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Türkiye's First Multidisciplinary Gene Therapy Education Program: History and Plans for the Future

Türkiye'nin İlk Multidisipliner Gen Tedavisi Eğitim Programı: Geçmiş ve Geleceğe Yönelik Planlar

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Abstract

Aim: Gene therapy is applied to regulate the functions of mutated or disease-causing genes in human cells and targets nucleotides. Recent years have seen an increasing number of publications reporting successful results from gene therapies, suggesting an increasing scientific curiosity among clinicians.

Material and Method: Gene Therapy Symposiums were hosted by the [blinded for review]. The participants answered pre-post-tests, and satisfaction scales.

Results: A total of 192 participants underwent training, none of whom had previously undergone gene therapy training. Of the sample, 71.9% were female and the median age of the participants was 32 years. Of the total, 84.9% were studying medicine and 15.1% were studying in non-medical fields. Among those studying medicine, 17.2% were students, 18.4% were main specialty research assistants, 38.0% were subspecialty research assistants, 17.2% were specialists and 9.2% were assistant professors/professors. An analysis of the completed pretests revealed that 32.3% had answered the questions correctly, while 58.6% answered the questions correctly after undergoing training. The overall satisfaction score was 91.8 out of 100.

Conclusion: The results of the pretest revealed the knowledge and awareness of gene therapy among the participants to be low, indicating a need for education programs addressing the subject. Gene therapy has moved beyond the theoretical realm in recent years and is today seeing practical applications. There is an urgent need to train the clinicians and other operatives required for the provision of gene therapies and to develop strategies for tertiary care centers in this field over the next 10 years.

Keywords: Education, future, gene therapy, inherited metabolic disorders, spinal muscular atrophy

Öz

Amaç: Gen terapisi, insan hücrelerinde mutasyona uğramış veya hastalığa neden olan genlerin fonksiyonlarını düzenlemek için uygulanan ve nükleotidleri hedef alan bir tedavi yöntemidir. Son yıllarda gen terapisi alanında başarılı sonuçlar bildiren yayınların sayısı artmış, bu da klinisyenler arasında bilimsel merakın artışına sebep olmuştur.

Gereç ve Yöntem: Gen Terapisi Sempozyumları [blinded for review] ev sahipliğinde düzenlendi. Katılımcılar ön-son testleri ve memnuniyet ölçeklerini yanıtladılar.

Bulgular: Hiçbiri daha önce gen terapisi eğitimi almamış olan toplam 192 katılımcıya eğitim verildi. Katılımcıların %71,9'u kadındı ve katılımcıların ortanca yaşı 32 yıldı. Toplamın %84,9'u tıp, %15,1'i ise tıp dışı alanlardandı. Tıp alanından katılımcıların %17,2'si öğrenci, %18,4'ü ana uzmanlık araştırma görevlisi, %38,0'ı yan dal araştırma görevlisi, %17,2'si uzman ve %9,2'si doçent/profesördü. Katılımcıların ön test analizinde soruların %32,3'ünü doğru yanıtladığı, eğitim sonrasında ise bu oranın %58,6'ya yükseldiği saptandı. Genel memnuniyet puanı 100 üzerinden 91,8'di.

Sonuç: Ön test sonuçları, katılımcılar arasında gen terapisine ilişkin bilgi ve farkındalık düzeyinin düşük olduğunu ortaya koymuştur ve bu da konuya yönelik eğitim programlarına ihtiyaç duyulduğunu göstermektedir. Gen terapisi son yıllarda teorik alanın ötesine geçmiştir ve bugün pratik uygulamalar görülmektedir. Önümüzdeki 10 yıl içinde gen tedavilerinin sağlanması için gerekli olan klinisyenlerin ve diğer uygulayıcıların eğitilmesine ve üçüncü basamak sağlık merkezleri için bu alanda stratejiler geliştirilmesine acil ihtiyaç vardır.

Anahtar Kelimeler: Eğitim, gelecek, gen tedavisi, kalıtsal metabolik hastalık, spinal muskuler atrofi

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INTRODUCTION

The idea of gene therapy was first brought to the table by Martine Cline in 1970 after she discovered that viruses transfer their genetic material to the host.[1] The subsequent development of recombinant DNA technologies made gene manipulation possible,[2,3] leading to the first application of human gene therapy for thalassemia[4] in 1982. Then, in 1990, two children diagnosed with severe combined immunodeficiency were subjected to gene therapy and subsequently cured of the condition.[5]

Gene therapy aims to regulate the functions of mutated or disease-causing genes in human cells and targets nucleotides.[6] In gene therapy, plasmids containing transgenes are transfected into the target cells. Since DNA is likely to be damaged during this process, the transfer is carried out through a vector that must carry the DNA fragment, must reach high concentrations, and must be specific to the target tissue, stable and effective, and provide long-term gene expression. The most commonly used viral vectors are adenovirus, adenovirus-associated virus (AAV), retrovirus/lentivirus and herpesvirus.[7]

Studies of gene therapy have witnessed a rapid increase in number since 2010, with over 30,000 publications related to gene therapy listed on PubMed in the last 3 years,[8,9] and a total of 33,406 studies involving clinical trials were conducted between 2010 and 2020.[9,10] Gene therapy research focuses on oncological and genetic diseases.[9] More than half of the gene therapy studies carried out over the last decade related to oncological and neurodegenerative diseases, while studies of hematological, immunological, inherited metabolic and cardiac diseases have gained popularity more recently. More than 25 percent of gene therapy studies of monogenic diseases relate to inherited metabolic diseases, and while most Phase 1 and Phase 2 clinical studies relate to cancer, Phase 3 clinical studies tend to favor genetic disorders.[9]

In recent years, with the increasing number of publications reporting successful results from gene therapies, the scientific curiosity of clinicians with an interest in genetic diseases has been raised.[11] Due to the high rate of consanguineous marriage in our country, the frequency of autosomal recessive monogenic diseases is relatively higher than in other countries,[12] and so developing the necessary infrastructure and providing the necessary training to healthcare personnel in gene therapy in the coming years is essential.

In the present study, we put forward a training program aimed at raising the awareness and knowledge of clinicians/researchers operating in various disciplines with an interest in monogenic inherited diseases that can benefit from gene therapy. To this end, gene therapy symposiums were organized with the financial support of a global grant, the success of which was measured based on the results of a satisfaction scale and pre- and post-tests applied to the participants. This is the first example of gene therapy training provided to a multidisciplinary cohort in our country.

MATERIAL AND METHOD

The three Gene Therapy Symposiums were hosted by the [**blinded for review**], with a 6-month interval between each, on 01.13.2023, 06.10.2023 and 12.8.2023. A Pfizer Global Independent Medical Education Grant RFP, Multidisciplinary Gene Therapy Education and Grant Program supported the project. The application of the RARE Center was one of hundreds made for such grants from all over the world and was the only application from Türkiye deemed worthy of the grant. The first of the symposiums was held face-to-face in [**blinded for review**], while the second and third were held online through a website with the [**blinded for review**] extension, which protects personal rights and contains features to prevent data theft.

The 7-hour/day training program included sessions with the following headings: "The History of Gene Therapy and its Story to the Present Day", "Preclinical Experiences for In-vivo Gene Therapy", "Clinical Considerations and an Overview of Gene Therapy" "Gene Therapy – the FDA/EMA Guide for Clinical Studies – the Situation in Türkiye", "Spinal Muscular Atrophy Clinical Program", "Hemophilia Clinical Program", "Immunodeficiency Clinical Program", "Clinical Program in Oncology", "AADC (Aromatic L-Aminoacid Decarboxylase Deficiency) Clinical Program", "OTC (Ornithine Transcarbamylase Deficiency) Clinical Program", "MLD (Metachromatic Leukodystrophy) Clinical Program" and "Preparations and Future Plans in Türkiye, given by experts in their fields.

To evaluate the benefits of the training program, the authors of the present paper prepared questions that were applied to the participants as pre- and post-tests. The pre-test was completed by the participants before joining the training, and the post-test was completed by the participants after the training. Participants accessed both tests via links sent to them and marked their answers electronically. The content of both the pre and post-tests consisted of questions related to the key points emphasized by the speaker on the topic and aimed at increasing awareness. The answers were analyzed as correct/incorrect. All the participants took part in a symposium satisfaction survey at the end of the symposium, with responses rated on a Likert type scale of 1–5, with "1" indicating the lowest satisfaction level and "5" indicating the highest satisfaction level. Satisfaction components included subject content, speakers, question-answer-discussion, symposium duration adequacy, contribution level to participant, preferred training method, preferred duration of training, willingness to participate in further training, willingness to recommend the program to friends working in the same field, and overall satisfaction score. The participants who were present throughout the training and who completed the final test were handed a "Gene Therapy Symposium Participation Certificate".

The Gene Therapy Symposium was the first multidisciplinary gene therapy training program to be conducted in Türkiye. The TTB STE/SMG Accreditation-Crediting Board accredited the Gene Therapy Symposium with 4.5 TTB STE/SMG Credits. The participants were able to obtain personal loans using their identification number through a link presented during the symposium. This study was conducted in accordance with the "Declaration of Helsinki". [**blinded for review**] Local Ethics Committee Approval number [**blinded for review**] was received on [**blinded for review**].

Statistical Analysis

IBM SPSS Statistics for Macintosh (Version 27.0. Armonk, NY: IBM Corp.) was used for all statistical analyses. Continuous and categorical variables were presented as medians [25th–75th percentiles] and numbers (percentage), respectively. A Chi-square test and a Fisher's test were used for the analysis of any differences between the independent groups. A p-value of less than 0.05 was accepted as statistically significant.

RESULTS

A total of 192 participants joined the training provided during the three gene therapy symposiums, none of whom had previously received training in gene therapy. Of the total, 71.9% were female, and the median age of the entire sample was 32 years [IQR: 25.0-38.0]. Furthermore, 139 of the participants (72.4%) were working in Ankara and 53 (27.6%) were working outside Ankara; and 163 (84.9%) were studying medicine and 29 (15.1%) were studying in non-medical fields. Of those studying medicine, 28 (17.2%) were students, 30 (18.4%) were main specialty research assistants, 62 (38.0%) were subspecialty research assistants, 28 (17.2%) were specialists, and 15 (9.2%) were assistant professors/professors. Among the non-medical fields represented were biology (27.5%), molecular biology (20.7%), pharmacy (13.8%), chemistry (13.8%), biotechnology (10.3%), nursing (6.9%), law (3.5%) and engineering (3.5%) (**Table 1**).

The pre- and post-tests were applied to the participants to evaluate the benefit of the training program. The pre-test was completed by the participants before the training, and the post-test was completed after the training. A total of 32.3% of the participants answered the questions correctly in the pre-test, and this figure increased to 58.6% after the training. The areas in which awareness/knowledge was raised the most were spinal muscular atrophy (pre-test and post-test correct answer percentages, 15.6% and 58.3%, respectively), ornithine transcarbamylase deficiency (13.8% and 43.8%, respectively), hemophilia (23.4% and 47.4%, respectively) and primary immune deficiencies (38.1% and 70.8%, respectively) (**Table 2**). The pre- and post-test data of the medical and non-medical professional groups were compared, revealing higher post-test scores among those working in the medical field than in those working in non-medical fields (61.1% vs 12.5% p=0.031).

Table 1. Sociodemographic characteristics of the participants

Sex, n (%)	
Female	138 (71.9)
Male	54 (28.1)
Age, years	
Mean (SD)	31.9 (8.6)
Median [IQR]	32.0 [25.0-38.0]
Min-max	18.0-63.0
City, n (%)	
Ankara	139 (72.4)
Outside Ankara	53 (27.6)
Geographic distribution of participation outside Ankara, n (%)	
Marmara region	12 (22.6)
Central Anatolian region	11 (20.8)
Aegean region	10 (18.9)
Mediterranean region	7 (13.2)
Black Sea region	5 (9.4)
Southeastern Anatolia region	5 (9.4)
Eastern Anatolia region	3 (5.7)
Fields, n (%)	
Medicine	163 (84.9)
Non-medicine	29 (15.1)
Title distribution of participants from the field of medicine, n (%)	
Student	28 (17.2)
Main specialty research assistants	30 (18.4)
Subspecialty research assistants	62 (38.0)
Specialist	28 (17.2)
Associate professor/professor	15 (9.2)
Distribution of clinicians by department, n (%)	
Main specialty research assistants (n=30)	
Pediatrics	18 (60.0)
Internal Medicine	6 (20.0)
Ophthalmologist	6 (20.0)
Subspecialty research assistants (n=62)	
Metabolism-Endocrinology	28 (45.1)
Immunology and Allergy	8 (12.9)
Neurology	8 (12.9)
Hematology-Oncology	7 (11.2)
Genetics	6 (9.6)
Gastroenterology	3 (4.8)
Pulmonology	2 (3.2)
Specialist and associate professor/professor (n=43)	
Metabolism-Endocrinology	19 (44.1)
Neurology	7 (16.2)
Genetics	6 (13.9)
Immunology	4 (9.3)
Hematology-Oncology	4 (9.3)
Neonatology	2 (4.6)
Ophthalmologist	1 (2.3)
Occupational distribution of participants from non-medical fields, n (%)	
Biology	8 (27.5)
Molecular Biology	6 (20.7)
Pharmacy	4 (13.8)
Chemistry	4 (13.8)
Biotechnology	3 (10.3)
Nursing	2 (6.9)
Law	1 (3.5)
Engineering	1 (3.5)

Table 2. Educational success of the symposium

	Pretest Correct answer rate (%)	Posttest Correct answer rate (%)
Spinal Muscular Atrophy Clinical Program	15.6	58.3
Ornithine Transcarbamylase Deficiency Clinical Program	13.8	43.8
Hemophilia Clinical Program	23.4	47.4
Primary Immunodeficiency Clinical Program	38.1	70.8
Aromatic L-Aminoacid Decarboxylase Deficiency Clinical Program	45.9	62.5
Metachromatic Leukodystrophy Clinical Program	45.3	59.4
Subjects outside the Clinical Program	44.4	67.7
Total score	32.3	58.6

Table 3. Satisfaction Scale

Subject content, score	4.63/5
Speakers, score	4.57/5
Question-answer-discussion, score	4.20/5
Symposium duration adequacy, score	4.30/5
Contribution level to participant, score	4.50/5
Preferred training method, %	
Face-to-face	60
Online	40
Preferred duration of training, %	
One day	60
Two days	40
Willingness to participate in further training, %	96.7
Willingness to recommend the program to friends working in the same field, %	100
Overall satisfaction score average	91.8/100

*Likert-type scale, from 1 (low) to 5 (high).

The post-test results of the academicians were higher than those of the students in the "hemophilia clinical program (52.4% vs. 17.8%, p=0.001)", "spinal muscular atrophy clinical program (34.7% vs. 14.2%, p=0.032)", "immunodeficiency clinical program (75.0% vs. 46.4%, p=0.002)" and "fundamentals (72.5% vs. 39.2%, p=0.001)".

A symposium satisfaction survey was administered to all participants at the end of the training in which the participants were asked to answer each question on a Likert-type scale of 1–5 for the lowest and highest satisfaction levels, respectively. The symposium topic content received an average score of 4.63/5, the speakers received an average rating of 4.57/5, the question-answer-discussion sections received an average rating of 4.20/5, the duration of the symposium averaged 4.30/5, and the contribution to the participants received an average rating of 4.50/5. When asked whether they preferred online or face-to-face education, 60% of the respondents preferred the face-to-face format. Furthermore, 60% of the participants stated that they would prefer the training to last one day, while 40% preferred the topics to be spread over two days. Some 96.7% of the participants stated that they thought the gene therapy symposiums should continue and declared a willingness to participate in further symposiums. All of the participants stated that they would recommend the training to their friends working in the same field. Finally, the participants were asked to give an overall satisfaction score to the symposium, resulting in an average of 91.8%.

DISCUSSION

Türkiye's first multidisciplinary gene therapy training symposiums were organized to increase the level of knowledge of the participants related to gene therapies, to open new horizons and to serve as a platform for discussions of current treatments. The targeted numbers of participants from both inside and outside Ankara were achieved, with participants from a broad range of disciplines other than medicine, including biologists, engineers, pharmacists, and lawyers. The pre-test results revealed the level of knowledge and awareness of gene therapy to be very low, suggesting the importance of education programs in the field of gene therapy. The pre-test and post-test data indicated a 1.8-fold increase in the knowledge level, while the correct answer rate in the post-test remained below 60%. For healthcare professionals from various disciplines and specialties, while listening to an expert in the field once can provide a certain level of insight, it is essential to attend repeated training tailored to subgroups within disciplines to stay updated on extremely new and current treatment methods. This encouraged us to continue improving ourselves in Gene Therapy education. Taking a holistic perspective, the post-test data indicates that continuing the training will further contribute to increases in awareness and knowledge, and almost all of the participants expressed a desire to see the training continue.

Spinal muscular atrophy (SMA) is a monogenic disease that is high on the agenda in our country, being an autosomal recessive hereditary disease characterized by progressive hypotonicity affecting the motor nuclei of the cranial nerves and anterior horn motor neurons in the spinal cord, it develops due to biallelic mutations in the SMN1 (MIM *600354) gene and has a reported frequency of 1–3/10,000 worldwide.[13] In Türkiye, the carrier frequency of the SMN1 gene mutation is 1/40–1/60, and although the exact incidence of SMA disease in Türkiye is unknown, the Ministry of Health of the Republic of Turkey suggests that there are 130–180 new cases annually, with approximately 3000 SMA patients under follow-up.[14] A premarital SMA carrier screening program was launched, in Türkiye in 2021, followed by a newborn SMA screening program in 2022.

Couples who apply for a premarital health report undergo spinal muscular atrophy carrier screening, while those who

are married can request it.[15] Being a disease caused by dysfunction of the SMN1 gene, gene therapy is considered a promising treatment option. The SMN1 gene is small and has been successfully packaged and transcribed with the help of a viral vector.[16] Adenovirus-associated virus serotype 9 (AAV9) is the preferred option for the transfer of the SMN1 gene, being a viral vector that can cross the blood-brain barrier.[17] There have been groundbreaking developments in the treatment of SMA disease in recent years, and gene therapy for SMA has emerged as a popular treatment approach in our country. The global follow-up of patients undergoing treatment is continuing to understand the long-term effects. Despite the disease being high on the agenda in Türkiye and the presence of a screening program in the country, only 15.6% of the participants of the symposiums gave correct responses in the field related to SMA in the pre-test applied before the start of Gene Therapy Symposium training, rising to 58.3% after the training, suggesting that the applied training raised awareness and knowledge of SMA. In our country, parents create calls for financial support for their children with SMA through many personal social media channels. Since the level of awareness of this issue in society is low, the clinical conditions of children diagnosed with SMA can sometimes be used for emotional exploitation by parents. Increasing the awareness and knowledge of physicians related to gene therapy is vital to achieving social improvement, both medically and socially, and the problem may be reduced through the involvement of trained physicians at events informing the public about SMA treatment options.

The majority of gene therapy research is in the field of inherited metabolic diseases, followed by eye and blood coagulation diseases, and these three disease groups combined account for more than half of all studies of gene therapies.[9,18] Our training symposium included training sessions on the diagnosis of ornithine transcarbamylase deficiency, aromatic l-amino acid decarboxylase deficiency and metachromatic leukodystrophy, which is an inherited metabolic disease. The ornithine transcarbamylase deficiency, aromatic l-amino acid decarboxylase deficiency and metachromatic leukodystrophy clinical programs increased the level of knowledge by 3.2, 1.4 and 1.3, respectively. It was observed that a higher proportion of physicians working in the field of metabolism participated in the training. Although OTC is an inherited metabolic disease, experiences and knowledge related to gene therapy are recent. For comparison, higher scores have been obtained in the field of primary immunodeficiencies, where gene therapy has been on the agenda for many years. This situation can be explained by the historical chronological process and accumulated experience. While only a quarter of the participants were aware of the hemophilia clinic program, half answered the questions correctly after the completion of the training, and their level of knowledge was doubled. It was initially intended to host a gene therapy session on eye diseases, however the lack of any academician working in this field in Türkiye led to the idea being abandoned. Should we continue the training series, this would be one of the main topics we would like to cover.

The satisfaction scale applied to the symposium participants revealed subject content to be the source of the greatest satisfaction, with scores of 4.5/5 and above being obtained regarding the speakers and their contributions to the program. The lowest score was achieved by the question-answer-discussion field, with 4.2/5 points, which may be attributed to the short amount of time allocated (5–10 minutes) due to the intensity of the training program. It should be noted that although 60% of the participants stated that the training should be held over a single day, the remaining 40% said that it should be a two-day program and spreading the program across two days would certainly allow a longer question-answer-discussion session to be accommodated. The program agenda reached a high satisfaction score of 91.8 out of 100, and although there are similar educational programs around the world, comparisons cannot be made since academic achievements are not shared in the form of an article. Increasing the knowledge and experience of the factors that contribute to educational success can be very valuable for the creation of content that best benefits academicians who will undergo training in gene therapy.

Our research reveals the characteristics and distribution of students, lab workers and academicians with an interest in Türkiye's first multidisciplinary gene therapy symposium program, and measures educational success and satisfaction. One significant reason for the lower-than-expected correct answer rates in the post-test may be the presence of participants from non-medical backgrounds. It was a limitation of our study. However, in our initial training program, we kept it open to all participants to promote awareness and advocacy. In the future, training sessions may be limited to the medical community to accurately measure medical knowledge. The discussion of experiences in gene therapies, which are gaining popularity worldwide, is vital for the academic community and for the raising of knowledge and awareness. Gene therapy has moved beyond the theoretical realm in recent years and is today seeing practical applications. The number of gene therapy products being used for the treatment of diseases is increasing daily. Aside from the approved therapies and those awaiting certification, there are also many clinical studies in the field suggesting a promising future for gene therapy.

In our country, where consanguineous marriages and autosomal recessive diseases are relatively common, there is a need for national strategies to support the necessary technological transformation, to reduce our external dependence on medicines, to ensure supply security, and to support the training of clinicians and other healthcare professionals in the field of gene therapy to support the operation of tertiary care centers over the next 10 years.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Ankara University Faculty of Medicine Local Ethics Committee Approval number İ01-31-24 was received on 01.18.2024

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Baltimore D. RNA-dependent DNA polymerase in virions of RNA tumour viruses. Nature. 1970;226(5252):1209-11.
2. Jackson DA, Symons RH, Berg P. Biochemical method for inserting new genetic information into DNA of Simian Virus 40: circular SV40 DNA molecules containing lambda phage genes and the galactose operon of Escherichia coli. Proc Natl Acad Sci U S A. 1972;69(10):2904-9.
3. Lobban PE, Kaiser AD. Enzymatic end-to end joining of DNA molecules. J Mol Biol. 1973;78(3):453-71.
4. Wade N. Gene therapy caught in more entanglements. Science. 1981;212(4490):24-5.
5. Blaese RM, Culver KW, Miller AD, et al. T lymphocyte-directed gene therapy for ADA- SCID: initial trial results after 4 years. Science. 1995;270(5235):475-80.
6. Smith CIE, Blomberg P. Genterapi – från idé till verklighet - Ännu har få patienter behandlats och preparaten är ofta mycket dyra – men utvecklingen går fort nu [Gene therapy – from idea to reality]. Lakartidningen. 2017;114:EWYL.
7. Smith KR. Gene Therapy: The Potential Applicability of Gene Transfer Technology to the Human Germline. Int J Med Sci. 2004;1(2):76-91.
8. **https://pubmed.ncbi.nlm.nih.gov/**
9. Arabi F, Mansouri V, Ahmadbeigi N. Gene therapy clinical trials, where do we go? An overview. Biomed Pharmacother. 2022;153:113324.
10. **https://clinicaltrials.gov/.**
11. Ogbonmide T, Rathore R, Rangrej SB, et al. Gene Therapy for Spinal Muscular Atrophy (SMA): A Review of Current Challenges and Safety Considerations for Onasemnogene Abeparvovec (Zolgensma). Cureus. 2023;15(3):e36197.
12. Eminoglu FT, Koc Yekeduz M, Dogulu N, et al. Inherited metabolic disorders in the neonatal intensive care unit: Red flags to look out for. Pediatr Int. 2022;64(1):e14953.
13. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20(1):27-32.
14. T.R. Ministry of Health 2021a. Premarital Spinal Muscular Atrophy (SMA) Carrier Screening Program. T.R. Ministry of Health. General Directorate of Public Health
15. T.R. Ministry of Health 2022. Newborn Metabolic and Endocrine Disease Screening Program. T.R. Ministry of Health. General Directorate of Public Health.
16. Waldrop MA, Kolb SJ. Current Treatment Options in Neurology-SMA Therapeutics. Curr Treat Options Neurol. 2019;21(6):25.
17. Schuster DJ, Dykstra JA, Riedl MS, et al. Biodistribution of adeno-associated virus serotype 9 (AAV9) vector after intrathecal and intravenous delivery in mouse. Front Neuroanat. 2014;8:42.
18. Rashnonejad A, Durmaz B, Özkınay F. The principles of gene therapy and recent advances. Ege J Med 2014;53(4):231-240.