UDK: 618.215-008.87

Nilufar ELOVA,
O‘zR FA Mikrobiologiya instituti katta ilmiy xodimi, biologiya f.b.f.d
E-mail:elova.nilufar@mail.ru
Tel: (97) 264 00 76
Shahlo MIRALIMOVA,
O‘zR FA Mikrobiologiya instituti yetakchi ilmiy xodimi, b.f.d
E-mail:mirshakhlo@mail.ru
Tel: (90) 975 70 50

O‘z MU biologiya fakulteti professori, b.f.d Q.T. Normurodova taqrizi asosida

THE SIGNIFICANCE OF THE INTESTINAL MICROBIOTA IN THE DEVELOPMENT OF AUTISTIC SPECTRUM DISEASES

Annotation

Autistic spectrum disorders (ASD or Russian RAS) have been widely researched as one of the diseases associated with the gut microbiome of the nervous system. Using the knowledge of microbes helps to understand this disease in a comprehensive way. Interestingly, researchers have also attracted the attention of the mother's oral cavity and vaginal microbiome as an important factor in the etiopathology of autism spectrum disorders (ASD). Thus, this review attempts to summarize knowledge about the microbiome and its relationship to the hypothesized etiology of ASK and related diseases. Effects of diet, prebiotics, probiotics, antibiotics, and fecal microbe transplantation on ASK have also been analyzed. Among them, the use of diet and probiotics is the most promising and advanced means due to the fact that they do not have side effects and are easy to take. Current gaps in knowledge and research call for larger and bolder investigations into the relationship between autism and the microbiome.

Key words: Autistic spectrum disorders, gut microbiome, prebiotics, probiotics, neuroendocrine and neuroimmune systems.

ЗНАЧЕНИЕ КИШЕЧНОЙ МИКРОБИОТЫ В РАЗВИТИИ ЗАБОЛЕВАНИЙ АУТИСТИЧЕСКОГО СПЕКТРА

Аннотация

Расстройства аутистического спектра (по англ. ASD или по русс. РАС) широко исследуются как одно из заболеваний нервной системы, связанных с кишечным микробиомом. Использование знаний о микробах помогает комплексно понять это заболевание. Интересно, что исследователи также привлекли внимание ротовой полости матери и вагинального микробиома как важного фактора этиопатологии расстройств аутистического спектра (РАС). Таким образом, в этом обзоре предпринята попытка обобщить знания о микробиоме и его связи с предполагаемой этиологией АСК и связанных с ним заболеваний. Также было проанализировано влияние пребиотиков, пробиотиков и трансплантации фекальных микробов на РАС. Среди них использование диеты и пробиотиков является наиболее перспективным и современным средством в связи с тем, что они не имеют побочных эффектов и их легко принимать. Текущие пробелы в знаниях и исследованиях требуют более масштабных и смелых исследований взаимосвязи между аутизмом и микробиомом.

Ключевые слова: Расстройства аутистического спектра, кишечный микробиом, пребиотики, пробиотики, нейроэндокринная и нейроиммунная системы.

ICHAK MIKROBIOTASINING AUTISTIK SPEKTR KASALLIKLARI RIVOJLANISHIDAGI AHAMIYATI

Annotatsiya

Autistik spektrdagi buzilishlar (ing. ASD yoki rus. RAS) asab tizimining ichak mikrobiomi bilan bog’liq holda yuzaga keladigan kasalliklardan biri sifatida keng tadqiq qilingan. Mikroblar haqidagi bilimlardan foydalanish ushbu kasallikni har tomonlama tushunishga yordam beradi. Qizig’i shundaki, tadqiqotchilar e’tiborini onaning og’iz bo’shlig’i va vaginal mikrobiomi ham autistik spektr kasalliklari (ASK) etiopatologiyasidagi muhim omil sifatida o’ziga jalb qilgan. Shunday qilib, ushbu obzorda mikrobiom va uning ASK va u bilan bog’liq kasalliklarning gipotetik etiologiyasi bilan aloqasi haqidagi bilimlarni umumlashtishriga harakat qilinadi. Parhez, prebiotiklar, probiotiklar, antibiotiklar va fekaliy mikroblari transplantatsiyasining ham ASK ga ta’siri tahlil qilingan. Ular orasida parhez va probiotiklardan foydalanish nojo’ya ta’sirlarga ega emasligi, qabul qilish usuli osonligi tufayli eng istiqbolli va ilg’or vositalardir. Bilimlar va tadqiqotlardagi mavjud bo’shliqlar autizm va mikrobiom orasidagi aloqadorlikni aniqlashda yanada kengroq va dadilroq izlanishlarni talab qiladi.

Kalit so‘zlar: Autistik spektr kasalliklari, ichak mikrobiomi, prebiotiklar, probiotiklar, neyroendokrin va neyroimmun tizimlari.

Kirish. Kasalliklar, jarohatlar va xavf omillari global yuklamasi (Global Burden of disease (GBD)) tomonidan 2016 yilda o’tkazilgan so’nggi tadqiqot natijasiga ko’ra dunyoda 62,2 mln. odamda ASK mavjud [4].

Autizmning etiologiyasi geterogen bo’lib, irsiy, ekologik omillar va ularning kompleksi ta’sirida kelib chiqadi. Ko’pchilik tadqiqotlarda ichak va miya orasida “ichak-miya o’qi” nomi bilan ma’lum ikkiyoqlama aloqa mavjudligini aniqlangan. Ichak mikrobiotasi va autizm orasidagi bog’liqlik mikrobiomni tadqiq qilish sohasining asosiy jihatlardan biri hisoblanadi. Bilamizki, odamlar ichak tarkibidagi moddalarni hayot faoliyati mahsuloti sifatida qarashgan, ammo texnologiyalar rivojlanishi bilan biz tushundik-ki, ichak murakkab asab tizimiga ega va u miya bilan to’g’ridan-to’g’ri ta’sirlashadi va axborotning ikkiyoqlama uzatilishi amalga oshadi. Ushbu o’zaro ta’sir hatti-harakatlar, kayfiyat va bilishga intilishga bizdagi oshqozon-ichakning ichidagi suyuqlik ta’sir ko’rsatishidan dalolat beradi [5].

ASK bilan bir vaqtda bemorlarda tutqanoq, tashvishlanish, depressiya, Tik kasalliklari, Turett sindromi, ovqat hazm qilish yo`li muammolari, aqliy zaiflik kuzatiladi [6, 7]. Ular orasida qorinda og`riq, ich qotishi va ich ketishi kabi ovqat hazm qilish tizimi bilan bog`liq muammolar ASK bo`lgan bemor bolalarning 9%-idan 70% igacha qismida qayd qilinadi. Ushbu oshqozon-ichak muammolarini davolash qiyin, shuningdek ko`p hollarda ularga standart terapiya ham ta`sir ko`rsatolmaydi

[8]. Ushbu muammolar ichak bakteriyalari bilan aloqador bo`lishi mumkin. Ichak-miya o`qi markaziy asab tizimi va ichakda yashovchi bir necha trillion mikroorganizmlar orasodagi o`zaro aloqadorlikni va ichak mikrobiotasidagi o`zgarishlar miyaning faoliyati va rivojlanishiga ta`sir qilishini ifodalaydi [9]. Shu tufayli, ichak mikrobiotasi tarkibi va funktsiyalari ASK davolashda muhim bo`lishi mumkin. Ushbu sharhda biz ASK tashxislangan bemorlar ichak mikrobiotasi tarkibining o`ziga xos xususiyatlari va probiotiklarning ichak-miya o`qi orqali ta`sir qilib oshqozon-ichak kasalliklari va ASK simptomlariga ta`sir qilishiga oydinlik kiritishni maqsad qilib qo`ydik.

Mavzuga oid adabiyotlarning tahlili.

Ichak mikrobitasi disbiozi va ASK. Ko`pchilik ma`lumotlarga ko`ra, ASK bo`lgan bolalar ich qotishidan aziyat chekishadi, ichak mikrobiotasi tarkibida *Escherichia/Shigella* va *Clostridium* klasteri XVIII, Fusobacteriales tartibi, Actinomycetaceae oilasi, *Fusobacterium, Barnesiella, Coprobacter, Olsenella, and Allisonella* avlodlari vakillari sonining nisbiy ortishi, *Faecalibacterium prausnitzii, Bacteroides eggerthii, Bacteroides uniformis, Oscillospira plautii va Clostridium (C.) clariflavum* sonining kamayishi kuzatiladi [10, 11, 12]. Bundan tashqari, lactobatsillalar sonining kamayishi bemorlardagi ich qotishi bilan bog`liq bo`lishi mumkin, chunki ularning kamayishi ASK bo`lmagan sog`lom bolalarda ham surunkali ich qotishiga sabab bo`ladi [13, 14]. Allergiyasi bo`lgan ASK bo`lgan bemorlar axlatida autoimmun kasalliklar kelib chiqishiga sabab bo`luvchi *Proteobacteria* tipiga mansub bakteriyalarning nisbiy soni yuqoriligi qayd qilingan [15]. Shuningdek, OHQY simptomlariga ega ASK bemorlarda *Turicibacter sanguinis, C. lituseburense, C. disporicum, C. aldenense* va *O. plautii* soni ham yuqoriligi qayd qilingan. Yaqinda olimlar ASK bo`lgan bemorlar ichagida toksin ishlab chiqaruvchi bakteriyalar sifatida ma`lum *C. histolyticum* guruhi mikroorganizmlar soni yuqori ekanligini aniqlashdi [16].

ASK larida ichak-miya o`qidagi salbiy o`zgarishlar. Gipotalamus-gipofiz-buyrak usti bezi o`qi, adashgan nerv, neyroendokrin va neyroimmun tizim sifatida ma`lum bo`lgan simpatik va parasimpatik nerv va ichak nerv tizimi ichak va miya o`rtasidagi ikki yo`nalishga ega biokimyoviy signal yo`li hisoblangan ichak-miya o`qini tashkil qiladi [17]. Ko`plab tadqiqotlarda ushbu omilning ASK etiologiyasidagi ahamiyati o`rganilgan [18]. Ichak mikrobiotasi neyroendokrin, neyroimmun va vegetative asab tizimi orqali miyaning funktsiyalariga ta`sir ko`rsatadi [19].

ASK da ichak disbiozi va immun tizimining boshqarilishi buzilishi. Autizmda ichak mikrobiotasi disbiozi immunitetning buzilishiga olib keladi [20]. Interleykin-1 (IL-1), interleykin- 6 (IL-6), interferon (IFN) va shish nekrozi omili (ShNO) faol immune tizimi tomonidan ajratiladigan xemokinlar va sitokinlar bo`lib, ular gemoensefalitik to`siq orqali o`ta oladi. Ushbu mediatorlar (vositachilar) bosh miyaning endothelial hujayralariga yopishadi va immunologik reaksiyalarni chaqiradi [21]. Tadqiqotlar ASK guruhi qoni plazmasida IL-1, IL-6 va IL-8 miqdori nazorat guruhidagi normal rivojlangan odamlar qon plazmasidagi ushbu sitokinlarga nisbatan yuqori ekanligi ko`rsatilgan [22]. Bundan tashqari ushbu immun tizimining 80% I ichak shilliq qavatida va uning atrofida joylashadi [23].

**Probiotiklar ASK ichak-miya o`qini regulyatsiyalash orqali ta'sir qilishi.** Ichak mikrobiotasi-miya o`qini probiotiklar yordamida modulyatsiyalash ASK davolash va OHQT dagi buzilishlarni yengillashtirishda samarali strategiya bo`lishi mumkin. ASK bo`lgan bemorlarda olib borilgan probiotiklarni qo`llashga oid klinik tadqiqotlar *Clostridium* avlodiga mansub toksin ishlab chiqaruvchi turlarni probiotiklar yordamida kamaytirishga qaratildi. Probiotiklar ASK da qo`shimcha va muqobil terapiya sifatida tavsiflanadi [24]. 3 oy davomida probiotik qo`shimchalar olgan 5-9 yoshli, ASK bo`lgan bolalarda OI mikrobiotasi, OI simptomlari yaxshilanishi, ASK simptomlarining og`irlik darajasi kamayishi, xulq-atvor va faoliyatda ijobiy o`zgarishlar qayd qilindi [25]. Shuningdek, 12 yoshli bolaga 4 oy davomida kiritilgan 10 ta probiotikdan iborat multishtamm jamlanma ta'sirida ASK da kuzatiladigan oshqozon-ichak bilan bog`liq simptomlar kamayishi va yaxshilanishi qayd qilingan [26].

Probiotiklarning depressiya va tashvishlanish kabi belgilarga ta`siri yaxshi ma'lum. Og`iz orqali vankomitsin va *Bifidobacterium* qo`shimchalarini olgan autist bolalarda 3-(3-gidroksifenil)-3-gidroksiuron kislota, 3-gidroksifenilsirka kislota, va 3-gidroksigippur kislotaning siydikdagi miqdori sezilarli kamayadi [27]. 3-(3-gidroksifenil)-3-gidroksiuron kislota miyada katexolaminlar miqdorini kamaytirish orqali autism belgilari yuzaga kelishiga sabab bo`ladi [28]. Shunday qilib, ushbu metabolitlar miqdorining kamayishi autist bolalarda ko`z kontakti tiklanishi va ich qotish belgilari kamayishiga olib keladi [27].

Probiotiklar ASK belgilarini kamaytiruvchi birikmalarni modulyatsiyashi mumkin. Irsiy va atrof-muhitning xavfli omillari birlashib glutamat (Glu) bilan bog`liq qo`zg`atuvchi va γ-aminobenzoy kislotaga bog`liq tormozlovchi neyrotransmitter autism orasidagi muvozanatni buzadi [29]. Probiotiklar γ-aminobenzoy kislota, glutamat va 5-GT (5-gidroksitriptamin) kabi neyrotransmitterlarga ta'sir qila oladi [30]. Tabouy va boshq. (2018) Shank3 mutant sichqonlarida *L. reuteri* bilan davolash takrorlanuvchi odatlar kamayishi va gippokamp va prefrontal po`stloqda γ-aminobenzoy kislota retseptorlari genlari (GABRA1, GABRA1 va GABRB1) ekspressiyasi va oqsil miqdori ortishini qayd qilgan [31]. Bundan tashqari, *Lactobacillus* bilan davolash miya va ichakni bog`lab turuvchi adashgan nerv vositasida sichqonlarning emotsional va γ-aminobenzoy kislota retseptorlari ekspressiyasini boshqarishi ko`rsatilgan [32].

Tadqiqot metodologiyasi. So`nggi yillarda ichak mikrobiotasini o`rganishda MALDI-TOF mass-spektrometriya, *in situ* flyuoressent gibridizatsiya, real vaqt rejimida ishlaydigan miqdoriy PZR, immunoferment tahlil va keyingi avlod sekvenirlash kabi molekulyar genetik usullardan foydalanilmoqda [33].

Qator tadqiqotlarda real vaqt rejimida ishlaydigan miqdoriy PZR autizmi bo`lgan bolalar ichak mikrobiotasi tarkibidagi turli guruhga mansub mikroorganizmlarni miqdoriy o`rganishda foydalanish haqida ma'lumotlar berilgan. Real vaqt rejimida ishlaydigan miqdoriy PZR oddiy PZR ga nisbatan qator afzalliklarga ega. U oxirgi mahsulotning ko`pligiga emas mahsulot to`planishining logarifmik fazasiga yo`naltiriladi. Shu tufayli undagi natijalar aniq, chunki unga amplifikatsiyaning samaradorligi yoki reagentning kamayishi kam ta'sir ko`rsatadi.

Tahlil va natijalar. Shunday qilib, ASK ichak mikrobiotasi uchun xos bo`lgan xususiyatlarni o`rganish dolzarb hisoblanadi, chunki hozirgi paytgacha olingan ma'lumotlar autism belgilari rivojlanishida ichak disbiozining ehtimoliy etiopatogenetik roli katta ta'sir ko`rsatishidan darak beradi. Shuningdek, ASK tushunchasi qamrab oladigan holatlarning geterogenligi, ushbu holatlar etiologiyasining ko`p omilli ekanligi murakkab dizaynli va biologik ko`rsatkichlar va psixopatologik simptomlarini baholashning maksimal standartlaridan foydalanadigan keng ko`lamli tadqiqotlarni talab qiladi.

ADABIYOTLAR

1. Association, A.P. *Diagnostic and statistical manual of mental disorders (DSM-5®)*; American Psychiatric Pub: Washington, DC, USA, 2013.

2. Loomes, R.; Hull, L.; Mandy, W.P.L. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *J. Am. Acad. Child Adolesc. Psychiatry* 2017, *56*, 466-474, doi:10.1016/j.jaac.2017.03.013.
3. Catalá-López, F.; Ridao, M.; Hurtado, I.; Núñez-Beltrán, A.; Gènova-Maleras, R.; Alonso-Arroyo, A.; Tobías, A.; Aleixandre-Benavent, R.; Catalá, M.A.; Tabarés-Seisdedos, R. Prevalence and comorbidity of autism spectrum disorder in Spain: study protocol for a systematic review and meta-analysis of observational studies. *Syst. Rev.* **2019**, *8*, 141, doi:10.1186/s13643-019-1061-1.
4. Vos, T.; Abajobir, A.A.; Abate, K.H.; Abbafati, C.; Abbas, K.M.; Abd-Allah, F.; Abdulkader, R.S.; Abdulle, A.M.; Abebo, T.A.; Abera, S.F. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **2017**, *390*, 1211-1259, doi:10.1016/S0140-6736(17)32154-2.
5. Li Q, Han Y, Dy ABC, Hagerman RJ. The gut microbiota and autism spectrum disorders. Front Cell Neurosci. 2017;11:120.
6. Howes, O. D., Rogdaki, M., Findon, J. L., Wichers, R. H., Charman, T., King, B. H., et al. (2018). Autism spectrum disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. *J. Psychopharmacol.* 32, 3–29. doi: 10.1177/0269881117741766
7. Chaidez, V., Hansen, R. L., and Hertz-Picciotto, I. (2014). Gastrointestinal problems in children with autism, developmental delays or typical development. *J. Autism Dev. Disord.* 44, 1117–1127. doi: 10.1007/s10803-013-1973-x
8. Frye, R. E., and Rossignol, D. A. (2016). Identification and treatment of pathophysiological comorbidities of autism spectrum disorder to achieve optimal outcomes. Clin. Med. Insights Pediatr. 10, 43–56. doi: 10.4137/CMPed.S38337.
9. Wang, H.-X., and Wang, Y.-P. (2016). Gut microbiota-brain axis. Chin. Med. J. 129, 2373–2380. doi: 10.4103/0366-6999.190667.
10. Strati, F., Cavalieri, D., Albanese, D., De Felice, C., Donati, C., Hayek, J., et al. (2017). New evidences on the altered gut microbiota in autism spectrum disorders. Microbiome 5, 1–11. doi: 10.1186/s40168-017-0242-1.
11. Liu, S., Li, E., Sun, Z., Fu, D., Duan, G., Jiang, M., et al. (2019). Altered gut microbiota and short chain fatty acids in Chinese children with autism spectrum disorder. Sci. Rep. 9, 1–9. doi: 10.1038/s41598-018-36430-z
12. Luna, R. A., Oezguen, N., Balderas, M., Venkatachalam, A., Runge, J. K., Versalovic, J., et al. (2017). Distinct microbiome-neuroimmune signatures correlate with functional abdominal pain in children with autism spectrum disorder. Cell. Mol. Gastroenterol. Hepatol. 3, 218–230. doi: 10.1016/j.jcmgh.2016.11.008
13. Iovene, M. R., Bombace, F., Maresca, R., Sapone, A., Iardino, P., Picardi, A., et al. (2017). Intestinal dysbiosis and yeast isolation in stool of subjects with autism spectrum disorders. Mycopathologia 182, 349–363. doi: 10.1007/s11046-016-0068-6
14. Kushak, R. I., Winter, H. S., Buie, T. M., Cox, S. B., Phillips, C. D., and Ward, N. L. (2017). Analysis of the duodenal microbiome in autistic individuals: association with carbohydrate digestion. J. Pediatr. Gastroenterol. Nutr. 64, e110–e116. doi: 10.1097/ MPG.0000000000001458
15. Kong, X., Liu, J., Cetinbas, M., Sadreyev, R., Koh, M., Huang, H., et al. (2019). New and preliminary evidence on altered oral and gut microbiota in individuals with autism spectrum disorder (ASD): implications for ASD diagnosis and subtyping based on microbial biomarkers. Nutrients 11:2128. doi: 10.3390/nu11092128
16. Parracho, H. M., Bingham, M. O., Gibson, G. R., and McCartney, A. L. (2005). Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. J. Med. Microbiol. 54, 987–991. doi: 10.1099/jmm.0.46101-0
17. Dinan, T. G., and Cryan, J. F. (2015). The impact of gut microbiota on brain and behaviour: implications for psychiatry. Curr. Opin. Clin. Nutr. Metab. Care 18, 552–558. doi: 10.1097/MCO.0000000000000221
18. Li, Q., Han, Y., Dy, A. B. C., and Hagerman, R. J. (2017). The gut microbiota and autism spectrum disorders. Front. Cell. Neurosci. 11:120. doi: 10.3389/ fncel.2017.00120
19. Mayer, E. A. (2011). Gut feelings: the emerging biology of gut–brain communication. Nat. Rev. Neurosci. 12, 453–466. doi: 10.1038/nrn3071
20. Doenyas, C. (2018). Gut microbiota, inflammation, and probiotics on neural development in autism spectrum disorder. Neuroscience 374, 271–286. doi: 10.1016/j. neuroscience.2018.01.060
21. de Theije, C. G., Wu, J., Da Silva, S. L., Kamphuis, P. J., Garssen, J., Korte, S. M., et al. (2011). Pathways underlying the gut-to-brain connection in autism spectrum disorders as future targets for disease management. Eur. J. Pharmacol. 668, S70–S80. doi: 10.1016/j. ejphar.2011.07.013
22. Ashwood, P., Krakowiak, P., Hertz-Picciotto, I., Hansen, R., Pessah, I., and Van de Water, J. (2011). Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. Brain Behav. Immun. 25, 40–45. doi: 10.1016/j.bbi.2010.08.003
23. Critchfield, J. W., Van Hemert, S., Ash, M., Mulder, L., and Ashwood, P. (2011). The potential role of probiotics in the management of childhood autism spectrum disorders. Gastroenterol. Res. Pract. 2011, 1–8. doi: 10.1155/2011/161358
24. Cekici, H., and Sanlier, N. (2019). Current nutritional approaches in managing autism spectrum disorder: a review. Nutr. Neurosci. 22, 145–155. doi: 10.1080/ 1028415X.2017.1358481
25. Shaaban, S. Y., El Gendy, Y. G., Mehanna, N. S., El-Senousy, W. M., El-Feki, H. S., Saad, K., et al. (2018). The role of probiotics in children with autism spectrum disorder: a prospective, open-label study. Nutr. Neurosci. 21, 676–681. doi: 10.1080/1028415X.2017.1347746
26. Grossi, E., Melli, S., Dunca, D., and Terruzzi, V. (2016). Unexpected improvement in core autism spectrum disorder symptoms after long-term treatment with probiotics. SAGE Open Medical Case Reports 4:2050313X16666231. doi: 10.1177/2050313X16666231
27. Xiong, X., Liu, D., Wang, Y., Zeng, T., and Peng, Y. (2016). Urinary 3-(3-hydroxyphenyl)-3-hydroxypropionic acid, 3-hydroxyphenylacetic acid, and 3-hydroxyhippuric acid are elevated in children with autism spectrum disorders. Biomed Res. Int. 2016:9485412. doi: 10.1155/2016/9485412
28. Li, Q., and Zhou, J.-M. (2016). The microbiota–gut–brain axis and its potential therapeutic role in autism spectrum disorder. Neuroscience 324, 131–139. doi: 10.1016/j. neuroscience.2016.03.013

29. Borisova, T. (2018). Nervous system injury in response to contact with environmental, engineered and planetary micro- and nano-sized particles. *Front. Physiol.* 9:728. doi: 10.3389/fphys.2018.00728
30. Israelyan, N., and Margolis, K. G. (2019). Reprint of: serotonin as a link between the gut-brain-microbiome axis in autism spectrum disorders. *Pharmacol. Res.* 140, 115–120. doi: 10.1016/j.phrs.2018.12.023
31. Bravo, J. A., Forsythe, P., Chew, M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., et al. (2011). Ingestion of lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc. Natl. Acad. Sci.* 108, 16050–16055. doi: 10.1073/pnas.1102999108
32. Tabouy, L., Getselter, D., Ziv, O., Karpuj, M., Tabouy, T., Lukic, I., et al. (2018). Dysbiosis of microbiome and probiotic treatment in a genetic model of autism spectrum disorders. *Brain Behav. Immun.* 73, 310–319. doi: 10.1016/j.bbi.2018.05.015
33. Davenport M., Mach K.E., Shortliffe L.M.D., Banaei N., Wang T.H., Liao J.C. New and developing diagnostic technologies for urinary tract infections. Nat. Rev. Urol. 2017; 14(5): 296–310. https://doi. org/10.1038/nrurol.2017.20