cereals but also other crops. Starting in the 1920's material was accumulated systematically. Seed storage is managed in large cold chambers at –18 °C. Seeds are kept in glass jars, covered with bags containing silica gel (active collection) and in aluminum bags under vacuum (base collection). The maintenance of the collection requires regeneration. Each year between 8 and 10 thousand accessions are grown either in the field or in glasshouses. The collection has been widely characterized and evaluated. In the cereals, mainly wheat and barley, a number of bi-parental mapping populations and association mapping panels have been established to allow for the genetic analysis of various traits. The current focus covers resistance/tolerance to a number of biotic and abiotic stresses, in particular drought and cold.

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Kartseva T.[1], Alqudah A. M.[2], Aleksandrov V.[1], Doneva D.[1], Börner A.[3], Misheva S.[1]

[1]Institute of Plant Physiology and Genetics, Bulgarian Academy of Sciences, Sofia, Bulgaria, e-mail: slandjeva@gmail.com

[2]Aarhus University, Aarhus, Denmark

[3]Leibniz Institute of Plant Genetics and Crop Plants Research (IPK Gatersleben), Gatersleben, Germany

GENOME-WIDE ASSOCIATION STUDY REVEALS LOCI AND CANDIDATE GENES FOR GRAIN PROTEIN CONTENT IN BREAD WHEAT

Wheat is a primary source of nutrition for about 40% of the population and provides approximately 20% of calories and 22% of proteins in the human diet. The protein level in the grain of modern varieties is generally low, therefore improvement of the wheat nutritional quality, such as increased protein is a key breeding target. A considerable proportion of the variance in wheat grain protein content (GPC) is attributed to genetic factors. To identify genomic regions underlying the GPC, we evaluated a diverse panel of 255 wheat accessions from 27 countries from five continents using seeds from three-year field trials. The trait phenotyping revealed wide genetic variation. The association mapping performed with 17,093 SNP markers and based on the best linear unbiased estimations (BLUEs) over years

identified six significant marker-trait associations on chromosomes 1D, 3A, 3B, 3D and 5A. The candidate genes search revealed that most relevant putative candidate genes hit directly by the significant SNPs or present within a window of 2 Mbp from them, included sequences encoding: 11S globulin seed storage protein ("triticin"); a subtilisin-like serine protease; transporter proteins; transcription factors and proteins with post-translational regulatory functions; metabolic proteins involved in the biosynthesis of macromolecules, as well as a number of protective and structural proteins. For quantitative traits, finding associations with molecular markers within or near the detected putative candidate genes is a potential tool to reduce length of selection cycles and opens new possibilities for advancing crop improvement.

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Tynkevich Y. O.[1], Novikov A. V.[2], Chorney I. I.[1], Volkov R. A.[1]
[1] Yuriy Fedkovych Chernivtsi National University, Chernivtsi, Ukraine,
e-mail: r.volkov@chnu.edu.ua
[2] State Museum of Natural History, National Academy of Sciences of Ukraine, Lviv, Ukraine

MOLECULAR EVOLUTION AND TAXONOMIC APPLICATION OF 5S rDNA IN THE GENUS *ACONITUM*

The genus *Aconitum* L. includes a large number of poisonous and pharmaceutically important plants. One of the major diversity centers of this genus is located in the Eastern Carpathians area. In this region there are many representatives of the genus with unclear taxonomic status, in particular, members of the complex *A. anthora* s.l. The taxonomic position of this complex within the genus also remains controversial, as the regions of the chloroplast and nuclear genomes previously used for phylogenetic analysis appeared to be insufficiently variable. Therefore, the search for an optimal molecular marker with a high level of polymorphism within the genus *Aconitum* remains a relevant task.

The 5S rDNA intergenic spacer (IGS) is an evolutionarily variable region of the nuclear genome, which was previously successfully applied for phylogenetic reconstruction in many groups of angiosperms. Here we used analysis of IGS in order to clarify taxonomy of the genus *Aconitum*. Combining molecular cloning, sequencing, and bioinformatic methods, we obtained 5S rDNA IGS sequences for representatives of the *A. anthora* complex and phylogenetically distant species of the subgenera *Aconitum* and *Lycoctonum*. Analysis of IGS sequences showed that

this region is relatively long in species of the genus, ranging in length from 574 to 619 bp. The IGS variability is due to numerous nucleotide substitutions, while short oligonucleotide indels occur only at the 5′-end of the spacer. Four conserved regions were found in the IGS of *Aconitum*, two of which correspond to the external promoter and terminator elements of RNA polymerase III, while the function of the other two regions remains unknown. The first of them shows homology to the 5S rRNA coding region, while the second one demonstrates high similarity to the sequences from the genomes of representatives of taxonomically distant families of monocots and dicots, suggesting horizontal gene transfer. The phylogenetic analysis applying the 5S rDNA IGS supports the interpretation of *A. anthora* s.l. as a separate subgenus within the genus *Aconitum*.

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Griffiths S.[1], Wang F.[2], Wingen L.[1], Hawkesford M.[3], Riche A.[3], Leverington-Waite M.[1], Orford S.[1], Collier S.[1], Awal R.[1], Philp Ch.[1], Banson A.[1], Chayut N.[1], Steuernagel B.[1], Goram R.[1], Shewry P.[3], Lovegrove A.[3], Cheng Sh.[2]
[1] John Innes Centre, Norwich, United Kingdom
[2] Guangdong Laboratory of Lingnan Modern Agriculture, Genome Analysis Laboratory, Ministry of Agriculture and Rural Affairs, Agricultural Genomics Institute at Shenzhen, Chinese Academy of Agricultural Sciences (CAAS), Shenzhen, China
[3] Rothamsted Research, Harpenden, United Kingdom
e-mail: simon.griffiths@jic.ac.uk

BREAKING WHEAT BREEDING BARRIERS 1 AND 2

Wheat is an important crop, which provides about 20% of the calories consumed by the human population worldwide. Worryingly, world wheat production is under many threats, like heat and drought stress as consequences of climate chaos. Achieving food resilience is an important aim and breeding higher yielding and more resilient bread wheat varieties will be part of the solution.

The genetic, germplasm, and phenotypic resources of a large group of UK wheat scientists [1] has been combined with cutting edge technologies in genomics and innovative genomic analysis to give a unique insight into new and useful genetic variants in the AE Watkins landrace collection [2]. The genomics insights include the fact that the expansive diversity of the landraces are quite poorly represented in modern wheat and that many of these variants are functional. In many cases the new functions have clear benefits for the design of future wheat varieties. These include increased yield, mineral content, disease resistance and new alleles for adaptive variation. We show that these variants were missed by modern breeders by historical

and geographical chance and that there is no reason why unused ancestral groups cannot form the basis of new breeding gains for wheat. In addition, the wealth of phenotypic data derived from field experiments testing ~6000 recombinant inbred lines allows us to see why some traits, such as biomass, were difficult to select in early breeding programmes. Systematic labelling of chromosomal segments with haplotype analysis now allows us to select this missing variation and bring it into modern breeding. We think of these two barriers (breeding history and physiological antagonism) as breeding barriers 1 and 2.

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[1] John Innes Centre, Norwich, United Kingdom
[2] Guangdong Laboratory of Lingnan Modern Agriculture, Genome Analysis Laboratory, Ministry of Agriculture and Rural Affairs, Agricultural Genomics Institute at Shenzhen, Chinese Academy of Agricultural Sciences (CAAS), Shenzhen, China
[3] Rothamsted Research, Harpenden, United Kingdom
e-mail: luzie.wingen@jic.ac.uk

BREAKING WHEAT BREEDING BARRIERS 3, 4 AND …

The Designing Future Wheat programme [1] is developing novel wheat pre-breeding germplasm with increased yield potential, disease resistance, climate tolerance, bread making and nutritional qualities. Sets of new bread wheat lines, called Pre-Breeding Toolkits, aim to underpin the path to sustainable and productive agriculture. Novel genetic variety is coming, among different sources, from the A.E. Watkins bread wheat landrace collection [2]. Landrace cultivars from this near global collection are performing poorly under modern agricultural practices and are mostly not adapted to the UK environment. Putative useful genomic regions of individual landrace cultivars were previously identified by QTL mapping in the DFW landrace NAM panel [3]. In order to assess the benefit of a QTL in modern

adapted germplasm (the third breeding barrier), the genomic segment needs to be introgressed by markers assisted selection into this germplasm. The resulting Near-Isogenic-Lines (NILs) are evaluated in pairs or families for the QTL effect. The development of such freely available Toolkit-NIL-Sets is constantly ongoing in the DFW programme. Once a Toolkit-NIL-Set has reached the BC_2F_2 generation, it is genotyped using the Axiom Bread Wheat Breeders' Array and evaluated in field trials at two sites for agronomical and morphological traits. The best performing lines of these sets are selected for the Breeders' Toolkit (BTK), a smaller panel that is assessed in another round of field trials at up to seven different breeding companies. Some outstanding introgressed QTL segments demonstrate robust benefits for the NILs carrying the QTL over sister NILs not carrying them. Field trial results are shared and breeders may chose to introduce these beneficial QTL into their commercial elite lines (the fourth breeding barrier).

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Popovych Yu.A.[1], Blagodarova O.M.[2], Chebotar S.V.[1,2]
[1]Odesa I.I. Mechnikov National University, Ukraine,
e-mail: s.v.chebotar@onu.edu.ua
[2] Plant Breeding and Genetics Institute – National Center of Seed and Cultivar Investigations, Ukraine

BIOINFORMATIC ANALYSIS OF NUCLEOTIDE SEQUENCES OF *GLI-1* LOCI OF *TRITICUM AESTIVUM* L.

The wheat seed storage protein, gliadin, has immense and well studied polymorphism based on the multiple allelism at each of the six main *Gli* loci. Therefore, gliadin alleles provide a set of suitable genetic markers for the identification and comparison of wheat genotypes.

Gliadin genes are highly polymorphic. There are two classifications of gliadins developed on the base of acid PAGE method: by Sozinov and Poperelya [1] (often used in Ukraine) and by Metakovsky et al. [4] (international). Moreover, there are

PCR primers, that could be used for identification some allelic variants of gliadins and polymorphism studying [2, 6]. Recently most scientific works are devoted to sequencing of gliadin genes. Thereby, the aim of the study was to analyze *Gli-1* loci and microsatellite locus *Taglgap* (that were studied by PCR in the previous investigations [3, 5]) in the nucleotide sequences from Genebank using bioinformatic tools.

A set of 121 nucleotide sequences from Genebank was found and analyzed for apparentness of *Gli-A1* sequence that could be detected using PCR primers developed by Zhang et al [2]. *Gli-A1.1* allele was found in 70,1% of *Triticum aestivum* sequences, when *Gli-A1.2* allele in 29,9%. We have found large sequences MG560140 and EF426565 that have two copies of *Gli-A1.1* allele and both alleles *Gli-A1.1* and *Gli-A1.2,* respectively. Similar to *Gli-A1,* 101 nucleotide sequences of *Gli-D1* locus were analyzed. *Gli-D1.1* and *Gli-D1.2* alleles were found in 97% and 3% of *Triticum aestivum* sequences respectively.

The frequency of *Gli-A1.1* and *Gli-A1.2* alleles have the same tendency both in sample of sequences from NCBI, in worldwide wheat collection and in Ukrainian wheat collection analyzed by PCR previously. The frequency of *Gli-A1.1* is higher than *Gli-A1.2* allele. The frequency of *Gli-D1.1* allele is very high in the sample from NCBI, *Gli-D1.2* allele also prevails in worldwide wheat collection, whereas in Ukrainian wheat collection *Gli-D1.2* is dominant.

Only 17 nucleotide sequences from Genebank containing microsatellite locus *Taglgap* were found. Six different alleles: 219 bp, 237 bp, 249 bp, 252 bp, 270 bp, 285 bp were detected for *T. aestivum*. Five of them, were detected also by PCR in the previous study.

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Прокоп'як М.З., Майорова О.Ю., Колісник Х.М., Грицак Л.Р., Дробик Н.М.
Тернопільський національний педагогічний університет
імені Володимира Гнатюка, Тернопіль, Україна,
e-mail: mosula@chem-bio.com.ua

ОЦІНКА ГЕНЕТИЧНОГО ПОЛІМОРФІЗМУ *GENTIANA LUTEA* L. (ПОЛОНИНА КРАСНА, УКРАЇНСЬКІ КАРПАТИ)

Дослідження генетичного поліморфізму і генетичної структури рідкісних видів рослин є необхідною складовою програм їх збереження та відновлення. До таких видів належить високогірний лікарський вид *Gentiana lutea* L., що має природоохоронний статус «вразливий». Мета роботи полягала у дослідженні генетичної різноманітності популяції *G. lutea* з полонини (пол.) Красна Українських Карпат. Ця популяція розташована на висоті 950–1450 н.р.м., займає площу 3 га та перебуває на межі зникнення через критично низьку щільність (5 ос./га).

Генетичний поліморфізм *G. lutea* оцінювали з використанням 9 ISSR (Inter Simple Sequence Repeats)-праймерів [1]. Показники генетичного поліморфізму популяції (частку поліморфних ампліконів (P), очікувану гетерозиготність (He), індекс Шеннона (S)) розраховували з використанням програми GenAlEx 6.5.

Показники генетичного поліморфізму рослин з пол. Красна становили: He: 0,110±0,017, S: 0,160±0,025; P: 27,5%. Значення усіх цих показників було нижче за усереднені дані досліджених нами раніше 4 популяцій *G. lutea* з Чорногірського масиву і 2 – зі Свидовця [2]. Найбільше (в 1,3 рази) від усереднених (34,5%) значень відрізнявся показник частки поліморфних ампліконів. Виявлено, що за показниками генетичного поліморфізму популяція з пол. Красна наближена до зникаючої популяції з г. Гутин Томнатик (хр. Чорногора), яка у минулому теж зазнавала значного пасторального навантаження. Тривалий інтенсивний випас призводить до зміни структурно-функціональної організації фітоценозу, що позначається на популяційних параметрах видів та їх біологічних особливостях [3]. Тому, навіть за зниження рівня пасторального навантаження стабілізація чисельності особин *G. lutea* у таких оселищах відбувається повільно [3].

Отже, отримані дані свідчать про низький рівень генетичного поліморфізму популяції *G. lutea* з пол. Красна, що свідчить про необхідність впровадження заходів охорони цієї популяції, а також її поновлення.

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Martyniuk V.S.[1], Gromozova O.M.[2], Tseysler Yu.V.[1], Gretsky I.O.[2], Artemenko A. Yu.[1]

1 Taras Shevchenko Kyiv National University, Kyiv, Ukraine,
e-mail: vittorio.martini.office@gmail.com
2 Institute of Microbiology and Virology of the National Academy of Sciences of Ukraine, Kyiv, Ukraine, e-mail: gren.elen@gmail.com

TIME DYNAMICS OF BACKGROUND LUMINESCENCE SPECTRA OF *PHOTOBACTERIUM PHOSPHOREUM*

The intensity of bacterial luminescence depends on many factors but one of the strange phenomena is the correlation of the bacterial glow with the dynamics of cosmo-geophysical processes associated with space weather, in particular with variations of the natural electromagnetic background [1]. In previous studies, we revealed the coincidence of periods of the luminescence of *Photobacterium phosphoreum* and the physical-chemical properties of water, as well as their correspondence to the dynamics of space weather factors [2]. The purpose of this study was to find out the possible mechanisms of connection between these processes based on the analysis of the luminescence spectra of photobacteria.

We observed the bacterial luminescence in range from 240 to 700 nm with a dominant maximum at 460–500 nm which corresponded to the luminescence of FMN-containing proteins. It is known that the excitation of the electronic structure of FMN requires an energy of about 3 eV, which corresponds to the energy of light waves with a length of 412 nm. But we observed the bacterial suspensions also glow in the UV region of the spectrum that testify to much more energy generated in the enzymatic process of oxidation, which should exceed 5 eV. This fact allows us to assume the involvement in this process of active forms of oxygen, such as OH* and HOO* radicals, the recombination of which is accompanied by the emission of light quanta in the UV range. The generation of UV light in bacteria explains the nature of small local maxima in the bioluminescence spectra associated with the induced

fluorescence of aromatic amino acids – 270–290 nm (phenylalanine), 302–310 nm (tyrosine), 320–350 nm (tryptophan). At the same time, local maxima in the green, yellow, and red regions of the spectrum may be associated with the presence of other fluorophores, in particular fluorescent proteins *LumP*, etc. The analysis of the time variability of the background luminescence spectra of *P. phosphoreum* photobacteria in 240–700 nm showed the existence of periodic components of 20–25 min that are very close to the period of 18–19 min of collective spin ortho-para transitions in water molecules [3]. Such transitions can be sensitive to the influence of electromagnetic fields in wide frequency and amplitude ranges and are associated with changes in space weather, which requires additional study.

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Тістечок С.І.[1], **Мироновський М**.[2], **Федоренко В**.О.[1], **Лужецький А**.М.[2], **Громико О**.М.[1]
[1]Львівський національний університет ім. І. Франка, Львів, Україна, e-mail: oleksandr.gromyko@lnu.edu.ua
[2] Саарландський університет, Саарбрюккен, Німеччина

СКРИНІНГ ПРОДУЦЕНТІВ ТІОПЕПТИДНИХ АНТИБІОТИКІВ З ВИКОРИСТАННЯМ РЕПОРТЕРНОЇ СИСТЕМИ НА ОСНОВІ ПРОМОТОРА ГЕНА *tipA*

Одним із методів вирішення проблеми поширення інфекційних захворювань, часто спричинених мультирезистентними формами патогенних мікроорганізмів, є розробка нових терапевтичних засобів. Тіопептидні антибіотики привертають увагу дослідників через свою високу антибіотичну активність, в тому числі проти різних антибіотикорезистентних мікроорганізмів. Виявлення певних класів сполук з природних джерел стає значно ефективнішим за використання специфічних цільноклітинних біосенсорів [1].

У цій роботі ми зосередилися на скринінгу продуцентів тіопептидних антибіотиків серед природних штамів актинобактерій ризосфери *Juniperus excelsa*

(Bieb.), виділених на території Кримського п-ва. Для цього використали мікробний біосенсор *Streptomyces lividans* TK24 pMO16, основою якого є індуцибельний промотор гена *tipA* злитий з геном *neo*, який забезпечує стійкість до неоміцину/канаміцину в присутності тіопептидів [2]. Протестувавши 372 штами актинобактерій ми виявили два штами Je 1–79 і Je 1–613, які індукувати ріст біосенсора. За допомогою дереплікативного аналізу в екстрактах цих штамів ідентифікували тіопептидні антибіотики бернінаміцин А та В. Філогенетичний аналіз на основі нуклеотидної послідовності гену 16S rRNA та п'яти генів домашнього господарства (*gyrB, atpD*, *recA*, *rpoB* і *trpB*) класифікував їх як представників двох різних видів із роду *Streptomyces*. В геномі *Streptomyces sp*. Je 1–79 виявили кластер генів біосинтезу бернінаміцину, який має високий рівень подібності (93%) з *ber*-кластером *S. bernensis* (GenBank: KC894738). Таким чином, використання штаму-біосенсора *S. lividans* TK24 pMO16 є ефективним і може прискорити специфічне виявлення тіопептидних антибіотиків у природних ізолятах актиноміцетів.

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Roshka N. M., Volkov R. A.
Department of Molecular Genetics and Biotechnology,
Yuriy Fedkovych Chernivtsi National University, Chernivtsi, Ukraine,
e-mail: r.volkov@chnu.edu.ua

LONG AND SHORT 5S RDNA VARIANTS IN THE GENOMES OF *APIS* SPECIES

5S rDNA belongs to the class of moderately repeated, tandemly arranged sequences present in the genomes of all eukaryotes. Each repeated unit of 5S rDNA consists of a highly conserved coding region of approximately 120 bp and a variable intergenic spacer region (IGS). The IGS comparison is successfully used to study microevolution and molecular taxonomy in plants and animals. However, insect 5S rDNA is still poorly characterized. In this work we describe the results of the sequencing and analysis of the 5S rDNA for some members of the genus *Apis*.

The 5S rDNA repeats of several *A. mellifera* subspecies were amplified by PCR. Then the PCR products were cloned using a plasmid vector and sequenced. The 5S rDNA sequences of *A. cerana* were found in the Genbank database and used for the analysis.

It was shown that at least two different length classes of 5S rDNA IGS are present in the genomes of all examined members of the genus *Apis*. The length of the short IGS class ranges from 239 to 253 bp while that of the long class ranges from 706 to 714 bp. In addition to the variability in length, the obtained IGS sequences differ significantly by nucleotide substitutions and short indels. Several putative elements of the 5S rDNA promoter and terminator, such as TATTT, GAGAGAGA and oligoT motifs were detected, respectively, upstream and downstream of the rRNA coding region in both long and short IGS classes. However, the exact role of these motifs in the transcription of 5S rDNA in insects is currently unknown. Putative specific functions of two length classes of 5S rDNA also require further clarification.

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Livshits L.[1], Sirokha D.[1], Gorodna O.[1], Zelinska N.[2], Jaruzelska J.[3], Kusz-Zamelczyk K.[3], Lauber-Biason A.[4], Nef S.[5]

[1] Laboratory of Human Genomics, Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, Kyiv, Ukraine,
e-mail: Livshits@edu.imbg.org.ua

[2] Ukrainian Scientific and Practical Center for Endocrine Surgery, Transplantation of Endocrine Organs and Tissues, Ministry of Health of Ukraine, Kyiv, Ukraine

[3] Institute of Human Genetics, Polish Academy of Sciences, Poznań, Poland

[4] Department of Endocrinology, Metabolism and Cardiovascular Research, University of Fribourg, Fribourg, Switzerland

[5] Department of Genetic Medicine and Development, Faculty of Medicine, University of Geneva, Switzerland

NOVEL *STARD8* AND *STARD9* MUTATIONS IDENTIFIED IN 46, XY GONADAL DYSGENESIS PATIENTS LEND SUPPORT TO THESE GENES AS DSD CANDIDATES

Investigating mutation in genes, affecting gonad development is essential for understanding the genetic mechanisms causing Disorders/Differences in Sex Development (DSD). The aim of the research was to identify novel DSD genetic variants using whole exome sequencing (WES). The WES was performed for two unrelated 46, XY SRY positive patients with gonadal dysgenesis.

In the first patient the hemizygous missense mutation NM_001142503.2 c.2659C>T (p. Arg887Cys) (rs766188656) in *STARD8* gene (MAF = 0.0000251)

was identified and confirmed as pathogenic using bioinformatic tools. After analysis of the second patient two different mutations in compound heterozygous state were identified in *STARD9* gene: NM_020759.3 c.5585_5590del (p. Ser1862_Thr1863del) (rs528276071) – inframe deletion (MAF = 0.0019) combined with NM_020759.3 c.3514C>T (p.Arg1172Cys) (rs12594837) – missense mutation (MAF = 0.00837). The analysis of genetic background, which was performed for both patients, did not reveal any pathogenic variants implicated in DSD phenotype. All detected mutant variants were inherited from healthy parents – heterozygous carriers and were not previously implicated in the pathogenesis of any disease. Bioinformatic analysis revealed that mutant variant in *STARD8* and both mutations in *STARD9* genes located in positions that are conserved in primates.

Based on the results obtained in current study, previous reports of *STARD* gene family mutations in DSD patients, expression patterns of *STADR8* and *STARD9* genes and steroidogenic properties of there protein products we conclude that *STADR8* and *STARD9* are considered as 46, XY DSD causing genes.

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Monczak Yu.
Division of Molecular Genetics McGill University Health Center,
McGill University and University of Montreal, Canada

MYD88 AND *CXCR4*, TWO GENES THAT PLAY A CRUCIAL ROLE IN WALDENSTRÖM'S MACROGLOBULINEMIA

Waldenström's macroglobulinemia (WM) is a rare non-Hodgkin's lymphoma of clonal origin, classified as lymphoplasmacytic lymphoma in the REAL and WHO classification system. In Canada, with a population of approximately 38 million, 150–200 new cases of WM are noted each year (~5 cases per 1 million people), typically affecting twice as many males as females over the age of 65. This disease is considered a chronic, indolent lymphoproliferative neoplasm, and it usually presents itself with high levels of monoclonal IgM (immunoglobulin M) in the serum. It primarily manifests itself in the bone marrow, where abnormal B-lymphocytes replicate at an increased rate and crowd out normal leukocyte development. In time, high levels of IgM proteins from the malignant cells accumulate in the blood, impair circulation and cause further complications. If untreated, WM can become life-threatening, causing anemia, neutropenia and thrombocytopenia, among other complications.

Recently two genes, *MYD88* and *CXCR4* were discovered to play a pivotal role in the development and treatment of this disease. *MYD88* (myeloid differentiation

factor 88) was first described in 1990 as a differentiation factor and later as an adaptor for the IL-1R signaling pathway. It functions as a signal transducer of the NF-κB transcription factors. Using whole genome sequencing, Treon et al. [1] found a very specific mutation (nucleotide position 38182641 on chromosome 3p22.2) in the DNA of over 90% of WM cases. This mutation (T→C transversion) causes a single amino acid change, from leucine to proline (L265P), causing activation of a signal transduction pathway involving NF-κB, an event that is essential for the growth of the malignant WM cells. One of the key steps in *MYD88*-mediated activation is the constitutive phosphorylation of Bruton's tyrosine kinase (BTK), a critical step in B-cell signaling, immune response regulation and cell proliferation. The presence of the *MYD88* L265P mutation is used for molecular diagnosis of WM, which then justifies treatment with Ibrutinib, an effective BTK inhibitor.

The *CXCR4* (C-X-C motif chemokine receptor 4) gene codes for a transmembrane G-protein-coupled receptor involved in lymphopoiesis, having potent chemotactic activity for lymphocytes and is important, among other functions, in hematopoietic stem cell homing to the bone marrow. Some specific mutations (WHIM-type) [2] result in truncated or frame-shifted CXCR4 protein in its carboxy (C)-terminus, resulting in increased and deregulated receptor activity. Such mutations are associated with bone marrow involvement and more aggressive disease at diagnosis. They confer significant resistance to Ibrutinib, a drug used in the treatment of WM [3], resulting in a shorter treatment-free survival compared to patients with unmutated CXCR4. Again, molecular detection of CXCR4 mutations in the context of WM is essential [4].

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Segrè G.
University of Pennsylvania, Philadelphia, USA

GEORGE GAMOW AND DNA'S GENETIC CODE

This talk is meant to introduce George Gamow's role as a visionary scientist, a unique educator of the young and old, a famous introducer of humor into science and finally, as a pioneer of molecular biology.

Gamow is responsible for more original, interesting science ideas than almost any other theorist of the 20th century. Many of these ideas were wrong in the details, but they always had an important, stimulating, far reaching quality. The ideas he proposed first include the nucleus as liquid drop, the importance of neutrinos in supernova collapse, the origin of the elements in the Periodic Table, the Universe's Big Bang and the existence of a genetic code in DNA for the creations of amino acids and then of proteins.

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