Primary immunodeficiency registries

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Purpose of review

Research in the field of rare diseases such as primary immunodeficiencies can be significantly improved with sufficient patient numbers. Patient registries can help provide the basis for this by collecting data over a longer period of time and by connecting centres nationally or even internationally. The present article reviews recent publications both on database systems themselves and the research performed using results from these databases. The review also includes older publications on national registries that are considered relevant for the topic.

Recent findings

Databases that have been set up during past years and decade(s) now include a wealth of data for research on different primary immunodeficiencies and can be queried for studies. Database curation, however, remains an issue in most cases. A lack of time, funding and manpower is the main hurdle to be overcome by curators and participating centres

Summary

Several national databases have already produced results. The international patient databases are also ready to launch studies on multiple topics, while mutation data are accessible worldwide through the Internet. The present review introduces database systems as well as results obtained on this basis.

Keywords

database, primary immunodeficiency, register, registry

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Abbreviations

CVID	common variable immunodeficiency
ESID	European Society for Immunodeficiencies
IVIG	intravenous immunoglobulin
LAGID	Latin American Group for Primary Immunodeficiency Diseases
PID	primary immunodeficiencies
XLA	X-linked agammaglobulinaemia

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Introduction

Research in the field of primary immunodeficiencies (PID) requires a method of data collection that spans a considerable period of time and eventually also input from transnational centres. The need for patient and research databases has clearly been recognized by researchers; however, funding and curation of such projects always remains difficult. A survey on the curation of gene-specific databases states that more than one-half of the included curators found it difficult to maintain their database, mostly because of difficulties of funding [1]. The main goal is always to improve healthcare for the patient by improving diagnosis, treatment, prognosis, and by gaining deeper insight in the mechanisms of PID.

Databases on PID occur as national networks or even on a transnational level. International organizations have started to run online registries, which are accessible for users worldwide.

European Society for Immunodeficiencies database

Online databases are the most up-to-date form of data storage, providing easy access for users worldwide.

The European Society for Immunodeficiencies (ESID) has initiated an online database for clinical and laboratory data that went online in 2004 [2••]. The project is supported by the European Commission and the pharmaceutical industry (www.pptaglobal.org). It is at the moment one of the most comprehensive physician-driven registries of its kind in Europe, with 64 documenting centres in 29 countries.

The ESID database is available for users in registered centres who have applied for a user name and password. According to the status of individual users, a user-role management system handles the amount of visible and editable modules. Data submission is done online by the physicians or by other qualified staff. One of the advantages of online databases in general, and the ESID database in particular, is the fact that there is no need for additional technical equipment or software. A standard Internet browser is sufficient to access the database. Data protection is guaranteed through a number of security measures such as SSL encryption and the physical location of the server within the secure server network of the Information Technology centre of the University Hospital of Freiburg, Germany.

As stated by Guzman *et al.* [2••], the ESID database aims at data storage, data entry, reporting and the integration of preexisting sources. The central component of the system is the Toolwerk Enterprise Integration and Development Platform Application (http://www.toolwerk.de). The Enterprise Integration and Development Platform Application is a multitier Java Enterprise Development Platform that provides XML programming interfaces to the different components of a J2EE system. The system is prepared to handle large amounts of data, which is of particular importance considering the aim of the database to enable long-term and follow-up documentation. As of September 2007, the database counts 5113 patient datasets (information taken from ESID website: www.esid.org). Whereas Guzman *et al.* [2••] give a detailed technical description of the system, Eades-Perner *et al.* [3••] describe the clinical content and lessons from this database. The structure is depicted as a collection of 206 individual databases, each featuring a common core dataset with information about diagnosis, therapy, quality of life and important laboratory data. In addition, there are comprehensive disease-specific data models available for the most prevalent 28 diseases, common variable immunodeficiency (CVID) being the one with the most entries so far (1154 entries), followed by isolated IgG subclass deficiency (380 entries), X-linked agammaglobulinaemia (XLA) (369 entries) and IgA deficiency (353 entries). The database also holds a tool for the deposition of genetic mutation data. This tool is connected to the IDbases at the Institute of Medical Technology in Tampere, Finland.

Exemplary queries on the data have been performed on the age and gender distribution within the database, kinds of immunoglobulin replacement therapy, quality of life, and diagnostic delay. The purpose of the database, however, is to perform multicentre studies on well defined cohorts.

Despite the good progress of the database, the authors feel that entering data into a registry still means extra work for physicians. A lack of time and manpower is therefore perceived as one of the major hurdles to take. Furthermore, obtaining ethics and data protection approval is often time-consuming for the centres. The authors call for a standardization of ethical procedures in Europe to make this step easier for documenting centres.

MUTbase and IDbases

Piirilä *et al.* [4••] report on the IDbases, which are publicly available (http://bioinf.uta.fi/IDbases). The underlying system MUTbase [5] is programmed in Perl programming language and is therefore suitable for the programming of interactive forms and for handling databases. The IDbases are currently 115 locus-specific and patient-related mutation databases. This implies that there is a separate entry for each patient with a unique patient identity number and an accession number, which make it possible to refer to the database entry in publications. The individual databases are named according to the affected gene, following the HUGO nomenclature. The mutations are described at genomic, RNA and amino acid level, and links to reference sequences are available for every entry.

The databases receive input through direct submissions either from scientists sending their data to the respective curator or by using an interactive submission form on the Internet. This form checks for possible errors, compares the mutation with standard reference sequences, calculates the protein level change and checks for the numbering and type of the nucleotide(s) affected. This works for point mutations, deletions and insertions. Furthermore, the literature databases PubMed and Medline are searched for publications and IDbase entries are directly linked to PubMed. The IDbases are also linked to the ESID database, ensuring that information on both sides is matched.

At publication, the 107 IDbases contained 2273 different mutations and 4808 mutations from unrelated families, comprising 5758 mutations in affected alleles. The patient numbers in the individual IDbases vary a lot. BTKbase is the largest and oldest database, with 974 public entries [6], whereas others only have few entries. Still it is the aim of the project to contribute to public awareness of these rare diseases by making a database available as soon as a new ID-related gene and mutation have been reported.

ImmunoDeficiency Resource knowledge base

The same curators maintain the ImmunoDeficiency Resource knowledge base for PID [7••], which so far stores fact files about clinical, biochemical, genetic, proteomic, structural and computational information on 158 diseases. The database has recently been reformatted and is structured into document-centred XML and SHTML files. These files are linked to the IDbases and IDdiagnostics [8], as well as to the Online Mendelian Inheritance in Man database [9], and other Internet resources such as HUGO nomenclature [10], Swiss-Prot [11], Gene-Card [12] and SOURCE [13]. There is also a bioinformatics section available, as well as an updated animal models page and interest groups. The authors emphasize the accuracy and completeness of the knowledge base and its user friendliness.

Italian Primary Immunodeficiency Network

The Italian Registry for PID is run by the Italian Primary Immunodeficiency Network within the Italian Association of Pediatric Hematology and Oncology. A recent study has been conducted by Quinti *et al.* [14••] on a large cohort of patients with CVID. The underlying data were retrieved from the database that has been collecting data on CVID since 1999. Twenty-six centres contributed their patient data. The data collection was done through a semi-structured questionnaire filled out and collected

by one responsible physician per participating centre. On a yearly basis the filed data were processed in a database and sent to the Interuniversity Computing Centre (CINECA), which was responsible for processing and analysing the data. This database collects detailed personal information about the patient and includes the pedigree, date of diagnosis, immunological data and clinical manifestations as well as information about the immunoglobulin replacement therapy and laboratory data.

The 224 patients included in the study revealed that prominent clinical features are infections of the respiratory tract, autoimmune diseases, gastrointestinal manifestations and tumours. This is in accordance with results from an older study by Cunningham-Rundles and Bodian in 1999 [15]. Quinti *et al.* [14••] report the average age at diagnosis as 26.6 years, which is lower than previous studies had stated, whereas the median diagnostic delay has been found to be higher (8.9 years) [16,17]. The authors observe that despite intravenous immunoglobulin (IVIG) treatment, the prevalence of chronic sinusitis and chronic lung disease increased from 36.6 to 54.0 and from 33.9 to 46.4 for almost all age groups. During follow-up, however, the number of acute pneumonias and otitis was reduced significantly from 49% of all 224 patients at diagnosis to 20.5% at follow-up and from 38.4 to 25.5, respectively. The authors presume that since IVIG cannot substitute the main secretory antibody at mucosal surfaces, IgA, chronic respiratory and gastrointestinal diseases may still continue to progress. On the other hand, acute infections decreased under IVIG. The authors support the explanation by Carsetti *et al.* [18] for the observation that some CVID patients do not suffer from recurrent respiratory tract infections, despite severe hypogammaglobulinaemia. Carsetti *et al.* [18] suggest that this might be due to the differentiation of a B-cell subset, the so-called IgM memory B cells, producing low but detectable levels of antipolysaccharide antibodies. This IgM line of defence is lacking in patients with chronic lung disease. These patients might benefit from more aggressive antibiotic prophylaxis.

In 2002, Plebani *et al.* [19] ran a landmark multicentre study on XLA on the basis of the Italian Primary Immunodeficiency Network registry. This retrospective clinical and immunological survey was questionnaire-based and was conducted in 73 male patients with XLA. Since 1994, 39 Italian centres had submitted data on their XLA patients for the purpose of this study. The information was stored, controlled and analysed by VENUS, an integrated system of software facilities running on an IBM mainframe at CINECA.

The Italian Association of Pediatric Hematology and Oncology cooperates with ESID and exports data on a yearly basis to the ESID online database. The Italian National Registry for PID has thus already contributed 445 patients.

National registry of US residents with X-linked agammaglobulinaemia

In the USA, Winkelstein *et al.* [20•] recently published information from the national registry of US residents with XLA, which was established in 1999 by sending information to all members of seven academic societies and to all relevant departments with residency training. Physicians who followed XLA patients were then sent a four-page questionnaire, evaluating demographic information, laboratory findings, clinical characteristics and the status of the patient. Between 1999 and 2004, 201 patients were entered, and in 2004 a follow-up form was requested on the 148 patients who were alive when entered for the time before 2004. Follow-up data were obtained for 80 of those patients (54%).

The estimated minimal birth rate of XLA in the USA from 1988 through 1997 averaged 1/379 000 total births per year. The authors assume that this figure is underestimated since not all physicians in the USA were contacted or replied and not all patients may have been diagnosed.

The main initial clinical presentation was increased susceptibility to infection (86%), including otitis media (69%), pneumonia (53%), sinusitis (37%) and others. Almost all patients had reduced IgG levels at diagnosis and most of them also had reduced IgA and IgM levels. Fifty percent of patients were diagnosed with agammaglobulinaemia/hypogammaglobulinaemia by age 2 years, although a specific diagnosis of XLA may have followed years later.

The US Immunodeficiency Network (USIDnet: www.usidnet.org) has recently set up a national online registry for PID, based on the ESID system [2••]. Results from this new registry are yet to be expected.

Spanish Registry for Primary Immunodeficiencies

The Spanish Registry for Primary Immunodeficiencies (REDIP) was organized in 1993 with the aim to ascertain the epidemiology in PID [21] and to use the registry as a coordination centre for information on PID. A two-page form was developed. It contained fields for diagnosis, basic demographic information, date of birth, age at diagnosis, family history and treatment. Matamoros *et al.* [21] state that, in addition to the epidemiological information a registry may deliver, it has also increased the level of awareness of PID among physicians in Spain. Between 1993 and 1995, 1069 cases were collected from 33 centres; the data, however, had already been compiled in the individual centres since 1980. IgA deficiency was the most frequent diagnosis (36.9%), followed by CVID (19.9%).

The next numbers were significantly lower: severe combined immunodeficiency (5.7%), XLA (4.6%) and IgG subclass deficiency (4.5%), and so on. Between 1993 and 2004, 2607 cases were collected from 82 centres.

The authors highlight that the incidence data from the Balearic Islands is especially interesting since the particular geographical characteristics and healthcare set-up with a single referral hospital implies that an almost complete number of PID cases in the region are reported and could thus reflect real figures of prevalence per million inhabitants.

The Spanish Registry for Primary Immunodeficiencies recently went online with a new and up-to-date system replacing the old registry. By now 601 patients were collected, and new patients and patients already registered were introduced in the online register. Reports from this new online database are still to be expected.

Latin American Group for Primary Immunodeficiency Diseases registry

In 1993, Argentina, Brazil, Chile and Colombia formed the Latin American Group for Primary Immunodeficiency Diseases (LAGID). The goal was to set up registries in more countries in order to gain epidemiological information about PID in Latin America. A first report was given in 1998 [22]. Today LAGID includes 14 countries and has so far gathered 3321 patients [23••]. Data collection is carried out using a two-page form with information about the treating physicians, demographics, diagnosis with clinical and phenotypic characteristics, molecular defect, mode of inheritance, associated diseases, secondary diseases, malignancies and laboratory tests. The majority of entries are predominantly antibody deficiencies (53.2%), selective IgA deficiency being the most frequent. The authors state that this is true for the LAGID-wide analysis as well as in the individual participating countries, and that this is also consistent with previous reports [24–27]. It is made clear, however, that the total number of registered PID patients does not reflect the actual prevalence, which is due to diagnostic capabilities in the respective countries. The overall results from the latest report are perceived as being encouraging and showing increased awareness of PID in Latin America.

In 2006, the ESID online system was adopted for LAGID as well, and is currently in the process of implementation. In addition, a change from LAGID to the Latin American Society for Primary Immunodeficiency Diseases is in progress. Completion of this change is expected in 2007.

Iranian Primary Immunodeficiencies Registry

Over a period of 30 years, the Iranian PID Registry has followed 930 patients using a four-page questionnaire including personal data, demographic data, family history, clinical manifestations, laboratory findings, follow-up data, and so on [28•]. The forms were filed by the clinical immunologists from the participating centres and were sent back to Iranian PID Registry for validation and central documentation in an Access database. The personal data were coded by the database coordinator during registration. The diagnosis of patients was confirmed by the scientific committee of the registry, using standard criteria. Eventually DNA mutation analysis was performed to confirm a diagnosis. Here again it was shown that predominantly antibody deficiencies were the most common group of diseases (38.4%), CVID being the most frequent disorder (193 patients) followed by chronic granulomatous disease (166 individuals), ataxia teleangiectasia (94 patients), Btk deficiency (69 patients), selective IgA deficiency (55 patients), T–B severe combined immunodeficiency (55 patients), and so on. All analysis on the data has been performed with statistical software packages. The analysis showed that diagnosis of PID has increased in recent years from seven newly diagnosed patients per year in the 1980s to 30 patients per year in the early 1990 and 58 new patients per year after 2000. According to these data, the prevalence of PID in Iran can be estimated as six in 100 000 with a median diagnostic delay of 31 months. The authors, however, state again that these figures may not exactly reflect reality since many patients from remote areas of the country may not have been included in the registry. They also presume that many cases still remain undiagnosed.

The most common manifestation is pneumonia, which was seen in 54.9% of the patients, followed by diarrhoea (40.4%), sinusitis (37.1%), and otitis media (35.4%).

The authors confirmed the assumption that infections of the respiratory tract were the most frequent kind of infection (73.2%), followed by infections of the cutaneous (43.4%) and gastrointestinal system (40.4%).

In Iran, consanguineous marriages are still very common due to the cultural and religious background. A recent study aimed at determining the frequency of these in the families with PID patients [29•]; 515 patients were included in the study, in which a consanguineous marriage was defined as a marriage between a person and a third cousin or closer. In this cohort, the overall rate of consanguineous marriages was 65.6%, whereas the mean proportion in Iran in general is 38.6%. The authors state that a positive history of PID was found in 19% of their patients. They therefore call for better public education, more carrier detection, premarital examination, and prenatal diagnosis.

Australasian Society of Clinical Immunology and Allergy Register Australia and New Zealand

The Australasian register started collecting data through a longitudinal cross-sectional survey between 1990 and

1994. Results have already been published by Baumgart *et al.* in 1997 [30]. A new web-enabled ASCIA PID Register Australia and New Zealand was launched in 2003. It combines the existing data with that of an extension survey, information from the Australian Paediatric Surveillance Unit and new online registrations [31••]. Coded data are collected on a one-time basis. Patient consent was collected as required by ethics committees; however, the authors feel that this process has limited the acquisition of data.

Kirkpatrick and Riminton [31••] refer to a cohort of 1209 patients from 88 centres. Documentation was encouraged by offering easy web-based access and support by a network of voluntary PID officers. The geography of Australia and New Zealand brings about the fact that two major paediatric centres accounted for 20.1% of total cases, whereas 80% of all centres had registered less than 20 patients. The distribution of diagnosis was similar across regions, however. The overall prevalence of reported PID cases was given as 5.6/100 000, which is significantly more than calculated earlier by Baumgart *et al.* in 1997 (2.82/100 000) [30]. In this regard, the authors identify underreporting as a key problem for the evaluation of the true disease prevalence. Comparing national data on IVIG distributed for PID with data from the register on IVIG use, they estimate having captured approximately 33.8–37% of patients within the relevant target group. When extending these proportions to the whole population, they estimate a true prevalence of 13.2–14.5/100 000, rather than 5.6/100 000.

Seventy percent of the patients suffered from predominantly antibody deficiencies (CVID, 38.4% of all cases). Chronic lung disease and bronchiectasis are seen frequently in these patients, and Kirkpatrick and Riminton [31••] hypothesize that the high prevalence of these potentially preventable complications could be reduced by improving diagnostic awareness and interdisciplinary collaboration.

There are currently no PID registries reported from Asian and African countries.

Conclusion

The importance of registries in the field of PID has been widely recognized. Registries are vital components of any public health programme, and provide data necessary for planning services, monitoring public health, research and the care of individuals [32]. The collection of demographic data serves to increase awareness and gather clinical cohorts, whereas the analysis of disease specific registries, as demonstrated by Quinti *et al.* [14••] or Plebani *et al.* [19], actually improves patient care and management. The ESID registry provides a system, which has also been adapted by the North-American USIDnet and by the Latin-American LAGID, assuring and preparing for the integration of these registries, whereas the Australasian system differs significantly; thus, combined analysis will be challenging.

As the technical opportunities are manifold, so are the potential benefits. The design, realization, curation and, finally, the documentation into a database, however, is time consuming and requires dedication and substantial funding.

As a matter of course, results are strongly dependent on the respective people's dedication running the network and their financial frame. Funding is needed at the set-up stage, for maintenance and also for the continued documentation of patients. Therefore, the more sound the funding, the more likely substantial results will be obtained. Sponsors are, however, difficult to find in the field of rare diseases, and we therefore call for a strong commitment of the public bodies to support registries and research in rare disorders such as PID.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 589–590).

1 Cotton R, Phillips K, Horaitis O. A survey of locus specific database curation. J Med Genet 2007; 44:72–74.

2 •• Guzman D, Veit D, Knerr V, *et al.* The ESID Online Database network. Bioinformatics 2007; 23:654–655.
A technical and structural description of the ESID online database. The article illustrates how the system has been set up according to the specific aims of the project.

3 •• Eades-Perner AM, Gathmann B, Knerr V, *et al.* The European internet-based patient and research database for primary immunodeficiencies: results 2004–06. Clin Exp Immunol 2007; 147:306–312.
This publication resumes the first years of the ESID database. It summarizes what has been achieved since the launch in 2004 and gives an idea of the system's potential for the future.

4 •• Piirilä H, Väliaho J, Vihinen M. Immunodeficiency Mutation Databases (IDbases). Hum Mutat 2006; 27:1200–1208.
This publication introduces the IDbases, 115 locus-specific and patient-related mutation databases. It describes the system, the information that is currently available on it and the potential benefits to researchers.

5 Riikonen P, Vihinen M. MUTbase: maintenance and analysis of distributed mutation databases. Bioinformatics 1999; 15:852–859.

6 Vihinen M, Kwan SP, Lester T, *et al.* Mutations of the human BTK gene coding for Bruton tyrosine kinase in X-linked agammaglobulinemia. Hum Mutat 1999; 13:280–285.

7 •• Samarghitean C, Väliaho J, Vihinen M. IDR knowledge base for primary immunodeficiencies. Immunome Res 2007; 3:6.
The ImmunoDeficiency Resource knowledge base offers clinical, biochemical, genetic, genomic, proteomic, structural, and computational data on PID. This publication introduces its contents and potential.

8 Samarghitean C, Väliaho J, Vihinen M. Online registry of genetic and clinic immunodeficiency diagnostic laboratories, IDdiagnostics. J Clin Immunol 2004; 24:53–61.

9 Hamosh A, Scott AF, Amberger J, *et al.* Online Mendelian Inheritance in man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res 2002; 30:52–55.

10 Wain HM, Lush MJ, Ducluzeau F, *et al.* Genew: the Human Gene Nomenclature Database, 2004 updates. Nucleic Acids Res 2004; 32: D255–D257.

11 Boeckmann B, Bairoch A, Apweiler R, *et al.* The SWISS-PROT protein knowledgebase and its supplement TrEMBL in 2003. Nucleic Acids Res 2003; 31:365–370.

12 Rebhan M, Chalifa-Caspi V, Prilusky J, Lancet D. GeneCards: a novel functional genomics compendium with automated data mining and query reformulation support. Bioinformatics 1998; 14:656–664.

13 Diehn M, Sherlock G, Binkley G, *et al.* SOURCE: a unified genomic resource of functional annotations, ontologies, and gene expression data. Nucleic Acids Res 2003; 31:219–223.

14 •• Quinti I, Soresina A, Spadaro G, *et al.* Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007; 27:308–316.
This multicentre prospective study analyses 224 patients with CVID, the spectrum of the illness and the effects of immunoglobulin replacement therapy. The study is based on data from the Italian PID register.

15 Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999; 92:34–48.

16 Conley ME, Park CL, Douglas SD. Childhood common variable immunodeficiency with autoimmune disease. J Pediatr 1986; 108:915–922.

17 Hermanszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. QJM 1993; 86:31–42.

18 Carsetti R, Rosado MM, Donnanno S, *et al.* Te loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. J Allergy Clin Immunol 2005; 115:412–417.

19 Plebani A, Soresina A, Rondelli R, *et al.* Clinical, immunological, and molecular analysis in a large cohort of patients with X-linked agammaglobulinemia: an Italian multicentre study. Clin Immunol 2002; 104:221–230.

20 • Winkelstein JA, Marino MC, Lederman HM, *et al.* X-linked Agammaglobulinemia. Report on a United States Registry of 201 patients. Medicine 2006; 85:193–202.
The authors describe the set-up of a disease-specific national registry on XLA in order to collect sufficient patient numbers to develop a comprehensive clinical picture of the disorder. They give information about demographics, clinical presentation, age of diagnosis and outcome.

21 Matamoros N, Llambi JM, Espanol T, *et al.* Primary immunodeficiency syndrome in Spain: first report of the National Registry in Children and Adults. J Clin Immunol 1997; 17:333–339.

22 Zelazco M, Carneiro-Sampaio M, Cornejo de Luigi M, *et al.* Primary immunodeficiency diseases in Latin America: first report from eight countries participating in the LAGID. J Clin Immunol 1998; 18:161–166.

23 •• Leiva LE, Zelazco M, Oleastro M, *et al.* Primary immunodeficiency diseases in Latin America: the second report of the LAGID Registry. J Clin Immunol 2007; 27:101–108.
This report gives an overview over what has been achieved in the 12 Latin American countries participating in the LAGID registry. It gives an update on the first report from 1998.

24 Stray-Pedersen A, Abrahamsen T, Froland S. Primary immunodeficiency diseases in Norway. J Clin Immunol 2000; 20:477–485.

25 Llambi M, Etxagobe G, Matamoros F. The Spanish Registry of Primary Immunodeficiencies (REDIP). Allergol Immunopathol 2001; 29:122–125.

26 Lim D, Thong B, Ho S, *et al.* Primary immunodeficiency diseases in Singapore – the last 11 years. Singapore Med J 2003; 44:579–586.

27 Aghamohammadi A, Moein M, Farhoudi A, *et al.* Primary immunodeficiency in Iran: first report of the national registry of PID in children and adults. J Clin Immunol 2002; 22:375–380.

28 • Rezaei N, Aghamohammadi A, Moin M, *et al.* Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran. Update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol 2006; 26:519–529.
The authors describe how data have been collected and analysed in Iran, and present data that have been gained from this registry.

29 • Rezaei N, Aghamohammadi A, Fahroudi A, *et al.* Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. Am J Reprod Immunol 2006; 56:145–151.
In this study, the authors analyse the frequency of consanguineous marriages in Iran on the basis of 515 patients from the Iranian PID registry.

30 Baumgart KW, Britton W, Kemp A, *et al.* The spectrum of primary immunodeficiency disorders in Australia. J Allergy Clin Immunol 1997; 100:415–423.

31 •• Kirkpatrick P, Riminton S. Primary immunodeficiency diseases in Australia and New Zealand. J Clin Immunol 2007; 27:517–524.
The authors introduce the web-based register of the Australasian Society of Clinical Immunology and Allergy. They address key areas of interest, such as the prevalence of PID in Australia and New Zealand or the governance of immunoglobulin replacement therapy.

32 General Medical Council. Confidentiality: protecting and providing information. Frequently asked questions 2004; Question 6. http://www.gmc-uk.org/guidance/current/library/confidentiality_faq.asp#q6. [Accessed 25 September 2007]