Clinical Immunology 284 (2026) 110686



Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim



Commentary



# The MENAT Region Inborn Errors of Immunity Research Consortium Registry (MENAT-IEI-RCR): Establishing a regional framework for collaborative research

Mohamed-Ridha Barbouche [a,b,*], Waleed Al-Herz [c], Mohammed Yousuf Karim [d], Bernice Lo [e], Ahmet Ozen [f], Nima Rezaei [g], Mohamed H. Sayegh [h,**], for the MENAT Region Inborn Errors of Immunity Research Consortium Registry (MENAT-IEI-RCR)[1]

[a] Department of Microbiology, Immunology and Infectious Diseases, Arabian Gulf University, Manama, Bahrain
[b] Department of Immunology, Institut Pasteur de Tunis, Tunisia
[c] Department of Pediatrics, Kuwait University, Kuwait
[d] Department of Pathology, Sidra Medicine, Doha, Qatar
[e] Research Department, Sidra Medicine, Doha, Qatar
[f] Department of Pediatrics, Marmara University, Istanbul, Turkey
[g] Department of Immunology, Tehran University of Medical Sciences, Iran
[h] Department of Internal Medicine, American University of Beirut, Lebanon

The study of inborn errors of immunity (IEI), formerly known as Primary Immuno-Deficiencies (PID), is highly relevant because it provides crucial insights into the functioning of the human immune system, leads to the development of targeted therapies, and helps understand the pathogenesis of more common diseases such as autoimmunity, allergy, and malignancy. Consanguineous marriages in the Middle East, North Africa, and Turkey (MENAT region) are a deeply rooted tradition and are highly prevalent, resulting in an increased incidence of autosomal recessive (AR) genetic diseases, including IEI. The consanguinity prevalence in the MENAT region countries ranges from 20% to 60%, while it is estimated to be between 1% and 10% only in other parts of the world and as low as <0.2% in the Americas and Western Europe. Consistently, the IEI patients from the MENAT region show a high rate of parental consanguinity that reaches 61.9% accounting for the high frequency of family history including early deaths, similar clinical features, and/or previously identified IEIsin relatives. Furthermore, consanguineous marriages have also been found to affect the types of genetic defects causing these diseases. For example, recombinase-activating gene 1 or 2 deficiencies, which are transmitted in an AR pattern, are the most common causes of severe combined immunodeficiencies (SCIDs) in the MENAT region, whereas defects in the interleukin-2 common γ chain, which are X-Linked (XL), are the most common cause in other geographic areas and ethnicities. Similarly, AR forms of chronic granulomatous disease are the most common forms in the MENAT countries, while the XL form of the disease represents approximately two-thirds of chronic granulomatous disease patients in Western countries (1).

The study of highly consanguineous families from the MENAT region has aided in unraveling the molecular basis of many IEI conditions, as well as in the discovery of new genes and pathways involved in immune responses. Indeed, the efforts of the MENAT region scientific community, conducted through international collaboration and in situ capacity building, have led to the discovery of more than 150 novel genes involved in IEIs (2). Nevertheless, full access of patients in the region to next-generation genetic screening and targeted therapies is still limited.

The implementation of patient registries is a major step toward improving diagnosis, clinical trials, and research efforts in the region. Indeed, strong collaboration initiatives have been developed by leading scientists from the region to publish cohort studies and registries with documentation of >17,000 patients from 22 countries in this region (3). Regional and national societies such as the Arab Society for Primary Immuno-Deficiencies (ARAPID), the Iranian Primary Immuno-Deficiencies Network, and the Turkish Clinical Immunology Society have made remarkable contributions to this effort. However, so far, no state-of-the-art, fully digitized registry for the region is available. The

* Corresponding author at: Department of Microbiology, Immunology and Infectious Diseases, Arabian Gulf University, Manama, Bahrain.
** Corresponding author.
*E-mail address:* MedRidha.Barbouche@pasteur.tn (M.-R. Barbouche).
[1] The members of MENAT Region Inborn Errors of Immunity Research Consortium Registry are listed in Appendix 1 at the end of the article.

https://doi.org/10.1016/j.clim.2026.110686
Received 26 January 2026; Received in revised form 18 February 2026; Accepted 19 February 2026
Available online 20 February 2026
1521-6616/© 2026 Published by Elsevier Inc.

current MENAT-IEI Research Consortium Registry (MENAT-IEI-RCR) aims to fill this gap with the active contribution of all institutions in the region that are involved in the diagnosis, care, and investigation of IEI. The MENAT-IEI-RCR is an open registry and any center from the region involved in investigation and care of IEI is encouraged to join. The Consortium is committed to social responsibility and equity. A suitable interface with the existing national registries which minimizes the need for data double entry will be developed. Indeed, there are precedents of national and regional registries working alongside each other efficiently e.g. the ESID Registry and the French national Registry CEREDIH.

The rarity and phenotypic heterogeneity of IEI limit the statistical power and reproducibility of single-center studies. While individual research efforts are invaluable for hypothesis generation, they are constrained by small cohorts, variable methodologies, and limited follow-up. Regional and multinational registries address these limitations by enabling harmonized data collection, longitudinal monitoring, and multicenter collaboration. These are cornerstones of real-world evidence generation and clinical translation.

The European Society for Immunodeficiencies Registry (ESID-R), founded in 1994, is the largest international IEI registry, encompassing >30,000 patients from 33 countries and 194 centers, representing >800,000 patient-years of follow-up (4). With >80 peer-reviewed publications, ESID-R has provided real-world data on epidemiology, genotype–phenotype relationships, treatment outcomes, and survival trends. By harmonizing diagnostic systems across Europe, it has shaped guidelines for early diagnosis, hematopoietic stem cell transplantation, and gene therapy.

The United States Immunodeficiency Network (USIDNET), established in 2003 under the Immune Deficiency Foundation and supported by the National Institutes of Health (NIH), unifies data across >7000 patients representing >30 immune defects and > 2000 gene mutations (5). It has yielded more than 70 publications and informed the implementation of nationwide newborn screening for SCID, as well as longitudinal analyses of chronic granulomatous disease, common variable immune deficiency, and other antibody defects.

Other continental registries further expand global coverage, including LASID in Latin America and AusPIPS in Australia–New Zealand.

In 2022 the MENAT-IEI Network Initiative was started with the goal of bringing investigators interested in genetically mediated immune diseases to start discussing potential collaborations in the region and with participation of scientific experts from the intramural program of the National Institute of Allergy and Infectious Diseases (NIAID) at the U.S. National Institutes of Health (NIH). Several virtual and physical meetings were held, and the major theme was always the necessity of establishing a research consortium registry that allows centers across the region to share their experiences and develop strategies for research like the European and US registries. Indeed, we did seek the help of those registries and developed a working group that culminated in the formation of this consortium. The Registry will be hosted at Sidra Medicine in Doha, Qatar, with participation of centers across the MENAT region.

Recognizing the need for a robust, region-wide registry, a steering committee was formed, comprising representatives from all interested centers. This committee oversaw the creation of five specialized subcommittees: Policies & Procedures, Logistics & IT/Technical, Finance & Fundraising, Partnerships & Relationships, and Scientific Strategy & Oversight. An elected Governance and Sustainability body will be created as soon as the implementation phase is completed. As a timeline, once the research collaboration agreements between the host institution, namely Sidra Medicine, and the contributing member institutions in the MENAT region is achieved, we plan to perform training sessions for institutional coordinators. As soon as all initially identified and trained contributors are onboard, we will elect a governance and sustainability body which will be assisted by both, a scientific committee, and a quality assurance committee. We expect to complete these steps before the end of the current year. Access to the overall aggregated de-identified research data or limited datasets shall be determined by the Scientific Committee and the Governing Board. Member can submit research topics and data requests to the Scientific Committee for approval and will provide information as requested by the Scientific Committee to facilitate its review and approval decision. Accordingly, the Scientific Committee will make its recommendation for final decision by the Governing Board.

The Logistics & IT/Technical team conducted a feasibility analysis of registry platforms, ultimately recommending REDCap for its security, nonprofit accessibility, and compatibility with automated EMR integration. This choice was informed by Sidra Medicine's extensive experience with REDCap and its ability to support multi-site registry development.

A major milestone was the successful securing of technical infrastructure, expertise, and seed funding at Sidra Medicine. Sidra is committed to hosting the registry and providing REDCap as the technical platform, leveraging its IT team's expertise in automated EMR data extraction and registry management. The coordinated efforts of all subcommittees, combined with Sidra's commitment, provide the foundation for a sustainable, ethically governed registry that will elevate IEI research across the MENAT region and foster meaningful global partnerships.

The registry will be built to support secure privacy-preserving analytics and to integrate future artificial intelligence (AI) tools for early disease detection and genotype–phenotype integration. As capacity grows, this will allow centers to train models collaboratively without sharing raw data. Thus, advancing innovation while maintaining patient confidentiality.

To achieve the goals of the MENAT-IEI-RCR, several challenges and hurdles are expected. One of these challenges is physicians' motivation and health authorities' resistance to sharing data, as well as legal limitations. To encourage participation, member institutions should be informed about the importance of establishing such a regional registry, along with the benefits of patient-oriented research, opportunities for more publications, and contributions to clinical trials. Additionally, significant efforts will be made to develop inclusive data-gathering forms based on the defined inclusion criteria. The de-identified core demographic, clinical and biological data collected will include age at onset, current age, age at clinical diagnosis, confirmed laboratory diagnosis and involved gene if applicable/known, main disease manifestations (symptoms, phenotype, laboratory abnormalities, etc.), natural course of the disease including accompanying symptoms or sequelae (e.g., malignancies, various organ manifestations, disease activity and burden), alive/deceased status, major treatment events such as hematopoietic stem cell transplantation, gene therapy, immunoglobulin substitution therapy, immune modulating therapy or similar. Standardized diagnostic criteria (e.g. ESID diagnostic criteria) will be applied. This will be followed by further steps to maintain quality-controlled submissions. Indeed, quality control procedures that will ensure data accuracy and completeness by adapting standards from e.g. ESID registry, including validation checks and periodic audits, will be implemented.

We also expect some financial challenges, not only in establishing the registry but also in securing sustainable financial support. This can be overcome by informing different stakeholders—including, but not limited to, pharmaceutical companies, research institutions, charitable organizations, and patients' organizations —about the potential of such a registry for generating epidemiologic data and involvement in clinical trials, which will be reflected in patients' care and quality of life. Engaging patients and their caregivers in our registry activities by highlighting their clinical priorities and unmet needs will encourage physicians' participation and the development of research ideas, which will help ensure the success of the registry. Furthermore, collaboration with advocacy groups is also envisioned to enhance awareness, inform research priorities, and support navigation of genetic counseling and patient care.

It is, obviously, a considerable challenge to develop a collaboration agreement across multiple centers in the many nations that make up the MENAT region. The challenge is potentially more daunting compared to the USA, where institutions may reside in different states but are ultimately within the same country, or compared to Europe, where many countries belong to the European Union, and where the General Data Protection Regulation is widely applicable. In addressing the goal of establishing a fit-for-purpose agreement between the centers, we drew on the prior experience of investigators within the region, and the experience and practices of the ESID and USIDNET registries. It became clear that the most appropriate and easily applicable route was to develop a research collaboration agreement (RCA). This agreement would be established between the host institution, namely Sidra Medicine, and the member institutions in the MENAT region. The rationale for this decision was based on feedback from several institutions within the region that had already successfully implemented research collaboration agreements for other studies between centers in the region, and on the fact that the most recent iteration of the USIDNET registry was underpinned by a collaboration agreement between the Children's Hospital of Philadelphia, as host institution, and the member institutions across the USA. The proposed RCA provides the framework that defines the roles and responsibilities of the host and member institutions in the MENAT-IEI-RCR.

The host institution will function as the Data Coordinating Center (DCC) of the MENAT-IEI-RCR. Therefore, the design, implementation, and maintenance of this online registry will be supported by the host institution. The DCC is responsible for the secure and private electronic storage of the MENAT-IEI-RCR data, as well as its ongoing maintenance and quality control. The participating member institutions will provide the DCC with a limited de-identified data set as well as other data to be subsequently designated by the MENAT-IEI-RCR scientific committee. This will be subject to IRB approval at the host and member institutions. Data protection and access will be secured.

In summary, the MENAT-IEI-RCR represents a transformative step for immunology research in the region. Continued collaboration and innovation will be essential to realize its full potential and improve patient outcomes.

## CRediT authorship contribution statement

**Mohamed-Ridha Barbouche:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Waleed Al-Herz:** Writing – review & editing, Writing – original draft, Conceptualization. **Mohammed Yousuf Karim:** Writing – review & editing, Writing – original draft, Conceptualization. **Bernice Lo:** Writing – review & editing, Writing – original draft, Conceptualization. **Ahmet Ozen:** Writing – review & editing, Writing – original draft, Conceptualization. **Nima Rezaei:** Writing – review & editing, Writing – original draft, Conceptualization. **Mohamed H. Sayegh:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization.

## Acknowledgments

The authors would like to thank Nizar Mahlaoui from Necker-Enfants Malades University Hospital, Paris, France and Ramsay Fuleihan from Columbia University, New York, USA for sharing their experience with ESID and USIDnet registries, respectively as well as Helen Su and Raphaela Goldbach-Mansky from NIH/NIAID, Bethesda, USA for their support.

## Appendix 1

for the MENAT Region Inborn Errors of Immunity Research Consortium Registry

- Ahmed Abdellatief, Sidra Medicine, Doha, Qatar;
- Hassan Abolhassani, Karolinska Institute, Stockholm, Sweden and Tehran University, Tehran, Iran
- Tariq Abu Saqri, Sidra Medicine, Doha, Qatar
- Mohamed Abuzakouk, Cleveland Clinic, Abu Dhabi, United Arab Emirates
- Mehdi Adeli, The View Hospital, Doha, Qatar
- Fayhan Al Rogi, Ministry of National Guard Health Affairs, Kingdom of Saudi Arabia
- Bandar Al Saud, King Faisal Specialist Hospital and Research Center, Riyadh, Kingdom of Saudi Arabia
- Salem Al-Tamemi, Sultan Qaboos University Hospital, Muscat, Oman
- Raed Alzyoud, Queen Rania Children's Hospital, Jordanian Royal Medical Services, Amman, Jordan
- Ömür Ardeniz, Division of Immunology, Department of Internal Medicine, Ege University Medical Faculty, Izmir, Turkey
- Hasibe Artaç, Selcuk University, Konya, Turkey
- Deniz Çağdaş Ayvaz, Hacettepe University, Ankara, Turkey
- Shafqat Baig, Sidra Medicine, Doha, Qatar
- Safa Barış, Marmara University, Istanbul, Turkey
- Brahim Belaid, University of Ben Youcef Ben Khedda of Algiers, Faculty of Pharmacy and Medicine, Algiers, Algeria
- Imen Ben Mustapha, Institut Pasteur de Tunis, Tunis, Tunisia
- Aziz Bousfiha, University Hassan II, Casablanca, Morocco
- Ghassan Dbaibo, American University of Beirut, Beirut, Lebanon
- Ahmet Eken, Erciyes University, Kayseri, Turkey
- Jalila El Bakkouri, University Hassan II, Morocco
- Gehad ElGhazali, Sheikh Khalifa Medical City, Abu Dhabi, UAE
- Shuayb Elkhalifa, Cleveland Clinic, Abu Dhabi, United Arab Emirates
- Aisha El-Marsafy, Cairo University, Cairo, Egypt
- Saddiq Habiballah, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia
- Mehshad Hamza, Sidra Medicine, Doha, Qatar
- Anwar Haque, Sidra Medicine, Doha, Qatar
- Carla Nasr Irani, Saint Joseph University of Beirut, Beirut, Lebanon
- Betul Karaatmaca, Ankara City Hospital, Turkey
- Elif Aydıner Karakoç, Marmara University, Istanbul, Turkey
- Sevgi Keleş, Necmettin Erbakan University, Konya, Turkey
- Sara Sebnem Kilic, Uludağ University, Bursa, Turkey
- Ayça Kıykım, Cerrahpaşa University, Istanbul, Turkey
- Michel Massaad, American University of Beirut, Beirut, Lebanon
- Cybel Mehawej, Lebanese American University, Gilbert and Rose-Marie Chagoury School of Medicine, Beirut, Lebanon
- Uğur Muşabak, Başkent University, Ankara, Turkey
- Monia Ouederni, University of Tunis El Manar, Tunis, Tunisia
- Öner Özdemir, Sakarya University, Sakarya, Turkey
- Yazan Said, Sidra Medicine, Doha Qatar
- Ahmed Seri, Sidra Medicine, Doha, Qatar
- Hiba Shendi, Tawam Hospital, Al-Ain, United Arab Emirates
- Çağman Tan, Erciyes University Medical School, Kayseri, Turkey
- Azzeddine Tahiat, Rouiba Hospital and Algiers University of Health Sciences, Algiers, Algeria
- Esra Yucel, Cerrahpaşa University, Turkey
- Rima Wakim, American University of Beirut, Beirut, Lebanon.

## Data availability

No data was used for the research described in the article.

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