
TÜRKİYE VE DÜNYADA
TIBBİ GENETİK
Editör: Dr.Öğr.Üyesi Tuğçe YAŞAR KÜÇÜK
yaz
yayınları

Türkiye ve Dünyada
Tıbbi Genetik

Editör

Dr.Öğr.Üyesi Tuğçe YAŞAR KÜÇÜK

yaz
yayınları

2025

yaz yayınları

Türkiye ve Dünyada Tıbbi Genetik

Editör: Dr.Öğr.Üyesi Tuğçe YAŞAR KÜÇÜK

© YAZ Yayınları

Bu kitabın her türlü yayın hakkı Yaz Yayınları'na aittir, tüm hakları saklıdır. Kitabın tamamı ya da bir kısmı 5846 sayılı Kanun'un hükümlerine göre, kitabı yayınlayan firmanın önceden izni alınmaksızın elektronik, mekanik, fotokopi ya da herhangi bir kayıt sistemiyle çoğaltılamaz, yayınlanamaz, depolanamaz.

E_ISBN 978-625-8678-86-4

Aralık 2025 – Afyonkarahisar

Dizgi/Mizanpaj: YAZ Yayınları

Kapak Tasarım: YAZ Yayınları

YAZ Yayınları. Yayıncı Sertifika No: 73086

M.İhtisas OSB Mah. 4A Cad. No:3/3
İscehisar/AFYONKARAHİSAR

www.yazyayinlari.com

yazyayinlari@gmail.com

İÇİNDEKİLER

"Bu kitapta yer alan bölümlerde kullanılan kaynakların, görüşlerin, bulguların, sonuçların, tablo, şekil, resim ve her türlü içeriğin sorumluluğu yazar veya yazarlarına ait olup ulusal ve uluslararası telif haklarına konu olabilecek mali ve hukuki sorumluluk da yazarlara aittir."

CURRENT GENOMIC APPROACHES IN THE DIAGNOSIS OF RARE DISEASES

Serap KURT[1]

1. INTRODUCTION

Rare diseases impact millions globally, imposing significant burdens on individuals, their families, and healthcare systems (Genetics, 2023). While they may be infrequent to individual rare diseases, most of them are genetically inherited and show complicated, multisystemic features (Gürkan & Satkın, t.y.). Historically, the first-line testing approach in the diagnosis of genetic diseases, which was based solely on the target and sequential gene analysis technique, has led to long diagnostic journeys, the delay of the appropriate treatment, and huge economic and emotional costs (Incerti vd., 2022). However, recently, the progress in genomic medicine has changed the very foundation of medical genetics and has made it possible to diagnose genetically rarely occurring diseases by providing a holistic and more accurate examination of the patients either at the molecular or phenotype level (Jamalinia & Weiskirchen, 2025).

The implementation of whole-exome sequencing and whole-genome sequencing in clinical practice has markedly enhanced diagnostic yield, especially in people with varied or unusual clinical manifestations (Pucel vd., 2024). Sequencing of the genomes has, in short, yielded a considerable number of molecular diagnoses especially when trios that is to say the child and the parents loevel data were used and a phenotypic weighted

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

variant prioritization approach was employed together. Furthermore, advancements in bioinformatics have led to the introduction of new toolkits for evaluating the significance of genetic variants, such as those endorsed by the American College of Medical Genetics and Genomics, resulting in genomic findings that are both dependable and clinically applicable (Bagger vd., 2024; Behera vd., 2025).

The diagnostic field has progressively transformed with the advent of systematic reanalysis, the capability of identifying structural and copy number variants at a deeper level, and the fades into the multi-omics data being more and more systematic. All in all, these changes have resulted in a higher diagnostic rate and have gone beyond that, they have deepened our comprehension of the underlying mechanisms (Brancato vd., 2025; Molla & Bitew, 2024). In fact, genomic discoveries not only promote better medical treatment, genetic prognosis, and counseling but they also pave the way to personalized healthcare models. Keeping up with the latest in genomic medicine entails that one has a good grasp of the genomics technologies and their clinical uses, which, in turn, is crucial for driving up diagnostic efficiency in rare diseases (Khan vd., 2025).

2. RARE DISEASES AND DIAGNOSTIC CHALLENGES

Whilst contributions of individual rare illnesses may be less in number, collectively they are a major challenge in the public health sector as they are estimated to affect 6–8% of the global population (Chung vd., 2022). Most of these diseases are genetically determined and have their onset during the early years of life; still, there are cases of late-onset diseases (Oancea vd., 2025). Many times, the diagnosis is challenging due to the clinical

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

heterogeneity, the overlapping of phenotypes, and the variable expression of the disease. As a consequence, a lot of patients continue searching for a diagnosis for a long time, during which they are examined by several specialists and a myriad of tests are done but yet no molecular diagnosis is given (Curic vd., 2023; Visibelli vd., 2023).

The main difficulty with rare disease diagnosis is one of the most prominent medical hurdles which is the trouble with the traditional methods of diagnosis. Testing strategies that rely on the identification of the phenotype, single-gene analysis, and targeted panels may be insufficient when it comes to fully understanding the genetic basis of rare diseases, especially in situations where there is extensive locus heterogeneity or new disease genes. What is more, unusual presentations, reduced penetrance as well as variable expressivity may also make genotype-phenotype correlation unclear, thus resulting in missed or late diagnoses. These issues are mainly hard to overcome in the case of pediatric and patients with multisystemic diseases (Alsentzer vd., 2025; Vinkšel vd., 2021).

In addition to clinical uncertainty, which is one of the main problems, late diagnosis leads to negative repercussions that affect not only the patients but also their families. Without a clear genetic diagnosis, the treatment that is most appropriate may be withheld, the patients might not have access to the specific therapies that would be more beneficial to them, and on top of that, genetic counseling might become even more complicated in terms of recurrence risks as well as family planning (Parikh vd., 2023). Under this condition, the urgency for more comprehensive and at the same time unbiased diagnostic methods has become more and more outstanding. The innovations in genome technologies have proven to be the right reply to these issues by offering the possibility of withholding the diagnostic odyssey

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

and, further, improving the quality of life of people with rare genetic diseases (Blesson & Cohen, 2020).

3. WHOLE-EXOME AND WHOLE-GENOME SEQUENCING IN RARE DISEASE DIAGNOSIS

By the clinical launch of whole-exome sequencing (WES), the identification of rare genetic diseases has reached a new height. WES allows the measurement of thousands of genes associated with diseases in parallel. In fact, compared with conventional single-gene or targeted panel methods, WES offers a more comprehensive and unbiased approach, especially in the case of genetically highly heterogeneous disorders. In everyday clinical practice, WES is particularly helpful for patients with non-typical phenotypes, symptoms overlapping different diseases, or inconclusive previous tests, thus, it greatly raises the chances of a molecular diagnosis (Lai vd., 2024; Nguyen & Charlebois, 2015).

Driven by the achievement of exome-based methods, whole-genome sequencing (WGS) has gone even further in expanding the diagnostic potential of clinical genomics. WGS, by providing consistent coverage of coding as well as non-coding regions, enables the identification of DNA changes that might not be detected by WES, e.g., deep intronic DNA changes, regulatory DNA regions, and some structural DNA changes (Brlek vd., 2024). More and more data indicating the capability of WGS to increase diagnostic yield in highly specific patient groups, mainly in those cases, which have not been solved by exome sequencing. WGS is slowly becoming a more affordable option in clinical genetic diagnostics as sequencing costs go lower and analytical pipelines get better (Dillon vd., 2018; Ellingford vd., 2016).

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

Both WES and WGS, besides their proven advantages, have been accompanied by important challenges, interpretative ones as well as practical ones. It is still a hard puzzle to interpret variants, thus, it is necessary to have a very detailed clinical phenotyping to be able to connect it with genomic data. In addition, problems related to incidental findings, data interpretation overload, and infrastructure requirements have to be solved in order to assure a responsible clinical implementation (Brancato vd., 2025; J. K. Tan vd., 2024). However, if they are used in a multidisciplinary environment that combines clinical skills, bioinformatics, and standardized interpretation guides, then exome- and genome-based strategies can be regarded as the main instruments in the contemporary diagnosis of rare diseases.

4. TRIO-BASED SEQUENCING AND PHENOTYPE-DRIVEN VARIANT INTERPRETATION

Sequencing strategies designed for trios, where the affected individual is sequenced along with both parents, have turned into a key element of rare disease diagnosis. By providing the possibility to study inheritance patterns, trio analysis makes it easier to detect de novo variants, identify compound heterozygous changes and understand recessive disease mechanisms which, without the parental DNA, would have been difficult to discern (Kaschta vd., 2025; Malmgren vd., 2025). In clinical practice, trio-based methods have been a constant successful leading system in unveiling results especially when it comes to children cases and patients exhibiting severe and/or early-onset phenotypes.

Accurate identification of variants along with the detailed clinical presentation is as crucial as the sequencing method itself. Standardized phenotype vocabularies, e.g., Human Phenotype

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

Ontology, largely facilitated the connection between the phenomic and genomic data (Shefchek vd., 2025). Phenotype-led variant searching programs are enabling medical professions as well as laboratory experts to weed the candidate variants out in the most time-effective way, thereby, making labor interpretation much less time-consuming and boosting diagnostic confidence. Such a holistic method dictates the detoxification resulting from the interaction between clinicians, genetic counselors, and bioinformaticians (Jacobsen vd., 2022).

Communicating genetic information is one of the areas that have witnessed transformations due to trio-based sequencing apart from its technical merits. Lab results which have patterns of inheritance clearly displayed by trio sequencing enable doctors to be more certain in their interpretation of the findings and further assist in the process of genetic counseling by making the communication with the patients and their families more appropriate (Schroeder vd., 2023). Most times, the isolation of a de novo or inherited pathogenic variant provides diagnostic clarity and, at the same time, may turn out as the source of emotional comfort for the family through the end of their long-standing uncertainty. From a medical point of view, the knowledge obtained as a result of thorough investigation is pivotal in strategic planning and acts as a guide in the further steps to be taken, also in helping the patient's consent to the diagnosis and in aligning them with expected realistic outcomes. Therefore, instead of analytical tools, the working of trio-based sequencing along with phenotype-driven interpretation reflects the hallmarks of personalized genomic-medicine-of-the-rare-diseases-care (Burke vd., 2022; Narbona-Arias vd., 2025).

5. REANALYSIS STRATEGIES AND IMPROVING DIAGNOSTIC YIELD

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

Patients with rare diseases who initially undergo genomic testing may still end up without diagnoses, despite the use of advanced sequencing technologies (Cipriani vd., 2025; Sciascia vd., 2023). On the contrary, a growing collection of research shows that genomic data are not fixed and that over time their reinterpretation can bring significant diagnostic results. Reanalysis strategies based on continuous progressions in gene-disease knowledge, enhanced variant databases, and updated bioinformatics tools, help uncover the previously unrecognized variants by re-evaluating them in the new clinical and scientific context (Setty vd., 2022).

Each year, new genes responsible for diseases are identified, variant classification criteria get updated, and we understand better the non-coding and regulatory regions all of which can help in cases that initially tested negative. Besides that, reanalysis makes the most substantial impact when it is also combined with updated clinical information because an evolving phenotype sometimes may show the features that were not obvious at the time of initial testing (Hiatt vd., 2018). Importantly, reanalysis is most effective when combined with updated clinical information, as evolving phenotypes may reveal features that were not apparent at the time of initial testing (Schobers vd., 2022). It is this continuous interaction of genomic information and extended clinical observation that implies the diagnosis should be considered as an unfolding journey and not a single outcome.

In doing reanalysis, it is of importance for a facility to have the necessary infrastructure and also to keep the communication with patients and families open about the possibility of diagnostic updates at a later date. Continuous engagement with unresolved cases thus reanalysis not only increases diagnostic yield but also, when embedded in everyday

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

clinical workflows, strategies genomic medicine gain the trust of the patients. As a result, reanalysis is a vehicle which links the exponentially increasing genomic knowledge to real-world patient care in rare disease settings (Iwuajoku vd., 2025).

6. CLINICAL IMPACT AND FUTURE PERSPECTIVES

The consequences of using genomic methods to obtain a molecular diagnosis go far beyond confirmation of the diagnosis. For many individuals with rare diseases, a definitive genetic diagnosis directly influences clinical management, informs prognosis, and enables access to targeted therapies or clinical trials. Genomic diagnoses are equally crucial since they clarify genetic counseling and help make well-informed decisions about recurrence risk and family planning. In this context, the value of genomic testing lies not only in technological capability but in its tangible impact on patient care (Katsanis & Katsanis, 2013). In the future, it is anticipated that the use of complementary techniques, including as transcriptomics, epigenomics, and functional validation studies, would increase the role of genomics in the diagnosis of rare diseases (Soden vd., 2012; J. W. Tan vd., 2024). Diagnostic accuracy is expected to be substantially enhanced by developments in long-read sequencing, better identification of complicated structural variations, and growing usage of artificial intelligence-assisted interpretation tools. To turn these advancements into clinical benefits, however, interdisciplinary cooperation between physicians, lab experts, bioinformaticians, and genetic counselors will continue to be crucial (Begum vd., 2021; Khan vd., 2025)

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

It will be crucial to keep a patient-centered viewpoint as genomic medicine develops. The future of rare disease treatment will be shaped by striking a balance between technical advancement, ethical responsibility, transparent communication, and fair access to diagnostic services. Medical genetics is well-positioned to continue enhancing the quality of life and diagnostic results for people with uncommon genetic illnesses by embracing current genomic methods while being flexible to new developments.

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

REFERENCES

Alsentzer, E., Li, M. M., Kobren, S. N., Noori, A., Kohane, I. S., & Zitnik, M. (2025). Few shot learning for phenotype-driven diagnosis of patients with rare genetic diseases. *Npj Digital Medicine*, *8*(1), 380. https://doi.org/10.1038/s41746-025-01749-1

Bagger, F. O., Borgwardt, L., Jespersen, A. S., Hansen, A. R., Bertelsen, B., Kodama, M., & Nielsen, F. C. (2024). Whole genome sequencing in clinical practice. *BMC Medical Genomics*, *17*, 39. https://doi.org/10.1186/s12920-024-01795-w

Begum, G., Albanna, A., Bankapur, A., Nassir, N., Tambi, R., Berdiev, B. K., Akter, H., Karuvantevida, N., Kellam, B., Alhashmi, D., Sung, W. W. L., Thiruvahindrapuram, B., Alsheikh-Ali, A., Scherer, S. W., & Uddin, M. (2021). Long-Read Sequencing Improves the Detection of Structural Variations Impacting Complex Non-Coding Elements of the Genome. *International Journal of Molecular Sciences*, *22*(4), 2060. https://doi.org/10.3390/ijms22042060

Behera, S., Catreux, S., Rossi, M., Truong, S., Huang, Z., Ruehle, M., Visvanath, A., Parnaby, G., Roddey, C., Onuchic, V., Finocchio, A., Cameron, D. L., English, A., Mehtalia, S., Han, J., Mehio, R., & Sedlazeck, F. J. (2025). Comprehensive genome analysis and variant detection at scale using DRAGEN. *Nature Biotechnology*, *43*(7), 1177-1191. https://doi.org/10.1038/s41587-024-02382-1

Blesson, A., & Cohen, J. S. (2020). Genetic Counseling in Neurodevelopmental Disorders. *Cold Spring Harbor Perspectives in Medicine*, *10*(4), a036533. https://doi.org/10.1101/cshperspect.a036533

Brancato, D., Treccarichi, S., Bruno, F., Coniglio, E., Vinci, M., Saccone, S., Calì, F., Federico, C., Brancato, D., Treccarichi, S., Bruno, F., Coniglio, E., Vinci, M., Saccone, S., Calì, F., & Federico, C. (2025). NGS Approaches in Clinical Diagnostics: From Workflow to Disease-Specific Applications. *International Journal of Molecular Sciences*, *26*(19). https://doi.org/10.3390/ijms26199597

Brlek, P., Bulić, L., Bračić, M., Projić, P., Škaro, V., Shah, N., Shah, P., & Primorac, D. (2024). Implementing Whole Genome Sequencing

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

(WGS) in Clinical Practice: Advantages, Challenges, and Future Perspectives. *Cells*, *13*(6), 504. https://doi.org/10.3390/cells13060504

Burke, W., Parens, E., Chung, W. K., Berger, S. M., & Appelbaum, P. S. (2022). The challenge of genetic variants of uncertain clinical significance: A narrative review. *Annals of internal medicine*, *175*(7), 994-1000. https://doi.org/10.7326/M21-4109

Chung, C. C. Y., Chu, A. T. W., & Chung, B. H. Y. (2022). Rare disease emerging as a global public health priority. *Frontiers in Public Health*, *10*, 1028545. https://doi.org/10.3389/fpubh.2022.1028545

Cipriani, V., Vestito, L., Magavern, E. F., Jacobsen, J. O. B., Arno, G., Behr, E. R., Benson, K. A., Bertoli, M., Bockenhauer, D., Bowl, M. R., Burley, K., Chan, L. F., Chinnery, P., Conlon, P. J., Costa, M. A., Davidson, A. E., Dawson, S. J., Elhassan, E. A. E., Flanagan, S. E., … Smedley, D. (2025). Rare disease gene association discovery in the 100,000 Genomes Project. *Nature*, 1-9. https://doi.org/10.1038/s41586-025-08623-w

Curic, E., Ewans, L., Pysar, R., Taylan, F., Botto, L. D., Nordgren, A., Gahl, W., & Palmer, E. E. (2023). International Undiagnosed Diseases Programs (UDPs): Components and outcomes. *Orphanet Journal of Rare Diseases*, *18*, 348. https://doi.org/10.1186/s13023-023-02966-1

Dillon, O. J., Lunke, S., Stark, Z., Yeung, A., Thorne, N., Gaff, C., White, S. M., & Tan, T. Y. (2018). Exome sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders. *European Journal of Human Genetics*, *26*(5), 644-651. https://doi.org/10.1038/s41431-018-0099-1

Ellingford, J. M., Barton, S., Bhaskar, S., Williams, S. G., Sergouniotis, P. I., O'Sullivan, J., Lamb, J. A., Perveen, R., Hall, G., Newman, W. G., Bishop, P. N., Roberts, S. A., Leach, R., Tearle, R., Bayliss, S., Ramsden, S. C., Nemeth, A. H., & Black, G. C. M. (2016). Whole Genome Sequencing Increases Molecular Diagnostic Yield Compared with Current Diagnostic Testing for Inherited Retinal Disease. *Ophthalmology*, *123*(5), 1143-1150. https://doi.org/10.1016/j.ophtha.2016.01.009

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

Genetics, B. (2023, Eylül 25). The Economic Burden of Rare Diseases: Impacts & Challenges. *Baylor Genetics*. https://www.baylorgenetics.com/blog/the-economic-burden-of-rare-diseases-impacts-challenges/

Gürkan, H., & Satkın, N. B. (t.y.). The Importance of Genetic Diagnosis in Rare Diseases. *Balkan Medical Journal*, *42*(2), 92-93. https://doi.org/10.4274/balkanmedj.galenos.2025.2025-270125

Hiatt, S. M., Amaral, M. D., Bowling, K. M., Finnila, C. R., Thompson, M. L., Gray, D. E., Lawlor, J. M. J., Cochran, J. N., Bebin, E. M., Brothers, K. B., East, K. M., Kelley, W. V., Lamb, N. E., Levy, S. E., Lose, E. J., Neu, M. B., Rich, C. A., Simmons, S., Myers, R. M., … Cooper, G. M. (2018). Systematic reanalysis of genomic data improves quality of variant interpretation. *Clinical genetics*, *94*(1), 174-178. https://doi.org/10.1111/cge.13259

Incerti, D., Xu, X.-M., Chou, J. W., Gonzaludo, N., Belmont, J. W., & Schroeder, B. E. (2022). Cost-effectiveness of genome sequencing for diagnosing patients with undiagnosed rare genetic diseases. *Genetics in Medicine*, *24*(1), 109-118. https://doi.org/10.1016/j.gim.2021.08.015

Iwuajoku, V., Ekici, K., Haas, A., Khan, M. Z., Kazemi, A., Kasajima, A., Delbridge, C., Muckenhuber, A., Schmoeckel, E., Stögbauer, F., Bollwein, C., Schwamborn, K., Steiger, K., Mogler, C., & Schüffler, P. J. (2025). An equivalency and efficiency study for one year digital pathology for clinical routine diagnostics in an accredited tertiary academic center. *Virchows Archiv*, *487*(1), 3-12. https://doi.org/10.1007/s00428-025-04043-3

Jacobsen, J. O. B., Kelly, C., Cipriani, V., Research Consortium, G. E., Mungall, C. J., Reese, J., Danis, D., Robinson, P. N., & Smedley, D. (2022). Phenotype-driven approaches to enhance variant prioritization and diagnosis of rare disease. *Human Mutation*, *43*(8), 1071-1081. https://doi.org/10.1002/humu.24380

Jamalinia, M., & Weiskirchen, R. (2025). Advances in personalized medicine: Translating genomic insights into targeted therapies for cancer treatment. *Annals of Translational Medicine*, *13*(2), 18. https://doi.org/10.21037/atm-25-34

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

Kaschta, D., Post, C., Gaass, F., Al-Tawil, M., Arriens, V., Balachandran, S., Bäumer, T., Berge, V., Birgel, F., Dalski, A., Dittmar, M., Franke, A., Franzenburg, S., Fuß, J., Gehring, B., Gembicki, R., Greiten, B., Grohte, K., Hanker, B., … Spielmann, M. (2025). Evaluating genome sequencing strategies: Trio, singleton, and standard testing in rare disease diagnosis. *Genome Medicine*, *17*(1), 100. https://doi.org/10.1186/s13073-025-01516-7

Katsanis, S. H., & Katsanis, N. (2013). Molecular genetic testing and the future of clinical genomics. *Nature reviews. Genetics*, *14*(6), 415-426. https://doi.org/10.1038/nrg3493

Khan, A., Barapatre, A. R., Babar, N., Doshi, J., Ghaly, M., Patel, K. G., Nawaz, S., Hasana, U., Khatri, S. P., Pathange, S., Pesaru, A. R., Puvvada, C. S., Billoo, M., & Jamil, U. (2025). Genomic medicine and personalized treatment: A narrative review. *Annals of Medicine and Surgery*, *87*(3), 1406-1414. https://doi.org/10.1097/MS9.0000000000002965

Lai, G., Gu, Q., Lai, Z., Chen, H., Chen, J., & Huang, J. (2024). The application of whole-exome sequencing in the early diagnosis of rare genetic diseases in children: A study from Southeastern China. *Frontiers in Pediatrics*, *12*. https://doi.org/10.3389/fped.2024.1448895

Malmgren, H., Kvarnung, M., Gustafsson, P., Anderlid, B.-M., Arthur, C., Carlsten, J., De Geer, K., Ehn, E., Grigelionienė, G., Hammarsjö, A., Helgadottir, H. T., Hellström-Pigg, M., Iwarsson, E., Kuchinskaya, E., Lindelöf, H., Mannila, M., Nilsson, D., Pettersson, M., Rudd, E., … Lagerstedt-Robinson, K. (2025). Diagnostic yield of 1000 trio analyses with exome and genome sequencing in a clinical setting. *Frontiers in Genetics*, *16*. https://doi.org/10.3389/fgene.2025.1580879

Molla, G., & Bitew, M. (2024). Revolutionizing Personalized Medicine: Synergy with Multi-Omics Data Generation, Main Hurdles, and Future Perspectives. *Biomedicines*, *12*(12), 2750. https://doi.org/10.3390/biomedicines12122750

Narbona-Arias, I., Blasco-Alonso, M., Monís-Rodriguez, S., Muñoz, C. G., González-Mesa, E., Lubián-López, D. M., Jiménez-López, J., Narbona-Arias, I., Blasco-Alonso, M., Monís-Rodriguez, S., Muñoz, C. G., González-Mesa, E., Lubián-López, D. M., & Jiménez-López, J.

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

(2025). More than a Diagnosis: How Prenatal Identification of Cantú Syndrome Transformed a Family's Medical Narrative. *Journal of Clinical Medicine*, *14*(17). https://doi.org/10.3390/jcm14176017

Nguyen, M. T., & Charlebois, K. (2015). The clinical utility of whole-exome sequencing in the context of rare diseases—The changing tides of medical practice. *Clinical Genetics*, *88*(4), 313-319. https://doi.org/10.1111/cge.12546

Oancea, C., Gherman, D. M., Popescu, F. G., Aurelian, S. M., Homentcovschi, C., Oancea, C., Gherman, D. M., Popescu, F. G., Aurelian, S. M., & Homentcovschi, C. (2025). The Uneven Effect of Rare Diseases on Functional Status and Work Capacity. *Healthcare*, *13*(6). https://doi.org/10.3390/healthcare13060594

Parikh, F., Athalye, A., Madon, P., Khandeparkar, M., Naik, D., Sanap, R., & Udumudi, A. (2023). Genetic counseling for pre-implantation genetic testing of monogenic disorders (PGT-M). *Frontiers in Reproductive Health*, *5*, 1213546. https://doi.org/10.3389/frph.2023.1213546

Pucel, J., Briere, L. C., Reuter, C., Gochyyev, P., & LeBlanc, K. (2024). Exome and genome sequencing in a heterogeneous population of patients with rare disease: Identifying predictors of a diagnosis. *Genetics in medicine : official journal of the American College of Medical Genetics*, *26*(6), 101115. https://doi.org/10.1016/j.gim.2024.101115

Schobers, G., Schieving, J. H., Yntema, H. G., Pennings, M., Pfundt, R., Derks, R., Hofste, T., de Wijs, I., Wieskamp, N., van den Heuvel, S., Galbany, J. C., Gilissen, C., Nelen, M., Brunner, H. G., Kleefstra, T., Kamsteeg, E.-J., Willemsen, M. A. A. P., & Vissers, L. E. L. M. (2022). Reanalysis of exome negative patients with rare disease: A pragmatic workflow for diagnostic applications. *Genome Medicine*, *14*, 66. https://doi.org/10.1186/s13073-022-01069-z

Schroeder, C., Faust, U., Kraußе, L., Liebmann, A., Abele, M., Demidov, G., Schütz, L., Kelemen, O., Pohle, A., Gauß, S., Sturm, M., Roggia, C., Streiter, M., Buchert, R., Armenau-Ebinger, S., Nann, D., Beschorner, R., Handgretinger, R., Ebinger, M., … Brecht, I. B. (2023). Clinical trio genome sequencing facilitates the interpretation of variants

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

in cancer predisposition genes in paediatric tumour patients. *European Journal of Human Genetics, 31*(10), 1139-1146. https://doi.org/10.1038/s41431-023-01423-8

Sciascia, S., Roccatello, D., Salvatore, M., Carta, C., Cellai, L. L., Ferrari, G., Lumaka, A., Groft, S., Alanay, Y., Azam, M., Baynam, G., Cederroth, H., Cutiongco-de la Paz, E. M., Dissanayake, V. H. W., Giugliani, R., Gonzaga-Jauregui, C., Hettiarachchi, D., Kvlividze, O., Landoure, G., … Taruscio, D. (2023). Unmet needs in countries participating in the undiagnosed diseases network international: An international survey considering national health care and economic indicators. *Frontiers in Public Health*, *11*, 1248260. https://doi.org/10.3389/fpubh.2023.1248260

Setty, S. T., Scott-Boyer, M.-P., Cuppens, T., Droit, A., Setty, S. T., Scott-Boyer, M.-P., Cuppens, T., & Droit, A. (2022). New Developments and Possibilities in Reanalysis and Reinterpretation of Whole Exome Sequencing Datasets for Unsolved Rare Diseases Using Machine Learning Approaches. *International Journal of Molecular Sciences*, *23*(12). https://doi.org/10.3390/ijms23126792

Shefchek, K., Ziniel, S. I., McMurry, J. A., Brownstein, C. A., Brownstein, J. S., Riggs, E. R., Might, M., Smedley, D., Clugston, A., Beggs, A. H., Paterson, H., Robinson, P. N., Vasilevsky, N. A., Holm, I. A., & Haendel, M. A. (2025). Development of self-phenotyping tools to empower patients and improve diagnostics. *eBioMedicine*, *121*, 105965. https://doi.org/10.1016/j.ebiom.2025.105965

Soden, S. E., Farrow, E. G., Saunders, C. J., & Lantos, J. D. (2012). Genomic medicine: Evolving science, evolving ethics. *Personalized medicine*, *9*(5), 523-528. https://doi.org/10.2217/PME.12.56

Tan, J. K., Awuah, W. A., Ahluwalia, A., Sanker, V., Ben-Jaafar, A., Tenkorang, P. O., Aderinto, N., Mehta, A., Darko, K., Shah, M. H., Roy, S., Abdul-Rahman, T., & Atallah, O. (2024). Genes to therapy: A comprehensive literature review of whole-exome sequencing in neurology and neurosurgery. *European Journal of Medical Research, 29*(1), 538. https://doi.org/10.1186/s40001-024-02063-4

Tan, J. W., Blake, E. J., Farris, J. D., & Klee, E. W. (2024). Expanding Upon Genomics in Rare Diseases: Epigenomic Insights. *International*

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

Journal of Molecular Sciences, *26*(1), 135. https://doi.org/10.3390/ijms26010135

Vinkšel, M., Writzl, K., Maver, A., & Peterlin, B. (2021). Improving diagnostics of rare genetic diseases with NGS approaches. *Journal of Community Genetics*, *12*(2), 247-256. https://doi.org/10.1007/s12687-020-00500-5

Visibelli, A., Roncaglia, B., Spiga, O., Santucci, A., Visibelli, A., Roncaglia, B., Spiga, O., & Santucci, A. (2023). The Impact of Artificial Intelligence in the Odyssey of Rare Diseases. *Biomedicines*, *11*(3). https://doi.org/10.3390/biomedicines11030887

Research Assistant, PhD. Manisa Celal Bayar University, Faculty of Medicine, Department of Medical Genetics, serap.kurt@cbu.edu.tr ORCID: 0000-0002-0186-7541.

CRISPR-BASED EPIGENETIC MODULATION: MECHANISMS, STRATEGIES, AND THERAPEUTIC APPLICATIONS

Tuğçe Yaşar Küçük[1]

1. INTRODUCTION

Epigenetics plays a key role in determining cell identity and function. It regulates gene expression without causing permanent changes to the DNA sequence. Cells carry out gene expression in a specific way depending on the time and tissue. They use methods such as DNA methylation, histone modifications, nucleosome positioning, and three-dimensional chromatin structure (Bird, 2022). The flexibility of the epigenome helps organisms respond to environmental signals during development, deal with stress, and create various types of functional cells. However, when these regulatory mechanisms are disrupted, it can lead to various health issues, including cancer, neurodegenerative disorders, metabolic syndrome, congenital malformations, immune problems, and psychiatric disorders (Allis & Jenuwein, 2016). Although the CRISPR-Cas9 system was first introduced as a tool to edit genomes by cutting target DNA sequences, it has quickly developed into a powerful platform for epigenome engineering. The creation of the catalytically inactive Cas9 protein, or dCas9, allows scientists to reprogram specific regions without cutting the genome. When dCas9 is combined with various epigenetic regulators—such as methyltransferase, demethylase, histone acetyltransferase, and repressor domains—it can suppress, activate, or reprogram target gene loci (Hilton et al., 2015). CRISPR-based epigenetic regulation is gaining attention as a method that maintains genome

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

integrity. It is reversible, safer, and offers therapeutic effects that are closer to natural expression profiles (Liu et al., 2023). In this section, the latest information on the application of CRISPR technology in epigenetic reprogramming will be thoroughly discussed, including molecular mechanisms, epigenetic regulation systems, clinical application, delivery systems, benefits and drawbacks, and future prospects.

2. ADAPTATİON OF CRISPR TECHNOLOGY TO EPİGENETİC APPLİCATİONS

2.1. dCas9 Platform: Catalytically Inactive Cas9

The mechanism of CRISPR epigenome editing begins with "dead Cas9" (dCas9), which lacks the DNA cleavage capability but preserves targeting to a specific DNA sequence. dCas9 is derived from mutations in the HNH and RuvC domains, which correspond to the two nuclease domains in Cas9. dCas9 targets a specific loci through a guide RNA sequence without generating a double-strand break (Qi et al., 2013). Therefore, dCas9 functions as a delivery protein for targeting epigenetic regulation enzymes to a given site.

2.2. dCas9 Fusion Systems

The dCas9 system can be combined with different epigenetic modifications to have varying functions:

- DNA methyltransferase (DNMT3A/DNMT3L) fusions: suppress specific promoter areas by methylating them (Vojta et al., 2016).
- TET demethylases fusions. Enable activation of genes through removal of methyl groups from DNA.
- Histone acetyltransferase (p300) fusions: Induce chromatin to adopt an open state and thus

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

stimulate transcription activation (Hilton et al., 2015).

- KRAB repressor domain: Encourages heterochromatin formation, thereby decreasing target gene expression.
- VP64, VPR, and SAM activator complexes support strong transcription activation.

These fusion systems offer precise control at the epigenome level. They allow for the reprogramming of single genes or whole genomic networks.

2.3. gRNA Design Strategies and Epigenetic Targeting

In epigenetic control, gRNA guides are designed to target areas around the promoter and enhancers and not around the cut site, compared to traditional gene editing. Targeting areas around the transcription start site (TSS) ensures maximum epigenetic efficiency of both CRISPRi and CRISPRa (Gilbert et al., 2013). In addition, multi-gRNA approaches induce strong and more stable epigenetic effects by targeting the same gene from different perspectives.

2.4. CRISPRi and CRISPRa Systems

- CRISPRi (CRISPR interference): Suppressing transcription with the dCas9-KRAB fusion.
- CRISPRa (CRISPR activation): Activating transcription using the dCas9-VP64, dCas9-VPR, or SAM system.

These two systems enable the regulation of target gene expression without cutting the genome and are particularly important for safety in therapeutic applications.

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

3. CRISPR-BASED EPİGENETİC REPROGRAMMİNG MECHANİSMS

3.1. Modulation of DNA Methylation with CRISPR

DNA methylation is generally known to be a repressive epigenetic mark. Methylation of promoters can be enhanced to repress oncogenes, inflammatory genes, or metabolically active genes through overexpression by using CRISPR-DNMT3A. It can be reversed; for instance, reactivating silenced genes in specific genetic disorders involves the use of dCas9-TET1 fusions to remove methylation.

3.2. Control of Histone Modifications

Histone modifications are basic control elements of chromatin structure.

- H3K27ac is a mark of activation,
- while H3K9me3 is a marker of repression.

Although dCas9-p300 systems trigger an activation of genes by acetylating the target region, dCas9-KRAB mediates silencing by H3K9me3 accumulation (Hilton et al., 2015).

3.3. Regulation of Enhancer and Promoter Activity

Enhancement regions are the major regulators of tissue-specific gene expression. Activation of the enhancer can be enhanced by CRISPRa, and the functional inhibition of the enhancer is performed by CRISPRi. This approach is widely used to knock out the super-enhancer elements in cancer.

3.4. Manipulation of Long-Range Chromatin Interactions

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

CRISPR-GO and CRISPR-loops technologies aim at regulating the three-dimensional organization of the genome.

It aims to change the contact of certain gene regions with nuclear lamina, heterochromatin, or active regions. This gives a new dimension to gene expression control-spatial organization.

4. THERAPEUTIC APPLICATIONS

CRISPR-based epigenetic reprogramming provides a safer and more flexible method compared to traditional gene therapy. The clinical areas with the greatest therapeutic potential are summarized below.

4.1. CRISPR-Epigenetic Interventions in Cancer Treatments

Global hypomethylation and local hypermethylation often occur in cancer cells. Silencing oncogenes or reactivating tumor suppressor genes is possible with CRISPR epigenetic tools. For example, using dCas9-TET1, researchers demethylated hypermethylated promoters and re-expressed tumor suppressor genes (Li et al., 2020).

Additionally, silencing immune checkpoint genes like PD-1, CTLA-4, or TIM-3 with CRISPRi boosts sensitivity to the immune response.

4.2. Gene Expression Modulation in Neurodegenerative Diseases

Epigenetic dysfunction plays a major role in diseases like Alzheimer's, Parkinson's, and Huntington's.

• CRISPRa can boost the activation of neuroprotective genes.

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

• CRISPRi can lower toxic proteins or gene products that create aggregates.

For example, lowering mutant HTT expression with CRISPRi in Huntington's disease greatly reduced the cellular stress response (Liu et al., 2023).

4.3. CrispR Approaches in Metabolic and Genetic Diseases

Epigenetic regulation:

• Insulin sensitivity can be improved.

• Obesity genes can be suppressed.

• Fetal hemoglobin expression may be increased in hemoglobinopathies.

CRISPRi-based approaches to silence BCL11A have already demonstrated preclinical success in the context of thalassemia and sickle cell anemia.

4.4. Epigenetic Reprogramming with CRISPR in Immunotherapy

Applications of epigenetic CRISPR in CAR-T cell therapies have picked pace.

• Repressing genes such as TOX, PD-1, and LAG-3 in T cells with characteristics of exhaustion through CRISPRi,

• improving cytotoxic function genes with CRISPRa,

to induce more robust and sustained CAR-T cell immune responses.

4.5. Use in Developmental Disorders

In the imprinting disorders Rett syndrome, Angelman syndrome, and Prader-Willi syndrome, the restoration of the

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

mutated gene alone, by overcoming the epigenetic silencing, also results in a therapeutic effect. One promising approach in this respect is the removal of the imprinting-induced silencing of UBE3A via dCas9-TET1.

5. CRISPR-EPIGENETIC DELIVERY SYSTEMS

5.1. Viral Vectors

AAV, lentiviral, and adenoviral vectors are some of the most frequently used vectors.

- AAV has the restriction of a small cargo size when using the dCas9 system.
- The lentiviral vector is more suitable to ex vivo technologies.

5.2. Non-Viral Vectors

Lipid nanoparticles (LNP), polymeric nanoparticles, and DNA/RNA-based delivery systems are some recent developments. The capacity to carry mRNA-based products for the CRISPR technology using LNPs makes them more promising for use.

5.3. In Vivo and Ex Vivo Delivery Strategies

- **Ex vivo:** The cells are taken out of the body to be modified in the lab and then returned; an example is CAR-T.
- **In vivo:** CRISPR is loaded directly into the tissue of interest, such as liver, muscle, retina, etc.

5.4. Tissue-Specific Delivery Challenges

One of the major challenges is to ensure the delivery of epigenetic regulators to the target tissue alone. Besides, long-term stability of epigenetic alterations remains a significant issue yet to be resolved.

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

6. ADVANTAGES, LIMITATIONS, AND SECURITY ISSUES

6.1. Off-Target Epigenetic Effects

Although the problem of off-target genomic effects is reduced, the fact is that epigenetic off-target risks are a possibility. The dCas9 protein can diffuse to the wrong locus and affect epigenetic marks.

6.2. The Genome Must Not Be Permanently Altered

The major advantage of epigenetic regulation is that it is reversible. If the treatment is stopped, the gene expression level usually returns to what it was before.

6.3. Immune Response Risks

Cas proteins are of bacterial origin. These proteins may trigger an immune reaction. Problems also arise due to immunogenicity with vectors like AAV.

6.4. Tissue Specificity and Persistence Issues

How long epigenetic modifications last depends on variables such as the rate of cell division, the potential for regeneration of the targeted tissue, and the half-life of dCas9.

6.5. Ethics and Regulatory Debates

Though genome editing can be skipped, there are validity concerns about epigenetic reprogramming of germlines.

7. FUTURE PERSPECTIVES

7.1. Combined Epigenetic Modulation with Base Editing and Prime Editing

The advent of next-generation genome editors, including both base editing and prime editing, presents a considerable safety

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

benefit over traditional CRISPR/Cas9 genome editing models based on cutting by allowing for pinpoint changes to the DNA code with pinpoint precision and without inducing double-strand breaks (Komor et al., 2016; Anzalone et al., 2019). The combination and eventual use of such models with epigenetic controllers based on dCas9 may therefore present a two-tiered treatment protocol which permits both correcting for genetic mutation and repurposing for epigenetic malfunction at the same site. In monogenetic disorders in particular, contemporaneous correction for a pathogenic mutation and eliminative reversal for secondarily epigenetically silenced gene regions due to disease may present a prospect for a more authentic and fuller conversion (Liu et al., 2023). In fact, this dual modality approach may present substantial long-term prospects in avoiding resistance and incomplete responsiveness.

7.2. Artificial Intelligence-Based gRNA Design

There has been growing interest in the application of artificial intelligence (AI) and machine learning algorithms to the design of gRNA sequences for CRISPR-based therapies. Machine learning algorithms that are trained using large genomic datasets can identify gRNA designs which are highly efficacious and also lack off-target effects by analyzing simultaneously the target sequence, the chromatin status, the epigenetic status, and the off-target regions (Chuai et al., 2018; Wang et al., 2019). In the context of epigenetics, this translates into a much more precise target hit within functional regions like promoters and enhancers. Therefore, the translational fidelity, reproducibility, and resistance to interindividual variation of CRISPR-based epigenetics therapeutics can be greatly enhanced. In the coming years, it is likely that “AI-designed” gRNA panels, which are patient-specific, would gain prominence.

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

7.3. CRISPR-Epigenetics in Regenerative Medicine

The fundamental goal in regenerative medicine is to produce functional cells or tissues that can replace damaged tissue and safely deliver them to the patient. In this regard, CRISPR-based epigenetic reprogramming has now forged an unparalleled position as a means to control the differentiation programs of not only stem cells but also somatic cells. Modulating specific epigenetic marks on embryonic stem cells or induced pluripotent stem cells can support more efficient and error-free differentiation into target cell types like cardiomyocytes, neurons, hepatocytes, or pancreatic β-cells. Similarly, in vivo epigenetic interventions to stimulate tissue regeneration at the site of injury, such as supporting cardiac muscle regeneration after myocardial infarction, open the door to such applications. Long-term, the capacity of the CRISPR-epigenetic combination to "rewrite cell fate" could be one of the basic paradigms of regenerative medicine.

7.4. Personalized Gene Therapy

The ability to extract patient-specific epigenetic signatures (DNA methylation profiles, histone modification patterns, chromatin accessibility maps, etc.) at high resolution will be a critical step in personalizing CRISPR-based epigenetic therapies (Clark et al., 2019). Even patients with the same genetic mutation may have different epigenetic landscapes depending on environmental factors, age, comorbidities, and previous treatments; this can limit the effectiveness of standard one-size-fits-all treatments. Therefore, in the future, each patient's genomic and epigenomic data will be analyzed together to select target gene sets, gRNA combinations, and the types of epigenetic effectors to be used on an individualized basis (Liu et al., 2023). Such an approach has the potential to both maximize treatment

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

response and minimize the risk of side effects. In conclusion, CRISPR-based epigenetic reprogramming could become one of the fundamental components of truly personalized gene therapy models tailored not only to disease class but also to the individual's unique “molecular fingerprint.”

8. RESULT

CRISPR epigenetic reprogramming represents a very effective biotech tool that, hopefully, can induce a paradigm change for gene therapy. A great advantage of this technique is that it can control the expression of target genes without altering the genome, which improves both safety and functionality. Noteworthy successes have already been achieved using this tool for various diseases, including cancers, neurodegenerative disorders, metabolic syndromes, and congenital maladies. However, challenges associated with delivery systems, epigenetic gene modifications, and safety data, among others, are still to be resolved. Looking forward, combined research using CRISPR, artificial intelligence, delivery systems using nanoparticles, and epigenomic maps can soon advance gene therapies based on epigenetics.

REFERENCES

Allis, C. D., & Jenuwein, T. (2016). The molecular hallmarks of epigenetic control. Nature Reviews Genetics, 17(8), 487–500.

Anzalone, A. V., Randolph, P. B., Davis, J. R., Sousa, A. A., Koblan, L. W., Levy, J. M., … Liu, D. R. (2019). Search-and-replace genome editing without double-strand breaks or donor DNA. Nature, 576(7785), 149–157.

Bird, A. (2022). DNA methylation and the epigenetic landscape. Genes & Development, 36(1), 1–20.

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

Chuai, G., Ma, H., Yan, J., Chen, M., Hong, N., Xue, D., … Liu, Q. (2018). DeepCRISPR: Optimized CRISPR guide RNA design by deep learning. Genome Biology, 19(1), 80.

Clark, S. J., Lee, H. J., Smallwood, S. A., Kelsey, G., & Reik, W. (2019). Single-cell epigenomics: Powerful new methods for understanding gene regulation and cell identity. Genome Biology, 20(1), 142.

Gilbert, L. A., et al. (2013). CRISPR-mediated modular RNA-guided regulation of transcription in eukaryotes. Cell, 154(2), 442–451.

Hanna, R. E., & Keren-Shaul, H. (2021). CRISPR-based technologies in regenerative medicine: State of the art and future prospects. Cell Stem Cell, 28(4), 559–575.

Hilton, I. B., et al. (2015). Epigenome editing by a CRISPR-Cas9-based acetyltransferase activates genes. Nature Biotechnology, 33(5), 510–517.

Komor, A. C., Kim, Y. B., Packer, M. S., Zuris, J. A., & Liu, D. R. (2016). Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage. Nature, 533(7603), 420–424.

Li, H., et al. (2020). CRISPR-based epigenome editing for cancer therapy. Cancer Research, 80(13), 2761–2768.

Liu, Y., et al. (2023). CRISPR-based epigenome editing for therapeutic modulation of gene expression. Trends in Molecular Medicine, 29(4), 345–360.

Nakamura, M., Gao, Y., Dominguez, A. A., & Qi, L. S. (2021). CRISPR technologies for precise epigenome editing. Nature Cell Biology, 23(1), 11–22.

Qi, L. S., et al. (2013). Repurposing CRISPR as an RNA-guided platform for sequence-specific control of gene expression. Cell, 152(5), 1173–1183.

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

Vojta, A., et al. (2016). Repurposing the CRISPR-Cas9 system for targeted DNA methylation. Nucleic Acids Research, 44(12), 5615–5628.

Wang, D., Zhang, C., Wang, B., Li, B., Wang, Q., Liu, D., … Yang, H. (2019). Optimized CRISPR guide RNA design for two high-fidelity Cas9 variants by deep learning. Nature Communications, 10(1), 4284.

[1] Department of Medical Genetics, Faculty of Medicine, Ağrı İbrahim Çeçen University, Ağrı, Turkey, e-mail: tkucuk@agri.edu.tr, ORCID: 0000-0002-0092-1032

TÜRKİYE VE DÜNYADA

TIBBİ GENETİK

yaz
yayınları

YAZ Yayınları
M.İhtisas OSB Mah. 4A Cad. No:3/3
İscehisar / AFYONKARAHİSAR
Tel : (0 531) 880 92 99
yazyayinlari@gmail.com • www.yazyayinlari.com