**Invited Review**

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# Historical Perspective of Inborn Errors of Immunity in Turkey

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**Abstract**

This article details the development of immunology as a scientific discipline based on basic research and clinical application in Turkey. Due to the valiant efforts of the Turkish Society of Immunology (TSI), immunology has become a fundamental discipline in its own right in Turkey. Immunology Laboratories were established at İstanbul Medical School, Cerrahpaşa Medical School, and Hacettepe Medical School in 1970. Since 1974, TSI has been the driving force organizing the '"National Immunology Congress" and joint meetings with international immunology and inborn errors of immunity (IEIs) centers. The immunological education program was established in some of Turkey's most prominent medical schools during the 2000-2001 academic year. Following the establishment of the immunological programs, all facets of modern immunology and clinical medicine began to diverge. Subsequently, the Turkish National Society of Allergy and Clinical Immunology, and Clinical Immunology Society were established and initiated to organize congresses, educational meetings, courses, and webinars. With the assistance of international experts, Turkish clinical immunologists defined many gene defects in Turkish patients. As clinicians gained additional immunological experience, new techniques and practices that allowed for better diagnosis and treatment of a larger variety of different immunodeficiencies were developed. Beginning in 2011, the Ministry of Health started to regulate patient care by allowing pediatric/adult allergists and immunologists to provide patient care at the tertiary level. Screening tests for IEIs and intravenous or subcutaneous immunoglobulin replacement treatment are now being offered to all patients. Human stem cell therapy treatments are accessible for patients with T-cell deficiency, and available monoclonal therapies are provided to IEIs patients in Turkey.

**Keywords:** History of immunology, clinical immunology, inborn errors of immunity, primary immunodeficiency, immunology in Turkey, Turkish Society of Immunology

## Introduction

The subject of immunology covers a diverse spectrum of topics, ranging from basic research to clinical research. Immunology as a scientific discipline was founded with the identification of phagocytic cells (Metchnikoff, 1845-1916), which was followed by the discoveries of opsonization, complement proteins, chemical structure of antibodies, different types of hypersensitivity reactions, identification of B and T lymphocytes, dendritic cells, natural killer cells, surface expression of pattern recognition receptors, human leucocyte antigens (HLA), major histocompatibility (MHC) I/II antigens, cytokines, cytokine-blocking monoclonal antibodies, and inhibitors of checkpoint control (1).

Due to the courageous work and efforts of the Turkish Society of Immunology (TSI) since 1974, the field of immunology has become a rich medical discipline in Turkey. The principal goals of the society were to implement a comprehensive and consensual immunological education by conducting regular training programs, courses, and congresses with continuing cooperation with international and national experts on immunology and inborn errors of immunity (IEI). The most important goal was to disseminate awareness of immunology and IEIs nationwide. Turkey has a high rate of consanguineous marriages; thus, the incidence of IEIs with autosomal recessive-AR inheritance is higher than in Western countries. Hence, many novel genetic mutations were identified in Turkish patients by collaborative studies with Western primary immunodeficiencies (PID) centers (2,3).

Basic immunology is essential to guide and promote clinical immunology. Recent scientific developments in

cellular, molecular, and genetic studies have facilitated rapid advances in clinical immunology and broadened the spectrum of IEIs. Due to improvements in collaboration between researchers and clinicians, there was a remarkable improvement in comprehensive insight into the diagnosis and treatment of many rare diseases. Classically, frequent and life-threatening infections were accepted as the most prominent clinical symptoms of PID. Over the years, it has been reported that severe allergy, autoimmunity, autoinflammation, and malignancy can also be a clinical manifestation of PIDs. Thus, the definition of PIDs has been switched to "inborn errors of immunity" to cover all types of defects in immunity. More specialized young immunologists, allergists, and rheumatologists were needed in the field (4,5).

Since 1970, the International Union of Immunological Societies, Expert Committee, comprising adult and pediatric clinical immunologists, clinicians/scientists, and researchers in basic immunology, has published an updated classification of IEI biennially (6).

This report documents societies, foundations, departments, and divisions of pediatric and adult clinical immunology, playing a key role in advances in clinical immunology in Turkey.

Societies dealing with IEIs are as follows;

**Turkish Society of Immunology (TSI)**

Prof. Dr. Asuman Müftüoğlu, a hematologist at İstanbul University, Cerrahpaşa Medical School, Department of Internal Medicine, was trained in the United States and received further education in immunology. She decided to establish an immunology association, and on 31 January, 1974, the Turkish Society of Immunology (TSI) was founded by Dr. Asuman Müftüoğlu (internal medicine), Dr. İzzet Berkel (pediatrician), Dr. Süleyman Yakacıklı (pediatrician), Dr. Suat Vural (microbiologist), Dr. Yücel Tangün (internal medicine), Dr. Zişan Saraçbaşı (microbiologist), Dr. Özdemir İlter (pediatrician), and Dr. Enver Tali Çetin (microbiologist). The association's founders were visionary leaders of İstanbul University, Cerrahpaşa Medical School, İstanbul Medical School, and Hacettepe University Medical School. Their research was mainly on basic and clinical immunology, which they presented and published in the IV. National Immunology Society Congress Book (7-10). The society became a member of the International Union of Immunological Societies (IUIS) in 1977, the European Federation of Immunological Societies (EFIS) in 1975, and the Balkan Association of Immunological Societies (BAIS) in 1996. Dr. Müftüoğlu had a distinguished role in society until her retirement. She had prominent positions in IUIS (1974-1986) and EFIS bodies (1975-1986). The number of TSI members has continuously increased with the addition of young scientists involved in basic and clinical immunology. From the beginning of the IEI, pediatricians have played a prominent role in determining society's focus (2,3,7-10).

Since 1974, TSI has been organizing the "National Immunology Congress", and since 2012, "Molecular Immunology and Immunogenetic Congresses" biannually. In 1982, despite economic and political upheavals at the time, the fifth EFIS Congress was successfully organized in İstanbul, Turkey, by TSI under the presidency of Dr. Müftüoğlu. TSI also hosted the IV$^{th}$ Balkan Congress of Immunology with pleasure, organized by President Dr. Yıldız Camcıoğlu in 2004 in İstanbul. To facilitate cooperation between international PID centers and to promote advanced training in immunological research, the Turkish-French Immunology Days were held in İstanbul for 3 consecutive years (1995, 1996, 1998) in collaboration with the Study Center for Primary Immunodeficiencies, Necker Hospital for Sick Children.

With the assistance of Prof. Dr. Kurt Blaser director of Swiss Institute of Allergy and Asthma Research (SIAF) and distinguished scientists Cezmi and Mubeccel Akdis, TSI also hosted "Turkish-Swiss Immunology Days" in İstanbul for 2 consecutive years (1998, 1999). Since 2001, İstanbul University, Institute of Aziz Sancar Experimental Medicine, Department of Immunology, and SIAF have conducted collaborative research and fellowship programs. Turkish scientists are continuing the beneficial practice of conducting collaborative studies such as A. Fischer, J.L. Casanova, A. Durandy, G. de Saint Basile from Immunology and Pediatric Hematology Department, Assistance Publique-Hôpitaux de Paris, France, R. Geha and T. Chatila from Harvard Medical School, USA, M. Hershfield from Duke University Medical Center USA, M. van der Burg from Department of Immunology, Erasmus University, Rotterdam, The Netherlands, and K. Boztuğ from CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria. Novel genetic causes of IEIs, such as IFN-γRI, IL-12Rbeta I deficiency in patients with tuberculosis, STAT1, interleukin (IL)-17RA, IL-17RC deficiencies in patients with chronic mucocutaneous candidiasis, MyD88 in a patient with acute bacterial meningitis, CARMIL2, STAT3, DOCK-8, LRBA, ADA, MHC class I deficiency syndrome, Serine/threonine kinase-4, CD55 deficiency, STAT6-GOF and many others were identified in Turkish IEI patients.

The TSI has a PID subgroup, which participates in the development of clinical immunology in Turkey, involving the organizations of PID, sessions at national congresses, immunology and PID chapters in fundamental pediatric books, specific courses, training and certification programs, celebrating "immunology day" with PID patients (www.turkimmunoloji.org).

The European Congress of Immunology 2021 (ECI 2021) was organized virtually due to COVID pandemic precautions by TSI and The Serbian Immunology Society. A pre-congress course, "Inborn Errors of Immunity: An Expanding Spectrum of Clinical Phenotypes", was organized successfully. Short videos about IEIs were prepared and demonstrated publicly to establish a basis for broader recognition (www.turkishimmunology.org).

**Turkish National Society of Allergy and Clinical Immunology (TNSACI)**

The TNSACI was founded on May 23, 1989. The founding members of the AID were Dr. Yıldız Saraçlar, Dr. Gönül Adalıoğlu, Dr. Kemal Özkaragöz, Dr. Ülker Öneş, Dr. Ayfer Tuncer, Dr. Emin Kansu, Dr. Emine Gönenç Ciliv, Dr. Muhsin Saraçlar, Dr. Zeynep Mısırlıgil, Dr. Fatih Özkaragöz, Aymelek Taşhan, and Asuman Çetin. The name was changed to "Turkish National Society of Allergy and Clinical Immunology (AID)" in 1995. The main objectives of AID are to provide solutions to allergy patients' medical, social, and economic problems and train staff who will provide services in the field of allergic diseases. AID has a partnership with the European Academy of Allergy and Clinical Immunology and the World Allergy Organization. Many International and national congresses, symposiums, and webinars have been organized in various cities of Turkey. The official journal of the society is Asthma Allergy Immunology (AAI). The community organizes specialized courses and webinars to update the members' immunology and PID knowledge (11) (www.aid.org.tr).

**Society of Clinical Immunology (KID)**

The Society of Clinical Immunology (KID) was established on March 24, 2014 by Dr. İlhan Tezcan, Dr. Aydan İkincioğulları, Dr. Necil Kütükçüler, Dr. Mustafa Yılmaz, Dr. İsmail Reisli, Dr. Caner Aytekin, and Dr. Çağman Tan (Ph.D.). Dr. Figen Doğu was a valuable team member during the establishment of KID. This society aimed to strengthen collaborative activities with international and national PID centers to advance physicians' and scientists' training in PID and raise awareness among pediatricians and the community about PID. Since then, the society has been organizing congresses and courses annually. They have a partnership with the J project, the coordinator of which is Dr. İsmail Reisli (www.klinikimmunolojidernegi.org.tr).

**Foundations and Laboratories working for IEIs**

**J Project**

The J Project was an important initiative in the early 2000s, and the aims were to increase awareness regarding IEIs among physicians, to facilitate diagnosis, including genetic tests, and to improve therapy and medical training. Recently, the project has extended to 32 countries, mostly in Eastern and Central Europe (ECE) and partly in Asia. More than 344 IEI-focused professional meetings were promoted and supported in the PID field for physicians, laboratory workers, and patient advocates between 2004 and 2021. Three J Project congresses were organized, in 2014, 2016, and 2019, in Antalya, Turkey, by İsmail Reisli, leader of the J Daughter Anatolia Project (12,13).

**Society of Immunodeficiency (IMYED)**

The IMYED is a Turkish patient organization and a member of the International Patient Organization of Primary Immunodeficiencies (IPOPI). It was founded by Selcan Kaya, Murat R Gülersen, Z. Elif Gülseren, Ertürk Kaya, Macide Kaya, Işıl B. Barlan, Yıldız Camcıoğlu, S. Özden Sanal, K. Aydan İkincioğulları, Günseli Bozdoğan on April 30, 2010 in İstanbul. İsmail Öğülür and Prof. Yıldız Camcıoğlu translated 10 leaflets of IPOPI into Turkish, intended for use by patients and their families. Booklets were distributed to all PID centers in Turkey. IMYED jointly organized educational meetings and conferences and celebrated "Immunology Day" at Cerrahpaşa Medical School with TSI or Marmara University School of Medicine.

**Jeffrey Modell Foundation (JMF)**

The JMF was founded in 2003 to implement the education of physicians and public awareness programs for IEIs. The Jeffrey Modell Centers Network (JMCN) currently consists of 909 expert physicians at 400 institutions from 316 cities and 86 countries spanning six continents. According to the JMF data, there was a 96.3% increase in patients with IEI followed in the US and an 86.1% increase globally from 2013 to 2021. Patients identified with a specific PI defect increased by 46.6% in the US and 47.9% globally (14).

Prof. Dr. Berat Işıl Barlan, a leading allergy and clinical immunology scientist, set up the first "Center of Immune Deficiency" at Marmara University in 2009 in Turkey in collaboration with the Jeffrey Modell Foundation. The next Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies was established at Ankara University, School of Medicine, with the cooperation of Prof. Aydan İkincioğulları and Prof. İlhan Tezcan from Hacettepe University, School of Medicine in 2012.

Can Sucak Candan Bi'şeyler Foundation was founded in 2018 by Ayhan and A. Gülsan Sucak to help patients with PID and to raise community awareness about IEIs.

**Can Sucak Translational Immunology Research Laboratory**

Hacettepe Can Sucak Translational Immunology Laboratory was established by Candan Bi'şeyler Foundation with the financial support of TANAP Dogalgaz Iletim A.S.

in Ankara to provide specialized laboratory studies and genetic analysis for patients with IEI. Dr. Baran Erman is the responsible person in the laboratory.

**Research Laboratory for Immunodeficiencies**

It was established by Prof. Mustafa Yavuz Köker at Erciyes University, School of Medicine, Department of Immunology, in 2016. Currently, HLA tissue typing, flow cytometric analysis, DHR 123 test, and anti-NADPH oxidase component antibodies are carried out in the diagnosis of chronic granulomatous disease (CGD) and its subgroups analysis.

**Journals**

**Turkish Journal of Immunology (TJI) (e-ISSN 2147-8325)**

Turkish Journal of Immunology (TJI) is the official and periodical journal of the Turkish Society of Immunology and it was begun to be published in 1996 by Dr. Birsen Yalçın Ülkü as editor-in-chief and Dr. Yıldız Camcıoğlu as co-editor. Currently, the chief editor is Prof. Günnur Deniz. TJI is an open-access journal complying with the definition of BOAI (Budapest Open Access Institute). It is published three times a year, in April, August, and December, and accepts original articles, case reports, short communications, and invited reviews. Its official language is English. It has been indexed in e-SCI, SCOPUS, TUBITAK/ULAKBIM, Türk Atıf Dizini (Turkish Citation Index) since September 2011, EBSCO and Gale.

**Asthma Allergy Immunology (AAI)**

AAI is the periodic, international journal of the Turkish National Society of Allergy and Clinical Immunology. The current editor-in-chief is Prof. İnsu Yılmaz. The publication language is English and has been published three times a year, in January, August, and December, since 2002. The journal aims to present advances in allergic diseases and clinical immunology and accepts original research, review, case reports, editorials, short reports, and letters about allergic diseases and clinical immunology. It is indexed in TUBITAK/ULAKBIM, EBSCO host Research Databases, Turkey Citation Index, Index Copernicus, CINAHL, SCOPUS, and ISI Web of Science - Emerging Sources Citation Index.

**Books**

In Turkey, immunology is rapidly developing and books have contributed to the development of basic immunology. The symposium abstract books from the National Immunology Congresses titled initially "*İmmünoloji*" and then "*İmmünolojide Gelişmeler*" have been published following each Immunology Congress since 1974. Prof. Ekrem Gülmezoğlu published the first Turkish book regarding basic immunology, titled "*İmmünolojinin Temelleri*" in 1975. Moreover, Prof. Kaya Kılıçturgay published "İmmünoloji" book in 1997. Prof. Dr. Asuman Müftfoğlu translated "Immunology", a book edited by J. Roitt, in 2007. Translating terms from one language to another poses challenges. Communication of basic concepts in any field is of the utmost importance. In immunology, efforts have been made to improve the understanding of comprehensive immunological principles and to facilitate communication among clinical scientists using Turkish terminology. In a concerted effort to increase the usage of the Turkish immunological language, a guidebook for immunological terms was published, including terms and definitions translated from English to Turkish by Y. Camcıoğlu, G. Erten, G. Deniz, and SS. Alkan (Bağışıklık Bilimi Terimler Kılavuzu, 2013). This was done to facilitate understanding, writing, and talking about the same Turkish terminology for learners. To support immunology education in Turkish, a group of distinguished TSI members translated 4 basic immunology books from English to Turkish for medical students, physicians, and microbiologists, including three Basic Immunology and one Functions and Disorders of the Immune System edited by Abbas AK, Lichtman AH, Pillai S. (2007, 2014, 2021) and Lippincott's Immunology (2014). Prof. Turgut İmir translated "Immunology" (D. Male, J. Brostoff, D.B. Roth, I. Roitt) in 2008. The first Turkish book about PID was published in 2013 by Y. Camcıoğlu (Bağışıklık Sistemi ve Yetersizlikleri). The second was published by Y. Camcıoğlu, G. Deniz, and S. Badur in 2020 (30 soruda Primer İmmün Yetersizlikler). Other volumes dedicated to PID were also published in the TJI and other clinical journals.

**Department of Immunology**

The first Department of Immunology in Turkey was established within İstanbul University, Aziz Sancar Institute of Experimental Medicine in 1989. Günnur Deniz, Ph.D., who received her immunology Ph.D. at Liverpool University, School of Medicine, Department of Immunology, United Kingdom, has been the head of the Department since 2002 and director of the Institute since 2016. The immunology department has many different units, such as Flow Cytometry Unite, Tissue Culture, Immunofluorescence Unite, ELISA Laboratory, and Cell Separation Laboratory. In these units, PID, allergy, transplantation, tuberculosis, neuroimmunology, and tumor immunology studies and projects have been successfully carried out in collaboration with other departments and faculties. "Applied Flow Cytometry Courses" have been organized every year since 1995. In addition, Immunology Master's and Doctorate programs are carried out in the Immunology Department. The number of immunology departments in medical schools continues to rise in Turkey.

**Clinical Immunology Divisions in Turkey**

Most IEIs are inherited in an autosomal recessive form; they are more common in areas with high rates of consanguineous marriages, like in Turkey (3,15). Prenatal genetic counseling is essential for parents at increased risk of having a child with IEI. Parents required definitive prenatal or pre-implantation genetic diagnosis. Since there were limited diagnostic options in Turkey, collaborative studies with various pediatric centers in Western countries have been initiated.

The first pediatric Immunology Division was established by Dr. İzzet Berkel in 1972. In the same year, Dr. Özdemir İlter and Dr. Günay Ezer founded Infectious Diseases and Immunology Division. Immunology Laboratory was founded in 1970 at the Department of Pediatrics at İstanbul University Cerrahpaşa Medical School. Since then, more than 20 immunology divisions have been established in different cities of Turkey. The first bone marrow transplantation (BMT) for the patient with severe combined immunodeficiency (SCID) was performed by Dr. İlhan Tezcan in 1994 at Hacettepe Children's Hospital. The second BMT unit was set at Ankara University, Department of Pediatrics, then the other transplantation units were organized in the community and private hospitals nationwide.

Initially, Clinical Immunology training was carried out for only 2 years, then increased to 3 years. Specialists in the divisions of immunology, pediatrics, and internal medicine provided training terms. Allergy training was also carried out by the division of allergy, the departments of pediatrics or internal medicine for just 3 years. The Republic of Turkey, Ministry of Health combined allergy and immunology training and approved the fellowship training program for just 3 years in 2011. TSI and a few immunologists were against this training program since the allergy program consisted of just allergic diseases and treatment. They were not trained enough in the fundamentals of immunology and PID until 2011. The separate allergist and immunologist certificates were switched to a certificate of "Allergy and Immunology" in the same year. An allergist became an immunologist without prior training in basic immunology and PID. A study done among pediatricians aimed to assess PID awareness and identify diagnostic criteria leading to correct diagnosis and it revealed that more comprehensive pre/postgraduate education in PID appeared necessary for physicians in Turkey in 2010 (16). Nowadays, the pediatric training program lasts for 5 years. Then the pediatric allergy and immunology program (a subspeciality) lasts for an additional 3 years. Fellow training involves gaining knowledge in basic and clinical allergy and immunology as well as the performance and interpretation of laboratory procedures in allergy and clinical immunology. Still, they may have limited knowledge of IEIs, especially for their immunological basis, due to shortened education programs.

The list of pediatric and adult clinical immunology centers is given in Table 1. Most pediatricians were trained mainly as immunologists before 2011. They are playing a pioneering role in diagnosing and treating patients with IEIs; they are also introducing the clinicians/researchers and investigating further for undetermined IEI patients in Turkey.

**Care of Patients with IEIs**

A healthcare-level system regulated by the Ministry of Health is available in Turkey. Pediatric allergists and immunologists provide patient care at the tertiary level.

Screening testing for suspected IEIs, including whole blood cell count, immunoglobulin G, A, M, E, immunoglobulin G subclasses, and lymphocyte phenotyping, are available in regional immunology laboratories. Advanced tests for IEIs such as detailed cell separation, cytokine levels, cytokine receptors, CFSE (5,6-carboxyfluorescein diacetate succinimidyl ester) T-cell proliferation assays are being done at İstanbul University, Aziz Sancar Institute of Experimental Medicine, Department of Immunology. Centers of allergy and clinical immunology in İstanbul are pleased to study in collaboration with the Institute for IEIs research.

Immunoglobulin G, 5 mL flacon injected intramuscularly was only applied in Immunoglobulin Replacement Treatment for patients with antibody deficiencies in Turkey until 1988, soon intravenous IgG (IVIG) treatment became the most used therapy for patients with antibody deficiencies (16). Subcutaneous immunoglobulin (SCIg) treatment was recommended for patients who experienced anaphylactic/anaphylactoid reactions to IVIG, had frequent infections despite IVIG, and increased the quality of the patient's life. Currently, many IEI patients prefer to receive SCIg therapy at home in Turkey (17-20).

As standard care, screening tests, IVIG and SCIg replacement treatment, antibacterial and antiviral prophylaxis, and immunomodulatory therapies during inflammatory or autoimmune complications are offered to patients with IEIs. HSCT is successfully done for patients with T-cell deficiencies; enzyme replacement therapy and current monoclonal therapies are delivered to patients in the IEIs centers (21,22). IVIG or SCIg replacement treatment and hematopoietic stem cell transplantation are provided for insured and non-insured patients under the age of 18 years in the national healthcare system. Genetic testing like Sanger sequencing, next-generation sequencing, whole exome/genome sequencing, or targeting gene panels have high diagnostic yield for IEIs and are being performed in the Department of Genetics in some university hospitals or a few private genetic laboratories. Department of Genetics at İstanbul University, Aziz Sancar Institute of Experimental Medicine, has identified some genetic mutations responsible for IEIs.

**Table1.** List of pediatric and adult clinical immunology divisions in Turkey

| Center | Clinical Immunology Division | Year/ Founder/ Facilities | Colleagues From Division | Interested topics (Selected from Pubmed) |
|---|---|---|---|---|
| Hacettepe University, School of Medicine, Department of Pediatrics<br><br>ANKARA | Division of Immunology | 1972<br>Prof. İzzet Berkel<br><br>1972<br>Immunology Laboratory<br><br>BMT Unit | Prof. Figen Ersoy<br>Prof. Özden Sanal<br>Prof. Leman Yel<br>Prof. İlhan Tezcan<br>Prof. Deniz Çağdaş Ayvaz | C1q deficiency, XLA, Ataxia-Telangiectasia, SCID, Griscelli, Artemis, ADA, Cernunnos, MHC class I /II, PNP, ITK, AID, CORO1A, ISG15, STAT1, CARD9, RASGRP1, IgM, LAD III, PRKCδ, IL-12Rbeta-1, IL-21R, ADA2, VPS45, PD-1 deficiency, DOCK8, WAS, AIRE mutation, Malignancy & PID, CGD, Congenital Neutropenia, Hyper IgM, HSCT for IEI, PID registry, Newborn screening. |
| İstanbul University, Cerrrahpaşa, Cerrahpaşa Medical School, Department of Pediatrics<br><br>İSTANBUL | 1972<br>Division of Infectious Diseases and Clinical Immunology<br>1989<br>Division of Infectious Diseases, Clinical Immunology and Allergy<br>2011<br>Division of Clinical Immunology and Allergy | 1972<br>Prof. Özdemir İlter<br>Prof. Günay Ezer<br>1970<br>Immunology Laboratory<br>"Pediatric Immunology" Certification was apart from allergy until 2011 | Prof. Şükran Yalçındağ<br>Prof. Necla Akçakaya<br>Prof. Yıldız Camcıoğlu<br>Prof. Haluk Çokuğraş<br>Assoc. Prof. Ayça Kıykım<br>Assoc. Prof. Esra Özek Yücel | Immunity in bacterial and viral infections, antibody deficiencies, Ataxia-Telangiectasia, CGD & gene mutations, Di-George syndrome, adverse reaction to IVIG, Transient hypogammaglobulinemia, Frequent infections & PID, XLA, SCID, IgA, ADA, CD3e, STAT3, DOCK8, IFNgR1, MyD88, STAT1, IL12Rβ1, IL17RA, IL17RC, CARMIL2, LBBA, CTLA-4, CD55, Notch1, TRAF3IP2, Biotidinase deficiencies, Hyper IgE syndrome, IPEX syndrome. |
| İstanbul University İstanbul Medical School, Department of Pediatrics<br><br>İSTANBUL | Division of Infectious Diseases and Clinical Immunology<br>1984<br>Division of Infectious Diseases, Clinical Immunology and Allergy | 1969<br>Prof. Süleyman Yakacıklı,<br>Prof. Ülker Öneş<br><br>1968<br>Immunology Laboratory | Prof. Işık Yalçın<br>Prof. Nuran Salman<br>1998<br>Division of Infectious Diseases and Immunology<br>Prof. Işık Yalçın<br>Nuran Salman<br>Prof. Ayper Somer<br>Prof. Selda Hançerli Torun<br><br>2011<br>Division of Clinical Immunology and Allergy<br>Prof. Nermin Güler<br>Prof. Zeynep Tamay | IG3 in wheezy children, CVID, Transient hypogammaglobulinemia IgA deficiencies, Iron deficiencies & immune system, Ataxia-Telangiectasia, SCID, AID deficiency & Salmonella infection, CGD, recognizing Immunodeficiency in children, IFN-γR1 and IL-12Rβ1, SMARCD2, CTLA-4, LRBA, TYK2 deficiencies, Netherton syndrome, HIES, COVID-19 & IEIs. |
| Çukurova University, School of Medicine, Department of Pediatrics<br><br>ADANA | Division of Clinical Immunology and Allergy | 1977<br>Seval Güneser<br><br>Immunology Laboratory | Prof. Derya Ufuk Altıntaş<br>Prof. Mustafa Yılmaz<br>Prof. Gülbin Bingöl<br>Assoc. Prof. Dilek Özcan<br>Assoc. Prof. Mahir Serbes | Autoinflammatory Diseases, FMF, CGD, LRBA, CTLA-4, IL-12Rβ1, LAD, IPEX, ADA2 deficiency, Griscelli Syndrome, TREX1 deficiency. |
| Akdeniz University, School of Medicine, Department of Pediatrics<br><br>ANTALYA | Division of Clinical Immunology and Allergy | 1982<br>Prof. Olcay Yeğin<br>Immunology Laboratory<br><br>BMT Unit | Prof. Ayşen Bingöl<br>Assoc. Prof. Dilara F. Kocacık Uygun | IgG subclass deficiencies, Transient Hypogammaglobulinemia, SCID, CGD, HLA I/II Studies, SCID, CTLA4, TLR4, CD40, IL-10, FCHO1 deficiencies, Hyper IgE IL-1alfa/IL- beta polymorphism, COVID&IEIs IFN&TB, Chaple disease, HSCT&IEIs. |

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|---|---|---|---|---|
| Marmara University, School of Medicine, Department of Pediatrics<br><br>İSTANBUL | Division of Clinical Immunology and Allergy | 1987<br>Prof. Müjdat Başaran<br><br>Immunology Laboratory | Prof. Berat Işıl Barlan<br>Prof. Dr. Nerin Nadir Bahçeciler<br>Prof. Dr. Cevdet Özdemir<br>Prof. Ahmet Özen<br>Prof. Elif Karakoç Aydıner<br>Prof. Safa Barış<br>Asist. Prof. Sevgi Bilgiç Eltan | IgG subclass deficiencies, SCID,<br>Hyper IgE syndrome, MALT1, DOCK8, LRBA, CTLA-4, STAT3, STAT6, IFNγR1, POLD1/POLD2, NFATC1, LRBA, CTLA-4, CD55, SMARCD2, PRKCδ, PIK3R1, CD27, CD70, CARMIL2, CD55, Notch1/CD22, FCHO1, TRAF3IP2, Biotidinase deficiency, Hyper IgE syndrome, iRHOM2, IPEX syndrome, congenital neutropenia, TREC/KREC, IVIG & SCIg treatment, COVID & IEIs, Chaple disease, immune dysregulation diseases. |
| Ege University, School of Medicine, Department of Pediatrics<br><br>İZMİR | Division of Clinical Immunology and Rheumatology | 1991<br>Prof. Necil Kütükçüler<br><br>Immunology Laboratory | Prof. Güzide Aksu<br>Prof. Neslihan Edeer Karaca | Igg Subglass deficiencies, Hyper IgM, CVID, Di-George, Ataxia-Telangiectasia, SCID, PTEN, PLAID, APLAID, MALTB1, FCSA3, LRBA, CTLA-4, IL12Rβ1, IPEX, Notch1, STAT1, DOCK-8, deficiency<br>*TNFRSF13B/TACI* alterations, WAS, CGD, IEIs registry. |
| Ankara University, School of Medicine, Department of Pediatrics<br><br>ANKARA | Division of Clinical Immunology and Allergy | 1993<br>Prof. Emel Babacan<br><br>Immunology Laboratory<br><br>BMT Unit | Prof. Aydan İkincioğulları<br>Prof. Figen Doğu<br>Prof. Şule Haskoloğlu | Antibody deficiencies, SCID, MHC I/II, Artemis deficiencies, BCG infections, Tuberculosis, XLA, WAS, Hyper IgM, Hyper IgE, LAD syndrome, IgA, PNP, DOCK-8, DOCK-2, IL-21, PD-1, MAGT1, PRKCδ, IL-17RA, IL-17RC, LRBA, CD40, ITK, CD70, G6PC3, LRBA, deficiency, CGD, blood lymphocyte subsets,<br>Thymopoiesis, HSCT & IEIs, initial presenting manifestations of IEIs,<br>Newborn screening for IEIs. |
| Bursa Uludağ University School of Medicine, Department of Pediatrics<br><br>BURSA | Division of Clinical Immunology and Rheumatology | 2000<br>Prof. S. Şebnem Kılıç<br><br>Immunology Laboratory | Dr. Yasin Karali | Antibody deficiencies, CVID/TACI mutations, Di-George syndrome, SCID, DOCK8 deficiency, LRBA, CTLA4, STAT1, STAT3, TYK2, DADA2 deficiency, Ataxia-Telangiectasia, APECED, Muckle-Wells syndrome, Dyskeratosis congenita, Schimke,<br>IFNG & TB, IVIG & COVID, Malignancy & IEI, IEI Registry, Monoclonal antibody treatment. |
| Ankara Hematology Oncology Children's Training and Research Hospital<br><br>ANKARA | Pediatric Allergy and Immunology Department | 2000<br>Prof. Ayşe Metin<br>Assoc. Prof. Betül Karaatmaca | | Antibody deficiencies, IgA deficiency, SCID, LRBA, CTLA-4, TYK2, CD27, CD70, LAD, ILC3, IL-21, DOCK-8, ZNF341, IL-12Rb, deficiency, IFN gamma, Type1 IFN deficiency, WAS, CGD, COVID & IEIs. |
| Necmettin Erbakan University School of Medicine, Department of Pediatrics<br><br>KONYA | Division of Clinical Immunology and Allergy | 2001<br>Prof. İsmail Reisli<br>2004 Immunology Laboratory | Prof. Sevgi Keleş<br>Prof. Şükrü Nail Güner | Antibody deficiencies, IgG subclass, B19 deficiency, CVID, SCID, DOCK-8, STAT3, STK4, FCHO1, STAT3, ZNF34, TYK, IL12Rβ1 deficiency,<br>ICF syndrome, Type I IFN immunity & COVID-19. |
| Dr. Behçet Uz Children's Training and Research Hospital<br><br>İZMİR | Pediatric Allergy and Immunology Department | 2003<br>Prof. Ferah Genel<br>2005 Immunology Laboratory | Prof. Nesrin Gülez | Antibody deficiencies, CVID, IVIG therapy, SCID, Griscelli, DiGeorge syndrome, IFN gamma R1 deficiency, DOCK8, LRBA, CTLA-4, TYK2, CD137, LAD, SLC8A13, PIK3CD, CORO1A, deficiencies, BCG-osis, Complement and, Properdin deficiency,<br>IEIs registry. |
| 19 May University, School of Medicine, Department of Pediatrics<br><br>SAMSUN | Division of Clinical Immunology<br>2011<br>Division of Clinical Immunology and Allergy | 2008<br>Prof. Alişan Yıldıran<br><br>Immunology Laboratory | | Antibody deficiencies, CVID, Hyper IgM syndromes, DNMT3B mutation, SCID, DOCK-8 deficiency, CGD, Hypereosinophilic syndrome,<br>MSMD, LRBA, CTLA-4, TLR3, PRKCδ, CARMIL2, deficiency, BCG vaccination, Newborn Screening. |

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| Selçuk University School of Medicine, Department of Pediatrics<br><br>KONYA | Division of Clinical Immunology and Allergy | 2013<br>Prof. Hasibe Artaç<br>Assoc. Prof. İlknur Külhaş Çelik<br><br>Immunology Laboratory | | Antibody deficiencies, BTK mutation, B19 deficiency, Transient hypogammaglobulinemia, CVID, SCID, Guidelines for IEIs, Genomic approaches to mendelian Disorders, Monogenic immune dysregulations diseases, DOCK-8 deficiency, NEMO deficiency, FCHO1 deficiency. |
| Zonguldak Bülent Ecevit University, School of Medicine, Department of Pediatrics<br><br>ZONGULDAK | Pediatric Clinical Immunology and Allergy | 2012 Prof.<br>Mutlu Yüksek | | CVID, SCID&HLA-haploidentical transplantations, Hyper IgE syndrome, PNP,<br>IL-12Rb deficiency, Treg,<br>PID awareness. |
| Sakarya University School of Medicine, Department of Pediatrics<br><br>SAKARYA | Pediatric Clinical Immunology and Allergy | 2013<br>Prof.<br>Öner Özdemir<br>Prof. Mehmet Halil Çeliksoy<br>Assoc. Prof. Pınar Gökmirza Özdemir | | COVID-19 & immune plasma therapy, COVID-19 & BCG, mast cells in SARS-CoV-2 infection, COVID-vaccination & side effects, primary immunodeficiency in Newborn, reference data of immunoglobulin values for Turkish newborns, CVID, WAS, ADA deficiency, flow cytometric cell-mediated cytotoxicity assay. |
| İstanbul Kanuni Sultan Süleyman Training and Research Hospital, Department of Pediatrics<br><br>İSTANBUL | Division of Clinical Immunology and Allergy | 2007<br>Assoc. Prof.<br>Çiğdem Aydoğmuş<br>Prof. Mehmet Halil Çeliksoy<br>Assoc. Prof. Pınar Gökmirza Özdemir | | Genetic mutations in XLA/SCID, Transient hypogammaglobulinemia<br>IFN gamma R1 deficiency, IL12Rβ1 deficiency, CD247 deficiency, Cernunnos/XLF, HAX-1, LRBA, CTLA-4, ITK, MALT1 deficiency, JAGN1 mutation, immediate adverse reaction to IVIG. |
| Dr. Sami Ulus Maternity and Children's Research and Training Hospital<br><br>ANKARA | Division of Clinical Immunology and Allergy | Assoc. Prof.<br>Caner Aytekin | | Antibody deficiencies,<br>IgA deficiency, SCID, LRBA, IRAK-4, IL-17RC, IL-12/IL-23, DOCK8, ICF, SPPL2b, TTC7A, IL-12 beta1, GGPC3, PD1, CORO1A mutation, Kostman,<br>IEIs & TB, MIS-C & IEI. |
| Ege University, School of Medicine, Department of Internal Medicine<br><br>İZMİR | Division of Clinical Immunology and Allergy | 1988<br>Prof. Tomris Kabakçı<br><br>1975<br>Immunology Laboratory | Prof. Aytül Sin<br>Prof. Ali Kokuludağ<br><br>Prof. Ömür Ardeniz<br>Assoc. Prof. Ceyda Tunakan Dalgıç | Granulomatous disease & Adult CVID, HSCT &CVID, Gastrointestinal findings & CVID, Clinical and immunological analysis & CVID, Chest computed graphs & CVID, β2-Microglobulin deficiency causes a complex immunodeficiency, CTLA-4 deficiency, Giardiasis & CVID, Artritis & CVID, D vitamin deficiency & CVID, COVID& PID, IVIG treatment. |
| 2000-2015<br>Gülhane Military Medical Academy, School of Medicine, Internal Medicine<br>2017-Başkent University, School of Medicine Internal Medicine<br><br>ANKARA | Division of Clinical Immunology and Allergy | 2000<br>Prof. Uğur Musabak<br><br>Immunology Laboratory | | Adult patients with CVID, CREBP Gene Mutation & CVID, effects of immunoglobulin replacement treatment (IRT), the killer-cell immunoglobulin-like receptor (KIR) genes& (HLA)-C alleles & CVID COVID & Immunological researches, arthritis & thymectomy patient,<br>cytokines& chronic inflammatory diseases (MS, FMF), CXCR-1/CXCR-2 & RA & Behcet's disease. |
| Necmettin Erbakan University Meram Medical School, Internal medicine<br><br>KONYA | Division of Clinical Immunology and Allergy | 2005-2019<br>Prof. Zafer Çalışkaner (Retired)<br>Prof. Şevket Arslan<br>Prof. Fatih Çölkesen | | Adult patients with CVID<br>Adult hypogammaglobulinemia and B-cell aplasia, Tuberculosis & IL-23-dependent IFN-γ immunity, DCLRE1C & SCID, J project. |

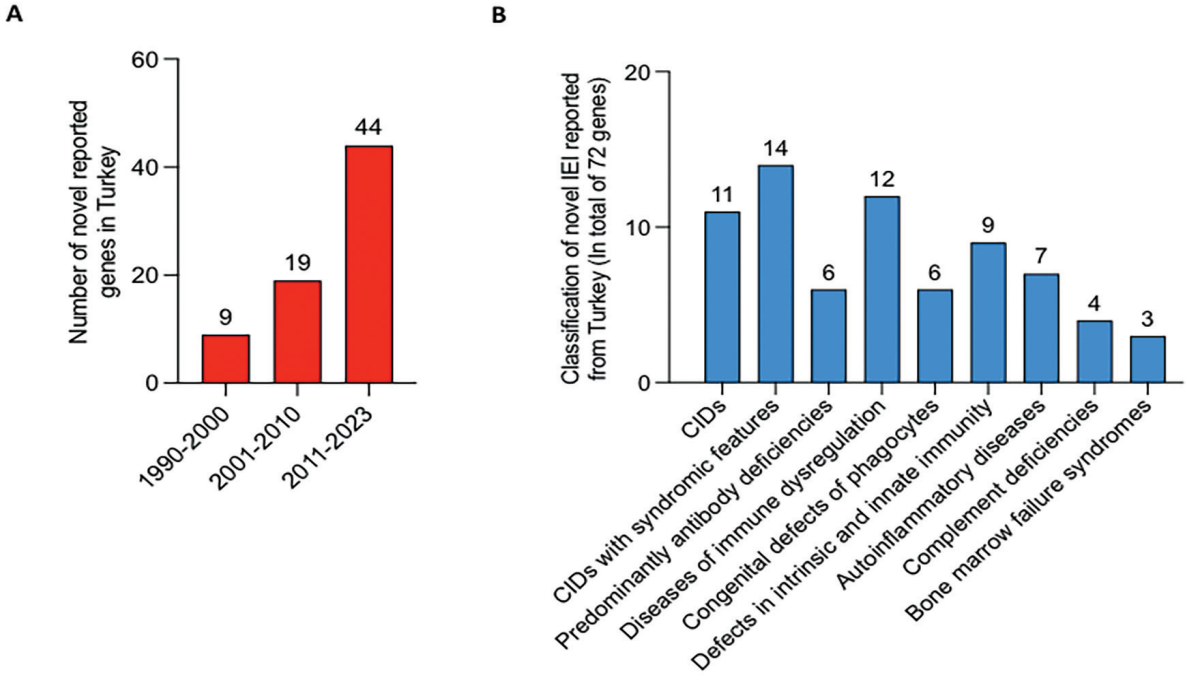


**Figure 1.** (A) Novel reported IEIs genes in Turkey. (B) Classification of novel IEIs reported from Turkey (prepared by Prof. Dr. Safa Barış).

Collaborative studies with European countries, the USA, and international and national genetic departments, contributed to discovering novel genes responsible for rare diseases among Turkish patients. Many pediatric IEI centers from Turkey contributed to the identification of novel genes for Mendelian Susceptibility to Mycobacterial Diseases, Hyper IgE syndrome, Hyper IgM syndrome, XLA, IPEX syndrome, Di-George syndrome, and defining deficiencies of ADA, PNP, Cernunnos, AID, CD19, LADIII, PD-1, DOCK-8, STAT-1, IL17-RA, IL-17RC, ITK, CORO1A, ISG15, STAT1, CARD9, RASGRP1, CARMIL2, LRBA, STAT6, POLD1/POLD2, NFATC1, CTLA-4, PKCδ, CD55 (Chaple disease), Notch1, TRAF3IP2, Biotidinase, new mutations for CGD, TACI, AIRE (23). The number of novel reported genes is increasing every other year in Turkey, and the classification of 72 novel IEIs reported from Turkey is shown in Figures 1A and B, respectively (prepared by Dr. Safa Barış).

A pilot project for newborn screening is continuing in Ankara, hoping to be published in due time. Currently, 34 centers deliver care for allergic and immunologic diseases in children. Twenty-four centers provide care for allergic and immunologic diseases of adults. Nowadays, approximately 250 pediatric, 150 adult allergists/immunologists, and 120 trainees are at the Divisions of Allergy and Clinical Immunology in Turkey.

**Laboratories of Immunology**

The first Immunology laboratory was established by Süleyman Yakacıklı and Ülker Öneş in 1968 at İstanbul University, School of Medicine, Pediatric Infectious Disease and Immunology Division. The immunology laboratory at Hacettepe University, Department of Pediatrics, was established in 1972 by Prof. Ahmet İzzet Berkel. Two Immunology laboratories were established in 1970 at İstanbul University Cerrahpaşa Medical School, one of them by Prof. Dr. Asuman Müftüoğlu and Prof. Dr. Birsen Ülkü at Internal Medicine, Hematology Division, and the second one by Prof. Dr. Özdemir İlter and Prof. Dr. Günay Ezer at Department of Pediatrics, Infectious Diseases, and Immunology Division.

Prof. Dr. Necla Akçakaya was a fellow in pediatrics at Cerrahpaşa Medical School; she was studying in the immunology laboratory to investigate Australian antigens in patients with viral hepatitis and serum immunoglobulin G, A, and M levels of healthy children. She was taking care of PID patients at the outpatient polyclinic. In those days, basic studies in Cerrahpaşa pediatric immunology laboratory were immunoelectrophoresis to define plasma proteins, Manchini's single radial immunodiffusion method to determine immunoglobulin G, A, and M levels, bactericidal test, CRP levels, ASO, serum opsonic activity and phagocytic activity of neutrophils, HLA typing. Prof. G. Ezer and Prof. B. Ülkü developed methods to perform E-rosette, EAC rosette, and active E-rosette tests at the laboratory in 1975 (24). Peripheral blood lymphocytes were separated by a Ficoll method and suspended in saline; after staining with fluorescence, immunofluorescence microscopy was used to count T and B-cells; 77-1% E rosettes (T lymphocytes) and 20-1%

EAC rosettes (B lymphocytes) were accepted as normal for healthy children/adult. Low or high levels are provided to identify immunodeficiencies and hematological diseases. Screening for complement diseases, total hemolytic activity (CH50) test, was used, and measurement of serum C1q, C2, and C3 levels were included. Purified protein derivative (PPD), Candidine, Tricophytone, and DNCB (Dinitrochlorobenzen) skin tests were applied to investigate T-cell function. Lymphocyte proliferation assay was performed since 1980 by H3 Thymidine uptake, until flow-based studies in Hacettepe Children's hospital and Cerrahpasa Medical School.

I started working at the department of pediatrics in 1974, was involved in immunology, and began to practice in an immunology laboratory in 1975 during my pediatric residency program. My mentor was Prof. G. Ezer, and my thesis for pediatrics certification was "The relationship of the skin delayed hypersensitivity reaction to the T lymphocyte subgroup in Tuberculosis". I continued to work at the division of infectious diseases and immunology after being certified in pediatrics. Immunofluorescence microscopy was used until 1996 to enumerate T and B-cells, and nephelometry was applied to measure serum Immunoglobulin G, A, M, and E levels in 1990 at Cerrahpaşa Medical School pediatric immunology laboratory. The flow cytometry machine was the size of a whole wall when I first saw it in the DeBakey Centre, Texas Children's Hospital. Since then, techniques have improved very fast; flow cytometry got smaller, allowing us to perform plenty of research. We had the chance to work with flow cytometry in Cerrahpaşa immunology lab in 1996; it allowed us to define T, B, and NK cells subpopulations to determine proliferative response to antigen or mitogens of T-cells, oxidative burst tests for neutrophil function. Later, the Ministry of Health increased the clinical immunology training program to 3 years.

**Turkish National Registry for Primary Immunodeficiency**

Clinical features of 1435 patients with PID disorders are registered in ESID Online Patient Registry by the Pediatric Immunology Departments of the Medical Faculties of Uludağ University and Ege University between 2004 and 2010 (25,26). These two centers are the significant contributors reporting PID patients to the ESID database from Turkey. The TSI-PID subgroup had attempted to organize the Turkish IEIs registry but failed due to legal restrictions, diagnostic difficulties, and conflicts among PID centers. The PID registry is available now in Turkey by KID.

**Immunology and Primary Immunodeficiencies in Faculty Curriculum**

The immune system is prominent in human health, covering an expansive network of tissues, cells, cytokines, and signaling processes. Consequently, failed immune systems underline many infectious, autoimmune, autoinflammatory diseases, malignancies, and immunodeficiencies. The context of clinical observations and laboratory findings requires the integration of basic immunology knowledge.

In the 2000-2001 academic year, immunology lessons were introduced as a half-term semester course in the curriculum of the İstanbul University, School of Medicine, and İstanbul University Cerrahpaşa Medical School in the second year of medical education. A wide range of topics, including innate and adaptive immunity, infectious diseases, vaccination, inflammation, allergy, tumor immunology, transplantation, autoimmunity, and PID, have been integrated with the fields of infectious diseases, pathology, pediatrics, hematology, oncology, neurology, and clinical laboratory testing. Immunology and PID lessons are integrated into the curriculum of those in other schools of medicine, not as a half-term semester program.

**Training in Clinical Immunology in Turkey**

Since 1952, there has been a fascinating increase in our knowledge of the clinical, immunological, and genetic features of IEIs disorders. The number of IEI disorders now exceeds 485. Continuing education is considered for physicians and nurses in health care settings and hospitals to increase awareness and decrease complications and mortality rates of IEIs. Allergy and Clinical immunology competencies were defined by a curricula in 2014 with the efforts of TUKMOS (Ministry of Health, Expert Board in Medicine, Medical Specialization Education Registration) in Turkey, including gain in clinical skills, such as gathering clues through history and physical examination of the patient, interpretation of laboratory results used in the investigation, using medical devices and doing procedures safely, the ability to evaluate and manage patients with suspected or confirmed diagnosis of the patients with allergy, PID, autoimmune disease, and auto-inflammatory disease in just 3 years. In addition, they have to be integrated with other subspecialties, such as rheumatology, infectious diseases, respiratory medicine, dermatology, hematology, and transplant services. Nowadays, the clinical immunology fellowship program is not separate; it has been combined with allergy, and only 3 years are required to receive a certificate for allergy and clinical immunology, without any research obligation and conducting a thesis related to the field, which is, in my opinion, not enough to learn basic immunology integrated with an inborn error of immunity.

Master of Science and Ph. D. programs on Immunology were initiated in 1983 in Hacettepe Pediatric Immunology Division, Hacettepe Institute of Pediatrics, followed by Aziz Sancar Institute of Experimental Medicine and other universities.

## Conclusion

The joint efforts of TSI, AID, and KİD have continued to raise awareness about clinical immunology, PID, and allergies in Turkey to facilitate the diagnosis and treatment of IEIs disorders early in life and definitive diagnosis and treatment of allergic diseases. Although training programs or certificated courses have been implemented at international, national, and regional levels, publishing journals and books, and despite the collaborative organizations of societies, IEI are still not well-known in medicine and by physicians nationwide. The incidence and prevalence data are limited for IEIs in Turkey.

The improvements in genetic technologies have provided definitive diagnosis and prenatal screening and promoted the development of new drugs for treating and caring for patients with IEI. The symbiosis of the three societies provided an excellent platform for well-trained, talented young scientists and assisted in the intensive exchange of ideas.

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