Review paper

Immunodeficiency information services

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Abstract

Primary immunodeficiency diseases are a group of inherited, mainly rare disorders affecting the immune system. We have created three, complementary, Internet services for the efficient retrieval and usage of immunodeficiency related data. The ImmunoDeficiency Resource (IDR) is a comprehensive knowledge base and starting point for many types of information regarding immunodeficiencies. To ensure the credibility of the data, experts validate all the information available on this site. The Immunodeficiency Databases (IDbases) contain mutation information on approximately 110 affected genes and more than 4100 patients. Patient-related mutation data indicate the frequency of certain mutations and facilitate genotype-phenotype correlations. The Immunodeficiency Diagnostics (IDdiagnostics) registry collects, describes, identifies and disseminates information about immunodeficiency tests from genetic and clinical diagnostic laboratories. The service is important, because only a few laboratories perform tests for rare IDs. All three services are freely available at http://bioinf.uta.fi/. The most recent project, the PIDexpert, is a medical expert system designed to suggest diagnoses based on symptoms, medical history, physical findings and laboratory tests. The PIDexpert service will be available in the near future.

Key words: *immunodeficiency, IDR, fact files, Internet services, IDbases, IDdiagnostics, databases, diagnostics, genetic tests, PIDexpert.*

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Introduction

Primary immunodeficiency diseases (IDs) consist of a group of inherited, often rare disorders affecting the immune system. They predispose individuals to various clinical symptoms such as recurrent and persistent infections, allergies, cancer and autoimmune manifestations [1, 2]. An immune defect can affect any part of the immune system. This has been used as the basis of the ID classification (fig. 1). A wealth of information concerning these rare diseases is available from the Internet, but it is scattered and very fragmented. We have compiled all the major immunodeficiency data and thousands of links onto one server, the Immunodeficiency Resource (IDR) [3, 4]. Fact files for each disease serve as the core of the IDR [5]. The server offers an extensive starting point for immunodeficiency information retrieval.

Around 150 primary immunodeficiency diseases have been identified since the 1950's. The molecular basis of more than 100 primary IDs have recently been identified [6]. Inheritance of primary IDs can be X-linked, autosomal recessive, or autosomal dominant (table 1). Diagnosis of an immunodeficiency can be difficult because similar symptoms characterise several disorders and mutations from the same gene can lead to distinct phenotypic consequences [7, 8]. Mutation detection is the most reliable method to confirm the diagnosis. New immunodeficiency-related genes and new mutations and patients are frequently found. We have established immunodeficiency mutation databases (IDbases) for most of the IDs for which the affected gene has been identified [2, 9] (table 2). These databases enable one to carry out detailed mutation studies and handle the ever-growing volume of information.

For the treatment and survival of the immunodeficiency patient, it is important to have the correct diagnosis as soon as possible. Because many IDs are very rare disorders there are only limited number of laboratories carrying out genetic testing for patients and it may be difficult for a physician to find the right laboratory. We maintain an online registry of genetic and clinical immunodeficiency diagnostic laboratories [10]. The IDdiagnostics service is primarily

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Table 1. Inheritance of the IDs

Inheritance	Disease	Mutations
X-linked	10%	50%
autosomal recessive	86%	49%
autosomal dominant	4%	<1%

directed for health care professionals enabling them to find a laboratory to contact for the required genetic and/or clinical diagnostics. The aim of the registry is also to increase the general awareness of IDs, which is important for fast and reliable diagnosis and proper treatment.

Diagnosis of the IDs with overlapping symptoms is often troublesome. PIDexpert is our most recent instrument for faster and more accurate diagnosis. It is a medical expert system designed to give the diagnostic picture of IDs based on symptoms, signs, medical history, physical findings and laboratory tests. The system is expected to contribute significantly to the diagnosis and treatment of patients and save money in health care. The PIDexpert system will be available on our server in the near future.

Immunodeficiency resource (IDR)

The IDR is a compendium of information on immunodeficiencies. It is freely available online via the Internet (http://bioinf.uta.fi/idr/) [3, 4]. It is maintained for collecting and distributing all the essential information and links related to immunodeficiencies. The Internet encompasses billions of web pages including a lot that contain questionable, even misleading data, and it may be hard to distinguish the relevant data from nonsense. The validation of information in the IDR is of prime importance. Experts check the data and approve only the data and sites with solid scientific and medical information to be linked to the IDR [4]. Links to external information sources are checked especially carefully by curators before being accepted.

The contents of the IDR are versatile. The IDR offers tens of thousands of validated links to other sites, which are periodically automatically checked. Navigation is logical and it is possible to search for any text string or multiple strings with Boolean logic across the IDR pages. The IDR is designed for different user groups: researchers, physicians, and nurses, as well as patients and their families and the general public.

The general introduction pages are extensive. From the IDR one can also find comprehensive classification and diagnostic criteria for some immunodeficiencies [8]. Genes causing immunodeficiencies are listed in accordance to disease classification, with hyperlinks to several bioinformatics databases. Further, there is information about analysis, reference sequences, protein structures, animal models and knock-outs, and a picture gallery.

There are several societies related to immunodeficiency research, treatment and care and patients. We have collected links to immunology societies, nurse societies and patient organizations. We also maintain a list of current immunology meetings and workshops. The immunology laboratories page

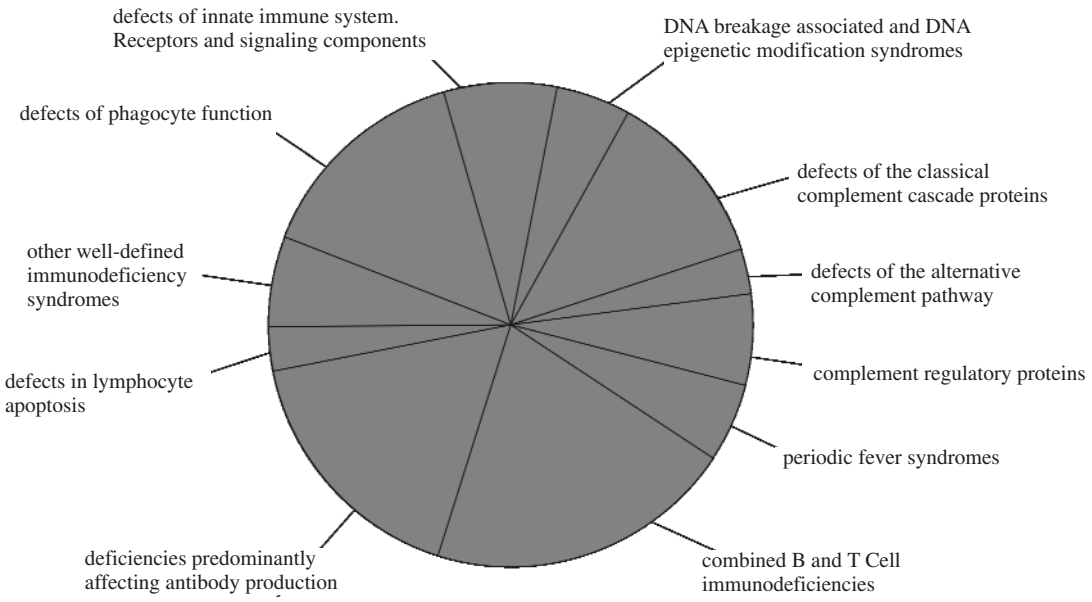

Fig. 1. Classification of immunodeficiencies. The classification of immunodeficiencies is based on the part of the immune system affected

contains a list of home pages of laboratories that are active in many fields of immunodeficiency research. Patient pages have useful links for immunodeficiency patients and their families, containing mostly personal reports about surviving and living with an immunodeficiency and contact information with some ID communities. The online library and Immunology resources provide further information about immunology and IDs. The IDR pages are extensively hyperlinked to our on-line immunology glossary of over 1,000 immunological terms. Descriptions for abbreviations and acronyms used in IDR pages are also available.

The basic information on IDs is stored as fact files [4]. Each fact file provides a succinct summary of information on one disease and the affected gene, including clinical information, molecular biology, and HTML hyperlinks to other Internet resources. Fact files are a compact package of information, and a good starting point for expansive data searching related to IDs. Currently we have 135 fact files. The fact files are created by using the IDML data model [4, 5]. IDML (Inherited Disease Markup Language) is based on the eXtensible Markup Language (XML) format. IDML integrates biomedical information related to hereditary diseases into a Web and WAP accessible knowledge base. The data model has been applied to primary immunodeficiencies, but it can be used for any group of hereditary diseases. The fact files are also accessible with mobile devices by using the BioWAP (http://bioinf.uta.fi/BioWAP/) service [11, 12].

Immunodeficiency mutation databases (IDbases)

Immunodeficiency mutation databases (IDbases) offer an easy way to find recently identified mutations, to compare genotype-phenotype correlations, and to discover a specific mutation or to examine the most common mutations in a single immunodeficiency related gene. We currently maintain databases for 110 IDs with more than 4100 public patient entries at IMT Bioinformatics (http://bioinf.uta.fi/IDbases/) (table 1). Databases are named according to the affected gene after systematic HUGO Gene Nomenclature (http://www.gene.ucl.ac.uk/nomenclature/). The IDbases are patient-related databases, where the mutation data has been collected into entries along with some clinical information. This allows the discovery of statistically relevant trends from large data sets. Patient-related mutation data makes it possible to find out which mutations are frequent among patients with certain symptoms. In addition to the actual mutations and clinical information, every database has further information about mutation types and visualisation of the distribution of mutations within the amino acid sequence. The pages are interactive, providing access to patient information, mutation information, and literature references. It is easy to trace all the publications related to a specific mutation. There are also links to reference sequences and other data sources, such as sequence databanks, GeneCard, OMIM and UniGene. In addition to our databases we have links to immunodeficiency databases maintained by others.

Mutation data submissions from the scientists analysing mutations are advantageous for keeping the databases up-to-date. Mutation data may be submitted either by contacting the curators or via the Internet. Each database has a specific electronic submission form. The interactive submission form, based on the MUTbase program [13], facilitates submission of the mutation. The program compares the given mutation information to standard reference sequences provided by the IDRefSeq (http://bioinf.uta.fi/IDRefSeq/) service, and warns of possible errors. It calculates the protein level change(s) caused by the mutation(s) and checks for the numbering and type of the nucleotide(s) affected. The MUTbase system generates a standardized representation of the information contained in the raw data, part of which is added to the database entry and the other part written on numerous interactive Web pages. Finally, the submission is sent to the curators by e-mail. The curator of the database validates all the submitted data before it is made public.

The European Society for Immunodeficiencies (ESID) registry (http://www.esid.org/esid_registry.php) has collected information about immunodeficiency patients. The database has undergone a complete rebuild during last two years. BTKbase for X-linked agammaglobulinemia (XLA) was the first IDbase established in 1994 [14-16]. Today the cooperation with the patient database continues, productively integrating the IDbase mutation service with the ESID registry. The ESID registry collects new patient information containing confidential clinical data and at the same time receives some new mutations. The mutations are validated by the IDbase submission system. The collaboration facilitates direct submission to both the ESID registry and IDbases, and thus allows both systems to be updated by a single submission.

Immunodeficiency diagnostics registry (IDdiagnostics)

Early and reliable diagnosis is often crucial for the efficient treatment of IDs. If diagnosis and treatment are delayed, it may even cost a patient's life. For most IDs, detecting the molecular defect is essential for the correct diagnosis. The number of the laboratories analysing the genetic defects of IDs is limited, due to rareness of immunodeficiencies. IDdiagnostics is a registry of laboratories performing genetic testing for patients with hereditary immunodeficiencies [3]. It is formed from two independent registries for laboratories performing genetic and clinical tests for IDs, respectively [10]. These registries provide a service for those trying to find the nearest and/or most suitable laboratory conducting ID testing. IDdiagnostics currently contains information for the analysis of defects in

Table 2. Immunodeficiency mutation databases

Database	Immunodeficiency	OMIM	Internet address of the database	Public cases	Reference
ADAbase	Adenosine deaminase deficiency	102700	http://bioinf.uta.fi/ADAbase/	67	
AICDAbase	Non-X-linked hyper-IgM syndrome	605257	http://bioinf.uta.fi/AICDAbase/	65	
AIREbase	Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECEC)	607358	http://bioinf.uta.fi/AIREbase/	132	
AP3B1base	Hermansky-Pudlak syndrome 2	603401	http://bioinf.uta.fi/AP3B1base/	4	
AP3B1	Hermansky-Pudlak syndrome 2	603401	http://albinismdb.med.umn.edu/hps2mut.htm	4	
ATbase	Ataxia-telangiectasia	607585	http://www.cbt.ki.se/ATbase/	47	
ATM	Ataxia-telangiectasia	607585	http://benaroyaresearch.org/investigators/concannon_patrick/atm.htm	621	[19]
BLMbase	Bloom syndrome	604610	http://bioinf.uta.fi/BLMbase/	33	[20]
BLNKbase	BLNK deficiency	604515	http://bioinf.uta.fi/BLNKbase/	1	
BTKbase	X-linked agammaglobulinemia (XLA)	300300	http://bioinf.uta.fi/BTKbase/	974	[14-16]
C1QAbase	C1QA deficiency	120550	http://bioinf.uta.fi/C1QAbase/	6	
C1QBbase	C1QB deficiency	120570	http://bioinf.uta.fi/C1QBbase/	4	
C1QGbase	C1QG deficiency	120575	http://bioinf.uta.fi/C1QGbase/	3	
C1Sbase	C1s deficiency	120580	http://bioinf.uta.fi/C1Sbase/	3	
C2base	C2 deficiency	217000	http://bioinf.uta.fi/C2base/	3	
C3base	C3 deficiency	120700	http://bioinf.uta.fi/C3base/	4	
C5base	C5 deficiency	120900	http://bioinf.uta.fi/C5base/	4	
C6base	C6 deficiency	217050	http://bioinf.uta.fi/C6base/	13	
C7base	C7 deficiency	217070	http://bioinf.uta.fi/C7base/	14	
C8Bbase	C8B deficiency	120960	http://bioinf.uta.fi/C8Bbase/	59	
C9base	C9 deficiency	120940	http://bioinf.uta.fi/C9base/	14	
CARD15	Blau syndrome and Chrohn's disease	605956	http://fmf.igh.cnrs.fr/infevers/	87	[21]
CASP10base	Autoimmune lymphoproliferative syndrome, type II	601762	http://bioinf.uta.fi/CASP10base/	2	
CASP10	Autoimmune lymphoproliferative syndrome, type II	601762	http://research.nhgri.nih.gov/ALPS/alpsII_mut.shtml	2	
CASP8 base	Caspase 8 deficiency	601763	http://bioinf.uta.fi/CASP8base/	2	
CD3Dbase	Autosomal recessive CD3δ deficiency	186790	http://bioinf.uta.fi/CD3Dbase/	6	
CD3Ebase	Autosomal recessive CD3ε deficiency	186830	http://bioinf.uta.fi/CD3Ebase/	1	
CD3Gbase	Autosomal recessive CD3γ deficiency	186740	http://bioinf.uta.fi/CD3Gbase/	3	
CD40Lbase	X-linked hyper-IgM syndrome (XHIM)	300386	http://bioinf.uta.fi/CD40Lbase/	212	[22]

Table 2. Continuation

Database	Immunodeficiency	OMIM	Internet address of the database	Public cases	Reference
CD59base	CD59 deficiency	107271	http://bioinf.uta.fi/CD59base/	1	
CD79Abase	Igα deficiency	112205	http://bioinf.uta.fi/CD79Abase/	1	
CD8Abase	CD8 deficiency	186910	http://bioinf.uta.fi/CD8Abase/	3	
CEBPEbase	Neutrophil-specific granule deficiency	600749	http://bioinf.uta.fi/CEBPEbase/	2	
CFH	Haemolytic ureamic syndrome	134370	http://www.fh-hus.org/	61	[23]
CHS1base	Chediak-Higashi syndrome	606897	http://bioinf.uta.fi/CHS1base/	31	
CHS1	Chediak-Higashi syndrome	606897	http://albinismdb.med.umn.edu/chs1mut.html	15	
CIAS1	Familial cold autoinflammatory syndrome, Muckle-Wells syndrome and chronic infantile neurological cutaneous and articular syndrome	606416	http://fmf.igh.cnrs.fr/infevers/	60	[21]
CTSCbase	Papillon-Lefevre syndrome	602365	http://bioinf.uta.fi/CTSCbase/	115	
CTSC	Papillon Lefevre Syndrome	602365	http://www.genetics.pitt.edu/mutation/pls/	48	
CXCR4base	WHIM syndrome	162643	http://bioinf.uta.fi/CXCR4base/	24	
CYBAbase	Autosomal recessive $p22^{phox}$ deficiency	608508	http://bioinf.uta.fi/CYBAbase/	33	
CYBBbase	X-linked chronic granulomatous disease (XCGD)	300481	http://bioinf.uta.fi/CYBBbase/	484	[24, 25]
DAFbase	Decay-accelerating factor (CD55) deficiency	125240	http://bioinf.uta.fi/DAFbase/	9	
DCLRE1Cbase	Artemis deficiency	605988	http://bioinf.uta.fi/DCLRE1Cbase/	21	
DFbase	Factor D deficiency	134350	http://bioinf.uta.fi/DFbase/	5	
DKC1base	Hoyeraal-Hreidarsson syndrome	300126	http://bioinf.uta.fi/DKC1base/	9	
DNMT3base	ICF syndrome	602900	http://bioinf.uta.fi/DNMT3Bbase/	14	[26]
ELA2base	Cyclic neutropenia and severe congenital neutropenias	130130	http://bioinf.uta.fi/ELA2base/	135	
EVER1base	Epidermodysplasia verruciformis	605828	http://bioinf.uta.fi/EVER1base/	7	
EVER2base	Epidermodysplasia verruciformis	605829	http://bioinf.uta.fi/EVER2base/	5	
FANCA	Fanconi anemia complementation group A	607139	http://www.rockefeller.edu/fanconi/mutate/	201	[27]
FANCB	Fanconi anemia complementation group B	300515	http://www.rockefeller.edu/fanconi/mutate/	4	
FANCC	Fanconi anemia complementation group C	227645	http://www.rockefeller.edu/fanconi/mutate/	9	[28]
FANCD2	Fanconi anemia complementation group D2	227646	http://www.rockefeller.edu/fanconi/mutate/	5	
FANCE	Fanconi anemia complementation group E	600901	http://www.rockefeller.edu/fanconi/mutate/	7	
FANCF	Fanconi anemia complementation group F	603467	http://www.rockefeller.edu/fanconi/mutate/	5	
FANCG	Fanconi anemia complementation group G	602956	http://www.rockefeller.edu/fanconi/mutate/	36	[29]
FANCL	Fanconi anemia complementation group L	608111	http://www.rockefeller.edu/fanconi/mutate/	1	

Table 2. Continuation

Database	Immunodeficiency	OMIM	Internet address of the database	Public cases	Reference
FCGR1Abase	CD64 deficiency	146760	http://bioinf.uta.fi/FCGR1Abase/	4	
FCGR3Abase	Natural killer cell deficiency	146740	http://bioinf.uta.fi/FCGR3Abase/	3	
FOXN1base	T-cell immunodeficiency, congenital alopecia, and nail dystrophy	600838	http://bioinf.uta.fi/FOXN1base/	2	
FOXP3base	Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked; IPEX	300292	http://bioinf.uta.fi/FOXP3base/	12	
GFI1base	Severe congenital neutropenia and nonimmune chronic idiopathic neutropenia of adults	600871	http://bioinf.uta.fi/GFI1base/	4	
HAEbd	Hereditary angioedema	606860	http://hae.biomembrane.hu/	183	[30]
HF1base	Factor H deficiency	134370	http://bioinf.uta.fi/HF1base/	71	
ICOSbase	ICOS deficiency	604558	http://bioinf.uta.fi/ICOSbase/	9	
IFbase	Factor I deficiency	217030	http://bioinf.uta.fi/IFbase/	6	
IFNGR1base	IFNγ1-receptor deficiency	107470	http://bioinf.uta.fi/IFNGR1base/	66	
IFNGR2base	IFNγ2-receptor deficiency	147569	http://bioinf.uta.fi/IFNGR2base/	8	
IGHG2base	IgG2 deficiency	147110	http://bioinf.uta.fi/IGHG2base/	5	
IGHMbase	μ heavy-chain deficiency	147020	http://bioinf.uta.fi/IGHMbase/	17	
IGLL1base	λ5 surrogate light-chain deficiency	146770	http://bioinf.uta.fi/IGLL1base/	1	
IKBKGbase	NEMO deficiency	300248	http://bioinf.uta.fi/IKBKGbase/	27	
IL12Bbase	Interleukin-12 (IL-12) p40 deficiency	161561	http://bioinf.uta.fi/IL12Bbase/	14	
IL12RB1base	Interleukin-12 receptor β1 deficiency	601604	http://bioinf.uta.fi/IL12RB1base/	49	
IL2RAbase	IL2RA deficiency	147730	http://bioinf.uta.fi/IL12RAbase/	1	
IL2RGbase	X-linked severe combined immnunodeficiency (XSCID)	308380	http://genome.nhgri.nih.gov/scid/	344	[31]
IL7Rbase	Interleukin-7 receptor α deficiency	146661	http://bioinf.uta.fi/IL7Rbase/	5	
IRAK4base	IRAK4 deficiency	606883	http://bioinf.uta.fi/IRAK4base/	5	
ITGB2base	Leucosyte adhesion deficiency I (LAD-I)	600065	http://bioinf.uta.fi/ITGB2base/	40	
JAK3base	Autosomal recessive severe combined JAK3 deficiency	600173	http://bioinf.uta.fi/JAK3base/	16	[32, 33]
LIG1base	DNA ligase I deficiency	126391	http://bioinf.uta.fi/LIG1base/	1	
LIG4base	LIG4 syndrome	601837	http://bioinf.uta.fi/LIG4base/	8	
LRRC8base	Non-Bruton type autosomal dominant agammaglobulinemia	608360	http://bioinf.uta.fi/LRRC8Abase/	1	
MASP2base	MASP-2 deficiency	605102	http://bioinf.uta.fi/MASP2base/	1	
MEFV	Familial Mediterranean fever	608107	http://fmf.igh.cnrs.fr/infevers/	113	[21]
MHC2TAbase	MHCII transactivating protein deficiency	600005	http://bioinf.uta.fi/MHC2TAbase/	8	

Table 2. Continuation

Database	Immunodeficiency	OMIM	Internet address of the database	Public cases	Reference
MLPHbase	Griscelli syndrome, type 3 (GS3)	606526	http://bioinf.uta.fi/MLPHbase/	1	
MPObase	Myeloperoxidase deficiency	606989	http://bioinf.uta.fi/MPObase/	39	
MRE11Abase	Ataxia-telangiectasia-like disorder (ATLD)	600814	http://bioinf.uta.fi/MRE11Abase/	16	
MVK	Hyper IgD Syndrome and periodic fever	251170	http://fmf.igh.cnrs.fr/infevers/	71	[21]
MYO5Abase	Griscelli syndrome, type 1 (GS1)	160777	http://bioinf.uta.fi/MYO5Abase/	2	
NCF1base	Autosomal recessive $p47^{phox}$ deficiency	233700	http://bioinf.uta.fi/NCF1base/	33	
NCF2base	Autosomal recessive $p67^{phox}$ deficiency	233710	http://bioinf.uta.fi/NCF2base/	11	
NFKBIAbase	Autosomal dominant anhidrotic ectodermal dysplasia and T-cell immunodeficiency	164008	http://bioinf.uta.fi/NFKBIAbase/	1	
NPbase	PNP deficiency	164050	http://bioinf.uta.fi/NPbase/	13	
PFCbase	Properdin deficiency	300383	http://bioinf.uta.fi/PFCbase/	36	
PRF1base	Familiar haemophagocytic lymphohistiocytosis, type II (FHL2)	170280	http://bioinf.uta.fi/PRF1base/	93	
PSTPIP1	Pyogenic sterile arthritis, pyoderma gangrenosum, and acne syndrome	606347	http://fmf.igh.cnrs.fr/infevers/	2	[21]
PTPRCbase	CD45 deficiency	151460	http://bioinf.uta.fi/PTPRCbase/	2	
RAB27Abase	Griscelli syndrome, type 2 (GS2)	603868	http://bioinf.uta.fi/RAB27Abase/	28	
RAC2base	Neutrophil immunodeficiency syndrome	602049	http://bioinf.uta.fi/RAC2base/	1	
RAG1base	Autosomal recessive severe combined RAG1 deficiency	179615	http://bioinf.uta.fi/RAG1base/	52	[34]
RAG2base	Autosomal recessive severe combined RAG2 deficiency	179616	http://bioinf.uta.fi/RAG2base/	34	[34]
RFX5base	MHCII promoter X box regulatory factor 5 deficiency	601863	http://bioinf.uta.fi/RFX5base/	8	
RFXANKbase	Ankyrin repeat containing regulatory factor X-associated protein deficiency	603200	http://bioinf.uta.fi/RFXANKbase/	28	
RFXAPbase	Regulatory factor X-associated protein deficiency	601861	http://bioinf.uta.fi/RFXAPbase/	7	
SBDSbase	Shwachman-Diamond syndrome	607444	http://bioinf.uta.fi/SBDSbase/	168	
SERPING1base	Hereditary angioedema	606860	http://bioinf.uta.fi/SERPING1base/	260	
SH2D1Abase	X-linked lymphoproliferative syndrome (XLP)	300490	http://bioinf.uta.fi/SH2D1Abase/	101	[35]
SLC35C1base	Leucosyte adhesion deficiency II (LAD-II)	605881	http://bioinf.uta.fi/SLC35C1base/	4	
SMARCAL1base	Schimke immuno-osseous dysplasia	606622	http://bioinf.uta.fi/SMARCAL1base/	25	
SPINK5base	Netherton syndrome	605010	http://bioinf.uta.fi/SPINK5base/	66	
STAT1base	STAT1 deficiency	600555	http://bioinf.uta.fi/STAT1base/	4	
STAT5Bbase	Growth hormone insensitivity with immunodeficiency	604260	http://bioinf.uta.fi/STAT5Bbase/	2	
STX11base	Familial haemophagocytic lymphohistiocytosis 4 (FHL4)	605014	http://bioinf.uta.fi/STX11base/	10	

Table 2. Continuation

Database	Immunodeficiency	OMIM	Internet address of the database	Public cases	Reference
TAP1base	TAP1 deficiency	170260	http://bioinf.uta.fi/TAP1base/	2	
TAP2base	TAP2 deficiency	170261	http://bioinf.uta.fi/TAP2base/	3	
TAPBPbase	Tapasin deficiency	601962	http://bioinf.uta.fi/TAPBPbase/	1	
TAZbase	Barth syndrome	300394	http://bioinf.uta.fi/TAZbase/	65	
TCIRG1base	Autosomal recessive osteopetrosis	604592	http://bioinf.uta.fi/TCIRG1base/	38	
TCN2base	Transcobalamin II deficiency	275350	http://bioinf.uta.fi/TCN2base/	6	
TNFRSF1A	Tumor necrosis factor receptor-associated periodic syndrome	191190	http://fmf.igh.cnrs.fr/infevers/	65	[21]
TNFRSF13Bbase	TACI deficiency	604907	http://bioinf.uta.fi/TNFRSF13Bbase/	35	
TNFRSF5base	CD40 deficiency	109535	http://bioinf.uta.fi/TNFRSF5base/	4	
TNFRSF6	Autoimmune lymphoproliferative syndrome, type 1A	134637	http://research.nhgri.nih.gov/ALPS/alpsIa_mut.shtml	69	
TNFSF6base	Autoimmune lymphoproliferative syndrome, type 1B	134638	http://bioinf.uta.fi/ TNFSF6base/	1	
UNC13Dbase	Familial hemophagocytic lymphohistiocytosis 3	608897	http://bioinf.uta.fi/UNC13Dbase/	18	
UNGbase	UNG deficiency (Hyper-IgM syndrome, type 5)	191525	http://bioinf.uta.fi/UNGbase/	3	
WASbase	Wiskott-Aldrich syndrome (WAS)	300392	http://bioinf.uta.fi/WASbase/	27	
WASPbase	Wiskott-Aldrich syndrome and X-linked thrombocytopenia	300392	http://homepage.mac.com/kohsukeimai/wasp/WASPbase.html	441	
ZAP70base	Autosomal recessive severe combined ZAP70 deficiency	176947	http://bioinf.uta.fi/ZAP70base/	14	

41 ID-related genes. The service is intended for physicians, researchers, and other health professionals involved with medical genetics.

Laboratories are included in IDdiagnostics on a voluntary basis. The registry includes only those laboratories willing to have their information posted on the Internet. Registration forms are available in both electronic and paper form. The IDdiagnostics data is regularly updated and laboratories are contacted to verify the accuracy of their information. The curators retain the right to remove information for a laboratory if there are problems, e.g., with the time schedule or quality of information.

Physicians have to contact the laboratory before sending in any samples as the standards vary between laboratories. The cost of the analysis varies depending, for example, on the method used, the type of laboratory, and the research interest of a particular disease. The gene test laboratories provide information about the time required for a diagnosis and the turnaround time, how often the samples are run, how many samples are studied annually and the cost of the analyses. Contact addresses for laboratories performing diagnosis are provided in the IDdiagnostics registry along with the assay method(s) used.

The search facilities of the IDdiagnostics database allow users to run text based search queries. Gene test laboratories can be searched by disease name (including alternative names), gene symbol, OMIM code, laboratory name, laboratory location and free text. A search engine facilitates finding laboratories for certain disease(s), methods and/or geographical locations. Further information and submission pages for both genetic and clinical testing can be found at http://bioinf.uta.fi/IDdiagnostics/.

PIDexpert

Medical expert systems (MESs) or medical diagnostic decision support systems (MDDS) [17] are an established component of medical technology. They are computer programs that use a set of rules applied to knowledge extracted from human experts. Medical expert systems help in diagnostic processes and report generation, improve consistency in decisions, and increase timeliness in decision-making and productivity. In medicine, expert systems have been used in a variety of fields, such as internal medicine, paediatrics, infectious disease, neurology, psychiatry.

Medical expert systems vary in complexity. They produce patient-specific and situation specific recommendations. MESs can be integrated with other applications, such as electronic patient records, systems for prescribing and dispensing medicines, and other information systems used in health settings. PIDexpert is a medical expert system, which aims to help with the diagnosis and management of primary immunodeficiency diseases. It can act as both an electronic textbook and an expert consultant program. PIDexpert generates a differential diagnosis from clinical symptoms, provides justification for a diagnosis and suggests potentially useful further clinical information that is required.

PIDexpert includes a knowledge acquisition system, a knowledge base, an inference engine and a user interface [Samarghitean and Vihinen, submitted]. The knowledge base is built with data and facts from IDR, IDdiagnostics, literature and medical experts. Additionally, real examples of differential diagnoses of patient cases will further enrich the knowledge base. The ESID/PAGID diagnostic guidelines [8] and practice parameters for the diagnosis and management of primary immunodeficiencies established by the American College of Allergy, Asthma and Immunology (ACAAI) and the Joint Council of Allergy, Asthma and Immunology [18] will also be included in the knowledge base. These guidelines provide heuristics for possible/probable/definitive diagnosis for some of the most common IDs. The inference engine includes the rules or facts used for deduction and in this case use decision tree algorithm. This algorithm is well suited due to its symbolic knowledge representation and explanations of decisions it makes. Decision tree methodology does not require as many known cases as some other artificial intelligence (AI) methods, and that is convenient in the case of rare IDs. The user-friendly interface will be web-based. The patient information is not submitted over the Internet because Java technology allows the analysis to run on the local computer. Physicians use an input form to indicate various signs and symptoms. The system also identifies other conditions that are associated with the disorder and how the diagnosis can be confirmed. If necessary, the program will also remind or suggest an additional test. The AI system is not intended to replace the physician, but to help in decision making. PIDexpert is still under development, but it will be available in the near future (http://bioinf.uta.fi/PIDexpert/).

Conclusions

The Internet provides an effective way to search information on countless databases and web pages, even for rare diseases like primary IDs. All the data found on the Internet is not qualified, and there is clearly a need for a reliable and comprehensive knowledge base for primary IDs. The content of our services has been extended over the recent years. The frequently expanding and detailed data of the IDR, the IDbases, and IDdiagnostics increasingly serve the needs of diverse user groups, such as physicians, nurses, researchers and patients as well as their families in their fight against primary IDs. The services also increase the common knowledge of primary IDs, which encourages physicians to consider the possibility of a primary ID, when warranted. This is important, because an early diagnosis provides better prognosis for the patient. The PIDexpert system will complement the services by providing a useful and efficient instrument for problematic ID diagnosis.

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