厚生労働科学研究委託費（難治性疾患実用化研究事業）
委託業務成果報告（業務項目）

PIDJ データベースシステムを用いた自己炎症疾患のバイオバンク整備に関する研究

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研究要旨

自己炎症性疾患データベースが構築され、順調に自己炎症疾患患者が登録されてきている。しかし、患者検体保存の有無、採取回数、生体試料の保存場所、検体の種類や、生体試料採取時の患者状況については、システム上やや困難である。自己炎症性疾患は炎症発作時と安定期では、患者病態が異なる可能性があり、今後管理された検体を用いて病態解析を行うためには前述の情報が必要である。さらに、解析を円滑に進めるため保管場所についても明記され検体へのアクセスが平易になることが望ましい。

そこで、原発性免疫不全症データベース（Primary Immunodeficiency Database in Japan, PIDJ）に既に作製してある検体歴データベース（免疫不全症検体登録)を活用し、同じ形式で自己炎症疾患のデータベースに作製し、患者検体保存の有無、採取回数、生体試料の保存場所、種類や、生体試料採取時の患者状況などの情報が入力できるシステムを構築することとした。この入力システムにより、病期・患者の病状についてもの情報が得られ、病態解析に有用である。

さらに、自己炎症疾患がPIDJのみに登録されていたり、逆に自己炎症疾患のみに登録されている場合があると考えられる。そこで、定期的に自己炎症のデータベースに入力された検体データとPIDJのデータベースのデータ補完を行う。

以上により、自己炎症疾患患者保存検体について、疾患の活動期か非活動期かなど、検体取得した時点での患者の臨床状態、臨床検査のデータがデータベース検索で分かるようになり、自己炎症性疾患患者検体の保存場所、必要とする患者サンプルの入手法について、より利便性が高いシステムを構築が可能になった。

A. 研究目的

自己炎症性疾患データベースが構築され、順調に自己炎症疾患患者が登録されてきている。しかし、現在の自己炎症疾患データベースにおいて検体保存の有無と種類についての入力は可能であるが、採取日や採取時の患者の状況、検体が今まで何度採取されているのかなど細かなデータは入力がやや困難である。しかし、自己炎症疾患は発作時と安定期で病態が異なる可能性があり、保存検体を用いて病態解析を行うためには前述の情

報が必要である。

また、解析を円滑に進めるため生体試料の保管場所も明記され、研究を行う際に生体試料へのアクセスが平易になることが望ましい。

そこで、こうした問題を解決するために、自己炎症疾患の患者検体について、免疫不全症のデータベース(Primary Immunodeficiency database in Japan, PIDJ)に既に作製してある検体歴データベース(免疫不全症検体登録)中のデータを自己炎症疾患データベースに移行すれば、採取日や採取時の患者の状況、検体が今まで何度採取されているのかなどの情報と、生体試料保存場所の情報が得られるようにする。これにより、患者検体を用いた病態の解明と治療法の確立に寄与することを目的として研究を行った。

B. 研究方法

現在のPIDJに含まれる免疫不全症検体歴データベースは、検体種類と採取日、保管場所について入力できるフォーマットであり、コメントで検体保管場所詳細や採取時の病期・病状、一般検査値(CRP値等)について記載可能である。複数回の採血などの生体試料についてもそれぞれ情報が記載できる。

PIDJに登録されている現在までの自己炎症疾患検体のデータを、この免疫不全症検体歴データベースから、自己炎症疾患データベースに移行する方法を、自己炎症疾患データベースに検体歴データベースを作成することにより可能であるか検討した。またデータ移行の方法についてもセキュリティの観点から最も安全な方法を検討した。さらに、自己炎症疾患データベースの情報をPIDJに移行する、双方向のデータ移行の方法を検討した。

(倫理面への配慮)

データは匿名化して取り扱う。臨床研究、遺伝子解析、PIDJ、自己炎症疾患データベースへの登録に関しては、本人ないし親権者からの同意書を得た。また、本研究は、小児感染症学会、防衛医大、理化学研究所、かずさDNA研究所で倫理委員会を通っている。

C. 研究結果

自己炎症疾患データベースに検体登録システムを構築することは、PIDJと同じ形式とすることで技術的には可能であることが判明した

現在までにPIDJに登録してある検体データのうち、自己炎症データベース登録患者分をコピーして移行することも可能であることが判明した。

PIDJと自己炎症疾患データベースの検体登録システム上のデータを補完しあう事については、PIDJと自己炎症データベースを常時つなげておくと、万一どちらかのデータベースにサイバーアタックが起きて侵入されたとき、２つのデータベースが同時に破壊、侵入を許すことになってしまうため、物理的には切り離した状況とし、定期的(例：１年毎)にPIDJと自己炎症疾患データベースの検体登録システム上のデータを可搬媒体などにより、双方向でデータ移行し、補完しあうこととした。定期的に自己炎症のデータベースとPIDJのデータベー

スの検体データの補完を行い、双方向でデータを共有し合うような形にできれば、検体情報の登録漏れを予防し、免疫不全症の中の自己炎症疾患の位置づけを確認できる。

なお、セキュリティは非常に高度になっているため、PIDJ９年間の運用でサイバーアタックで情報流出したことはない。しかし、セキュリティを出来るだけ確保するためにこの方式にした。

D. 考察

自己炎症疾患データベースに登録されている自己炎症疾患のデータとPIDJに登録されている自己炎症疾患のデータを、双方向に移行する方法を考案した。

この利点として、いくつかあげられる。下記に記す。

すでに活用されているシステムをそのまま移行するので、新たにシステムを構築する必要がない。

また、PIDJを入り口とすることで、患者データの脱落を予防できる。

IUIS分類では、自己炎症疾患は免疫不全症のカテゴリの１つであり、PIDJの情報と自己炎症疾患データベースの情報を共有することは、原発性免疫不全症の中の自己炎症疾患の国内での頻度を知ることが可能になる。

PIDJの中の検体歴データベースを利用すれば、患者検体保存の有無、採取回数、生体試料の保存場所、検体の種類や、生体試料採取時の患者状況や、診断、治療反応性についても情報を得ることができる。

追記が可能な形式なので、最新の患者情報への更新が容易である。

情報の共有、経時的なデータ収集、主治医に連絡してWEBベースで入力してもらうことが可能であり、データベース管理者の負担を少なく情報を蓄積できる。

欠点としては、実際のシステム移行作業にかかる時間・人件費・コストがかかることが問題となるが、PIDJですでに構築されたシステムであり新たなシステム構築を行う必要が無く、負担は少ないと考えられる。

また、自己炎症疾患の病態解析に必要な情報を収集するためには、この検体データベース形式では不足している可能性がある。これについては、自己炎症疾患データベースに特化した詳細なデータを自己炎症疾患データベースに入力してもらい、それをPIDJの閲覧権限を持っている研究者が、情報を入手できることにすれば問題は解決出来る。実際に、現時点で、自己炎症疾患データベースはPIDJの２階部分という構成になっており、PIDJの閲覧権限がある研究者は自己炎症疾患データベースの閲覧権限がある設定にしてある。

ただし、PIDJ-IDの入力がなされていない患者データは移行に工夫が必要である。PIDJ患者IDと自己炎症疾患患者IDが連結可能なので、双方向にデータ移行するでき、これにより患者入力漏れは解消できる。

こうしたデータベースを活用することにより、自己炎症疾患の病態解明について有用である。

PIDJに登録されている現在までの自己炎症疾患検体のデータを自己炎症疾

患データベースに移行することができれば、自己炎症性疾患の病態解析と治療法確立のために有用である。

E. 結論

PIDJ システムを活用することで、自己炎症性疾患検体情報および保存場所が WEB で容易に把握できるデータベースシステムが確立できる。自己炎症性疾患の病態と治療法解明に必要とする患者サンプルを入手するため、より利便性が高いシステムであると考えられる。

F. 研究危険情報

特になし。

G. 研究発表

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

学会等発表実績一覧表

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中條-西村症候群患者血中サイトカインの経時的解析（口頭発表）	金澤伸雄、中谷友美、稲葉　豊、国本佳代、古川福実	第438回日本皮膚科学会京滋地方会（京都）	2014.12.19	国内
新生児期発症の中條-西村症侯群様症状を呈した男児例（口頭発表）	金城紀子、中矢代真美、金澤伸雄、三嶋博之、木下晃、吉浦孝一郎	第8回日本免疫不全症研究会学術集会（東京）	2015.1.24	国内
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「インフラマソームとデンジャーシグナル」インフラマソームの自発的活性化を病態とする自己炎症症候群（口頭発表）	神戸直智	日本アレルギー学会第1回総合アレルギー講習会）	2014.12.20-21	国内
"HIGH-THROUGHPUT SINGLE-CELL SECRETION MESUREMENT ON AN OPTICAL WAVEGUDE CHIP"（ポスター）	Yoshitaka Shirasaki, Nobutake Suzuki, Mai Yamagishi, Asahi Nakahara, Shuichi Shoji, and Osamu Ohara	The 18th International Conference on Miniaturized Systems for Chemistry and Life Sciences	2014.10.26-30	国外
"１細胞分泌実時間測定によるIL-1β非古典的分泌機序の解明"（ポスター）	白崎善隆、劉霆、山口良文、山岸舞、鈴木信勇、井澤和司、水野潤、庄子習一、原田慶恵、西小森隆太、平家俊男、三浦正幸、小原收	第52回日本生物物理学会年会	2014.9.25-27	国内
"Time-resolved live-cell FluoroSpot assay on Total Internal Reflection Fluorescence Microscopy"(口頭発表)	Yoshitaka Shirasaki, Nobutake Suzuki, Mai Yamagishi, Osamu Ohara	EMBL Conference Series Microfluidics 2014	2014.7.23-25	国外
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Aicardi-Goutières syndrome is caused by *IFIH1* mutations	Hirotsugu Oda, Kenji Nakagawa, Junya Abe, Tomonari Awaya, Masahide Funabiki, Atsushi Hijikata, Ryuta Nishikomori, Makoto Funatsuka, Yusei Ohshima, Yuji Sugawara, Takahiro Yasumi, Hiroki Kato, Tsuyoshi Shirai, Osamu Ohara, Takashi Fujita, and Toshio Heike	American Society of Human Genetics	2014.10.19	国外
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臨床研究のための疾患遺伝子解析パイプラインの構築（口頭発表）	小原收	第59回日本人類遺伝学会	2014.11.20	国内
iPS細胞技術を介したNKT細胞療法の開発（口頭発表）	古関明彦	第35回日本炎症・再生医学会	2014.7.3	国内
Association between primary immunodeficiency diseases and vasculitis syndrome.（口頭発表＋ポスター）	Hara T, Ishimura M, Takada H, Kusuda Y, Nakashima Y, Murata K, Kanno S, Nishio H	16th Biennial Meeting of the European Society for Immunodeficiencies	2014.10.29-11.1	国外
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疾患特異的iPS細胞を用いた 免疫疾患の解析について（口頭発表）	齋藤潤	大阪リウマチカンファレンス	2014.4.19	国内
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再生医療用iPS細胞ストックの ドナーリクルートについて（口頭発表）	齋藤潤	日本臓器保存生物医学会	2014.11.28	国内
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学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名（連名の場合、全員の氏名を記入して下さい）	発表した場所（学会誌・雑誌等名）	発表した時期	国内・外の別
自己炎症性疾患の新展開（総説）	西小森隆太、中川権史、粟屋美絵、河合朋樹、八角高裕、平家俊男	臨床リウマチ	26巻2号Page79-87	国内
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Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency

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We report the updated classification of primary immunodeficiencies (PIDs) compiled by the Expert Committee of the International Union of Immunological Societies. In comparison to the previous version, more than 30 new gene defects are reported in this updated version. In addition, we have added a table of acquired defects that are phenocopies of PIDs. For each disorder, the key clinical and laboratory features are provided. This classification is the most up-to-date catalog of all known PIDs and acts as a current reference of the knowledge of these conditions and is an important aid for the molecular diagnosis of patients with these rare diseases.

Keywords: primary immunodeficiencies, IUIS, classification, genetic defects, genotype

BACKGROUND

The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency met in New York on 19th–21st April 2013 to update the classification of human primary immunodeficiencies (PIDs). This report represents the most current and complete catalog of known PIDs. It serves as a reference for these conditions and provides a framework to help in the diagnostic approach to patients suspected to have PID.

As in previous reports, we have classified the conditions into major groups of PIDs and these are now represented in nine different tables. In each table, we list the condition, its genetic defect if known, and the major immunological and in some conditions the non-immunological abnormalities associated with the disease. The classification this year differs slightly from the previous edition in that **Table 1** lists combined immunodeficiencies without non-immunologic phenotypes, whereas **Table 2** refers to combined

Table 1 | Combined immunodeficiencies.

Disease	Genetic defect/ presumed pathogenesis	Inheritance	Circulating T cells	Circulating B cells	Serum Ig	Associated features	OMIM number
1. T^-B^+ severe combined immunodeficiency (SCID)							
(a) γc deficiency	Mutation of *IL-2RG* Defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21	XL	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells	300400
(b) JAK3 deficiency	Mutation of *JAK3* Defect in Janus-activating kinase 3	AR	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells	600173
(c) IL7Rα deficiency	Mutation of *IL7RA* Defect in IL-7 receptor α chain	AR	Markedly decreased	Normal or increased	Decreased	Normal NK cells	146661
(d) CD45 deficiency[a]	Mutation of *PTPRC* Defect in CD45	AR	Markedly decreased	Normal	Decreased	Normal γ/δ T cells	151460
(e) CD3δ deficiency	Mutation of *CD3D* Defect in CD3δ chain of T cell antigen receptor complex	AR	Markedly decreased	Normal	Decreased	Normal NK cells No γ/δ T cells	186790
(f) CD3ε deficiency[a]	Mutation of *CD3E* Defect in CD3ε chain of T cell antigen receptor complex	AR	Markedly decreased	Normal	Decreased	Normal NK cells No γ/δ T cells	186830
(g) CD3ζ deficiency[a]	Mutation of *CD3Z* Defect in CD3ζ chain of T cell antigen receptor complex	AR	Markedly decreased	Normal	Decreased	Normal NK cells No γ/δ T cells	186740
(h) Coronin-1A deficiency[a]	Mutation of *CORO1A* defective thymic egress of T cells and defective T cell locomotion	AR	Markedly decreased	Normal	Decreased	Detectable thymus EBV associated B cell lymphoproliferation	605000
2. T^-B^- SCID							
(i) DNA recombination defects							
(a) RAG 1 deficiency	Mutation of *RAG1* Defective VDJ recombination; defect of recombinase activating gene (RAG) 1	AR	Markedly decreased	Markedly decreased	Decreased		601457
(a) RAG 2 deficiency	Mutation of *RAG2* Defective VDJ recombination; defect of recombinase activating gene (RAG) 2	AR	Markedly decreased	Markedly decreased	Decreased		601457
(b) DCLRE1C (artemis) deficiency	Mutation of *ARTEMIS* Defective VDJ recombination; defect in artemis DNA recombinase repair protein	AR	Markedly decreased	Markedly decreased	Decreased	Radiation sensitivity	602450
(c) DNA PKcs deficiency[a]	Mutation of *PRKDC*- Defective VDJ recombination; defect in DNA PKcs Recombinase repair protein	AR	Markedly decreased	Markedly decreased	Decreased	Radiation sensitivity, microcephaly, and developmental defects	600899
(ii) Reticular dysgenesis, AK2 deficiency	Mutation of *AK2* Defective maturation of lymphoid and myeloid cells (stem cell defect) Defect in mitochondrial adenylate kinase 2	AR	Markedly decreased	Decreased or normal	Decreased	Granulocytopenia and deafness	103020

(Continued)

Table 1 | Continued

Disease	Genetic defect/ presumed pathogenesis	Inheritance	Circulating T cells	Circulating B cells	Serum Ig	Associated features	OMIM number
(iii) Adenosine deaminase (ADA) deficiency	Mutation of ADA absent *ADA* activity, elevated lymphotoxic metabolites (dATP, *S*-adenosyl homocysteine)	AR	Absent from birth (null mutations) or progressive decrease	Absent from birth of progressive decrease	Progressive decrease	Decreased NK cells, often with costochondral junction flaring, neurological features, hearing impairment, lung and liver manifestations; partial ADA deficiency may lead to delayed or milder presentation	102700
Combined immunodeficiencies generally less profound than severe combined immunodeficiency							
3. CD40 ligand deficiency	Mutation of *CD40LG* defects in CD40 ligand (CD40L; also called TNFSF5 or CD154) cause defective isotype switching and impaired dendritic cell signaling	XL	Normal; may progressively decrease	$sIgM^+$ and $sIgD^+$ B cells present, other surface isotype positive B cells absent	IgM increased or normal, other isotypes decreased	Neutropenia, thrombocytopenia; hemolytic anemia, biliary tract and liver disease, opportunistic infections	300386
4. CD40 deficiency[a]	Mutation of *CD40* (also called TNFRSF5) defects in CD40 cause defective isotype switching and impaired dendritic cell signaling	AR	Normal	IgM^+ and IgD^+ B cells present, other isotypes absent	IgM increased or normal, other isotypes decreased	Neutropenia, gastrointestinal and liver/biliary tract disease, opportunistic infections	109535
5. Purine nucleoside phosphorylase (PNP) deficiency	Mutation of *PNP*, absent PNP, and T cell and neurologic defects from elevated toxic metabolites, especially dGTP	AR	Progressive decrease	Normal	Normal or decreased	Autoimmune hemolytic anemia, neurological impairment	164050
6. CD3γ deficiency[a]	Mutation of *CD3G* defect in CD3 γ – component of the T cell antigen receptor complex	AR	Normal, but reduced TCR expression	Normal	Normal		186740
7. CD8 deficiency[a]	Mutation of *CD8A*, defects of CD8 α chain – important for maturation and function of CD8 T cells	AR	Absent CD8, normal CD4 cells	Normal	Normal		186910
8. ZAP70 deficiency	Mutation in ZAP70 intracellular signaling kinase, acts downstream of TCR	AR	Decreased CD8, normal CD4 cells	Normal	Normal	Autoimmunity in some cases	269840
9. MHC class I deficiency	Mutations in *TAP1, TAP2*, or *TAPBP* (tapasin) genes giving MHC class I deficiency	AR	Decreased CD8, normal CD4	Normal	Normal	Vasculitis; pyoderma gangrenosum	604571
10. MHC class II deficiency	Mutation in transcription factors for MHC class II proteins (*CIITA, RFX5, RFXAP, RFXANK* genes)	AR	Normal number, decreased CD4 cells	Normal	Normal or decreased	Failure to thrive, diarrhea, respiratory tract infections, liver/biliary tract disease	209920
11. ITK deficiency[a]	Mutations in *ITK* encoding IL-2-inducible T cell kinase required for TCR-mediated activation	AR	Progressive decrease	Normal	Normal or decreased	EBV-associated B cell lymphoproliferation, lymphoma Normal or decreased IgG	613011

(Continued)

Table 1 | Continued

Disease	Genetic defect/ presumed pathogenesis	Inheritance	Circulating T cells	Circulating B cells	Serum Ig	Associated features	OMIM number
12. SH2D1A deficiency (XLP1)	Mutations in *SH2D1A* encoding an adaptor protein regulating intracellular signals	XL	Normal or increased activated T cells	Reduced memory B cells	Partially defective NK cell and CTL cytotoxic activity	Clinical and immunologic features triggered by EBV infection: HLH, lymphoproliferation, aplastic anemia, lymphoma Hypogamma globulinemia Absent iNKT cells	308240
13. Cartilage hair hypoplasia	Mutations in *RMRP* (RNase MRP RNA) involved in processing of mitochondrial RNA and cell cycle control	AR	Varies from severely decreased (SCID) to normal; impaired lymphocyte proliferation	Normal	Normal or reduced. antibodies variably decreased	Can present just as combined immunodeficiency without other features of short-limbed dwarfism Also see **Table 2**	250250
14. MAGT1 deficiency[a]	Mutations in *MAGT1*, impaired Mg^{++} flux leading to impaired TCR signaling	XL	Decreased CD4 cells reduced numbers of RTE, impaired T cell proliferation in response to CD3	Normal	Normal	EBV infection, lymphoma; viral infections, respiratory, and GI infections	300715
15. DOCK8 deficiency	Mutations in *DOCK8* – regulator of intracellular actin reorganization	AR	Decreased impaired T lymphocyte proliferation	Decreased, low CD27+ memory B cells	Low IgM, increased IgE	Low NK cells with impaired function, hypereosinophilia, recurrent infections; severe atopy, extensive cutaneous viral and bacterial (staph.) infections, susceptibility to cancer	243700
16. RhoH deficiency[a]	Mutations in *RHOH* – an atypical Rho GTPase transducing signals downstream of various membrane receptors	AR	Normal Low naïve T cells and RTE, restricted T cell repertoire and impaired T cells proliferation in response to CD3 stimulation	Normal	Normal	HPV infection, lymphoma, lung granulomas, molluscum contagiosum	602037
17. MST1 deficiency	Mutations in *STK4* – a serine/threonine kinase	AR	Decreased/increased proportion of terminal differentiated effector memory cells (TEMRA), low naïve T cells, restricted T cell repertoire in the TEMRA population, and impaired T cells proliferation	Decreased	High	Recurrent bacterial, viral, and candidal infections; intermittent neutropenia; EBV-driven lymphoproliferation; lymphoma; congenital heart disease, autoimmune cytopenias; HPV infection	614868

(Continued)

Table 1 | Continued

Disease	Genetic defect/ presumed pathogenesis	Inheritance	Circulating T cells	Circulating B cells	Serum Ig	Associated features	OMIM number
18. TCRα deficiency[a]	Mutations in *TRAC* – essential component of the T cell receptor	AR	Normal all CD3 T cells expressed TCRγδ (or may be better to say: TCRαβ T cell deficiency), impaired T cells proliferation	Normal	Normal	Recurrent viral, bacterial, and fungal infections, immune dysregulation autoimmunity, and diarrhea	615387
19. LCK deficiency[a]	Defects in *LCK* – a proximal tyrosine kinase that interacts with TCR	AR	Normal total numbers but CD4+ T cell lymphopenia, low Treg numbers, restricted T cell repertoire, and impaired TCR signaling	Normal	Normal IgG and IgA and increased IgM	Diarrhea, recurrent infections, immune dysregulation autoimmunity	153390
20. MALT1 deficiency[a]	Mutations in *MALT1* – a caspase-like cysteine protease that is essential for nuclear factor kappa B activation	AR	Normal impaired T cells proliferation	Normal	Normal Impaired antibody response	Bacterial, fungal, and viral infections	604860
21. IL-21R deficiency[a]	Defects in *IL-21R* – together with common gamma chain binds IL-21	AR	Abnormal T cell cytokine production; abnormal T cell proliferation to specific stimuli	Normal	Normal but impaired specific responses	Susceptibility to cryptosporidium and pneumocystis and cholangitis	605383
22. UNC119 deficiency[a]	Defects in *UNC119* – an activator of src tyrosine kinases	AD	Low T cells CD4+ T cell lymphopenia, impaired TCR signaling	Mostly low	Normal	Recurrent bacterial, fungal, and viral infections	604011
23. CARD11 deficiency[a]	Defects in *CARD11* – acts as a scaffold for NF-κB activity in the adaptive immune response	AR	Normal predominance of naive T lymphocyte, impaired T cells proliferation	Normal predominance of transitional B lymphocytes	Absent/low	*Pneumocystis jiroveci* pneumonia, bacterial infections	615206
24. OX40 deficiency[a]	Defects in *OX40* – a co-stimulatory molecule expressed on activated T cells	AR	Normal T cell numbers Low levels of antigen-specific memory CD4+ cells	Normal B cell numbers Lower frequency of memory B cells	Normal	Kaposi's sarcoma; impaired immunity to HHV8	615593
25. IKBKB deficiency[a]	Defects in *IKBKB* – encodes IkB kinase 2 a component of the NF-κB pathway	AR	Normal total T cells; absent regulatory and gd T cells; impaired TCR activation	Normal B cell numbers; impaired BCR activation	Decreased	Recurrent bacterial, viral, and fungal infections; clinical phenotype of SCID	615592
26. Activated PI3K-δ	Mutation in *PIK3CD*, PI3K-δ	AD gain-of-function	Decreased total numbers of T cells	Decreased total peripheral B cell and switched memory B cells; increased transitional B cells	Reduced IgG2 and impaired antibody to pneumococci and hemophilus	Respiratory infections, bronchiectasis; autoimmunity; chronic EBV, and CMV infection	602839

(Continued)

Table 1 | Continued

Disease	Genetic defect/ presumed pathogenesis	Inheritance	Circulating T cells	Circulating B cells	Serum Ig	Associated features	OMIM number
27. LRBA deficiency	Mutations in *LRBA* (lipopolysaccharide responsive beige-like anchor protein)	AR	Normal or decreased CD4 numbers; T cell dysregulation	Low or normal numbers of B cells	Reduced I IgG and IgA in most	Recurrent infections, inflammatory bowel disease, autoimmunity; EBV infections	606453
28. CD27 deficiency[a]	Mutations in *CD27*, encoding TNF-R member superfamily required for generation and long-term maintenance of T cell immunity	AR	Normal	No memory B cells	Hypogamma globulinemia following EBV infection	Clinical and immunologic features triggered by EBV infection, HLH Aplastic anemia, lymphoma Hypogammaglobulinemia Low iNKT cells	615122
29. Omenn syndrome	Hypomorphic mutations in *RAG1, RAG2, artemis, IL7RA, RMRP, ADA, DNA ligase IV, IL-2RG, AK2*, or associated with DiGeorge syndrome; some cases have no defined gene mutation		Present; restricted T cell repertoire, and impaired function	Normal or decreased	Decreased, except increased IgE	Erythroderma, eosinophilia, adenopathies, hepatosplenomegaly	603554

XL, X-linked inheritance; AR, autosomal recessive inheritance; AD, autosomal dominant inheritance; SCID, severe combined immune deficiencies; EBV, Epstein–Barr virus; Ca^{++}, calcium; MHC, major histocompatibility complex, RTE, recent thymic emigrants, HPV, human papillomavirus.

[a]*Ten or fewer unrelated cases reported in the literature.*

Infants with SCID who have maternal T cells engraftment may have T cells that do not function normally; these cells may cause autoimmune cytopenias or graft versus host disease. Hypomorphic mutations in several of the genes that cause SCID may result in Omenn syndrome (OS), or "leaky" SCID or a less profound CID phenotype. Both OS and leaky SCID can be associated with higher numbers of T cells and reduced rather than absent activation responses when compared with typical SCID caused by null mutations. A spectrum of clinical findings including typical SCID, OS, leaky SCID, granulomas with T lymphopenia, autoimmunity, and CD4+ T lymphopenia can be found with RAG gene defects. RAC2 deficiency is a disorder of leukocyte motility and is reported in ***Table 5****; however, one patient with RAC2 deficiency was found to have absent T cell receptor excision circles (TRECs) by newborn screening, but T cell numbers and mitogen responses were not impaired. For additional syndromic conditions with T cell lymphopenia, such as DNA repair defects, cartilage hair hypoplasia, IKAROS deficiency, and NEMO syndrome, see* ***Tables 2*** *and* ***6****; however, it should be noted that individuals with the most severe manifestations of these disorders could have clinical signs and symptoms of SCID. Severe folate deficiency (such as with malabsorption due to defects in folate carrier or transporter genes SLC10A1 or PCFT) and some metabolic disorders, such as methylmalonic aciduria, may present with reversible profound lymphopenia in addition to their characteristic presenting features.*

immunodeficiencies with syndromic features, as increasing numbers of these are being identified. The title and classification of **Tables 3–8** present the same major PID groups as in the previous report.

In this updated version, we have added a new category in **Table 9** in which "Phenocopies of PID" are listed. This has resulted from our understanding and study of conditions that present as inherited immunodeficiencies, but which are not due to germline mutations and instead arise from acquired mechanisms. Examples include somatic mutations in specific immune cell populations that give rise to the phenotype of autoimmune lymphoproliferative syndrome (ALPS), and also autoantibodies against specific cytokines or immunological factors, with depletion of these factors leading to immunodeficiency. It is likely that increasing numbers of PID phenocopies will be identified in the future, and this may be the start of a much longer table.

As with all complex diseases, any classification cannot be strictly adhered to. Certain conditions fall into more than one category and so appear in more than one table. For example, CD40L ligand deficiency is reported in both **Tables 1** and **3** as it was initially identified as a defect of B cell isotype switching but is now known to be a defect of co-stimulatory T cell help and function. Similarly, XLP1 due to defects in SH2D1A is listed in **Table 1** – combined immunodeficiencies, due to defects of T cell cytotoxicity, T cell help, and B cell maturation, but also in **Table 4** – diseases of immune dysregulation, due to the susceptibility to hemophagocytosis. There is a growing appreciation that there can be wide phenotypic viability within a specific genotype that is a product of varied specific mutations between different patients as well as other host and/or environmental factors. The complexities of these conditions in terms of clinical and immunological presentation and heterogeneity cannot be easily captured in the limited space of a table format. For this reason, the furthest left column contains the Online Mendelian Inheritance in Man (OMIM) reference for each condition to allow access to greater detail and updated information.

Table 2 | Combined immunodeficiencies with associated or syndromic features.

Disease	Genetic defect/ presumed pathogenesis	Inheritance	Circulating T cells	Circulating B cells	Serum Ig	Associated features	OMIM number
1. Congenital thrombocytopenia							
(a) Wiskott–Aldrich syndrome (WAS)	Mutations in *WAS*; cytoskeletal, and immunologic synapse defect affecting hematopoietic stem cell derivatives	XL	Progressive decrease, abnormal lymphocyte responses to anti-CD3	Normal	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE	Thrombocytopenia with small platelets; eczema; lymphoma; autoimmune disease; IgA nephropathy; bacterial and viral infections. XL thrombocytopenia is a mild form of WAS, and XL neutropenia is caused by missense mutations in the GTPase binding domain of WASP	301000
(b) WIP deficiency[a]	Mutations in *WIPF1*; cytoskeletal and immunologic synapse defect affecting hematopoietic stem cell derivatives	AR	Reduced, defective lymphocyte responses to anti-CD3	Low	Normal, except for increased IgE	Recurrent infections; eczema; thrombocytopenia. WAS-*like* phenotype	614493
2. DNA repair defects (other than those in **Table 1**)							
(a) Ataxia–telangiectasia	Mutations in *ATM*; disorder of cell cycle checkpoint; and DNA double-strand break repair	AR	Progressive decrease	Normal	Often decreased IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased	Ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased alpha fetoprotein and increased radiosensitivity; chromosomal instability	208900
(b) Ataxia–telangiectasia-like disease (ATLD)[a]	Hypomorphic mutations in *MRE11*; disorder of cell cycle checkpoint and DNA double-strand break repair	AR	Progressive decrease	Normal	Antibodies variably decreased	Moderate ataxia; pulmonary infections; severely increased radiosensitivity	604391
(c) Nijmegen breakage syndrome	Hypomorphic mutations in *NBS1 (Nibrin)*; disorder of cell cycle checkpoint and DNA double-strand break repair	AR	Progressive decrease	Variably reduced	Often decreased IgA, IgE, and IgG subclasses; increased IgM; antibodies variably decreased	Microcephaly; bird-like face; lymphomas; solid tumors; increased radiosensitivity; chromosomal instability	251260
(d) Bloom syndrome	Mutations in *BLM*; RecQ-like helicase	AR	Normal	Normal	Reduced	Short stature; bird-like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability	210900

(Continued)

Table 2 | Continued

Disease	Genetic defect/ presumed pathogenesis	Inheritance	Circulating T cells	Circulating B cells	Serum Ig	Associated features	OMIM number
(e) Immunodeficiency with centromeric instability and facial anomalies (ICF)	Mutations in DNA methyltransferase *DNMT3B* (ICF1) resulting in defective DNA methylation	AR	Decreased or normal; responses to PHA may be decreased	Decreased or normal	Hypogamma globulinemia; variable antibody deficiency	Facial dysmorphic features; macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multiradial configurations of chromosomes 1, 9, 16; no DNA breaks	242860
(f) Immunodeficiency with centromeric instability and facial anomalies (ICF)	Mutations in *ZBTB24* (ICF2)	AR	Decreased or normal; responses to PHA may be decreased	Decreased or normal	Hypogamma globulinemia; variable antibody deficiency	Facial dysmorphic features; macroglossia; bacterial/opportunistic infections; malabsorption; cytopenias; malignancies; multiradial configurations of chromosomes 1, 9, 16	242860
(g) PMS2 deficiency	Mutations in *PMS2*, resulting in class switch recombination deficiency due to impaired mismatch repair	AR	Normal	Switched and non-switched B cells are reduced	Low IgG and IgA, elevated IgM, abnormal antibody responses	Recurrent infections; café-au-lait spots; lymphoma, colorectal carcinoma, brain tumor	600259
(h) RNF168 deficiency[a]	Mutations in *RNF168*, resulting in defective DNA double-strand break repair	AR	Normal	Normal	Low IgG or low IgA	Short stature; mild motor control to ataxia and normal intelligence to learning difficulties; mild facial dysmorphism to microcephaly; increased radiosensitivity	611943
(i) MCM4 deficiency	Mutations in *MCM4* (minichromosome maintenance complex component 4) gene involved in DNA replication and repair	AR	Normal	Normal	Normal	Viral infections (EBV, HSV, VZV) Adrenal failure Short stature	609981
3. Thymic defects with additional congenital anomalies							
(a) DiGeorge anomaly	Contiguous gene defect in 90% affecting thymic development; may also be due to heterozygous mutation in *TBX1* (chromosome 22q11.2 deletion or TBX1 haploinsufficient syndrome)	*De novo* defect (majority) or AD	Decreased or normal; 5% have <1500 CD3 T cells/μL	Normal	Normal or decreased	Hypoparathyroidism, conotruncal malformation; abnormal facies; large deletion (3 Mb) in 22q11.2 (or rarely a deletion in 10p)	188400

(Continued)

Table 2 | Continued

Disease	Genetic defect/ presumed pathogenesis	Inheritance	Circulating T cells	Circulating B cells	Serum Ig	Associated features	OMIM number
(b) CHARGE syndrome	Variable defects of the thymus and associated T cell abnormalities often due to deletions or mutations in *CHD7, SEMA3E*, or as yet unknown genes	*De novo* defect (majority) or AD	Decreased or normal; some have <1500 CD3 T cells/μL	Normal	Normal or decreased	Coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies	214800 608892
4. Immune-osseous dysplasias							
(a) Cartilage hair hypoplasia	Mutations in *RMRP* (RNase MRP RNA) involved in processing of mitochondrial RNA and cell cycle control	AR	Varies from severely decreased (SCID) to normal; impaired lymphocyte proliferation	Normal	Normal or reduced. Antibodies variably decreased	Short-limbed dwarfism with metaphyseal dysostosis, sparse hair, bone marrow failure, autoimmunity, susceptibility to lymphoma and other cancers, impaired spermatogenesis, neuronal dysplasia of the intestine	250250
(b) Schimke syndrome	Mutations in *SMARCAL1* involved in chromatin remodeling	AR	Decreased	Normal	Normal	Short stature, spondiloepiphyseal dysplasia, intrauterine growth retardation, nephropathy; bacterial, viral, and fungal infections; may present as SCID; bone marrow failure	242900
5. Hyper-IgE syndromes (HIES)							
(a) AD-HIES (Job's syndrome)	Dominant-negative heterozygous mutations in *STAT3*	AD Often *de novo* defect	Normal Th-17 and T follicular helper cells decreased	Normal Switched and non-switched memory B cells are reduced; BAFF level increased	Elevated IgE; specific antibody production decreased	Distinctive facial features (broad nasal bridge), eczema, osteoporosis, and fractures, scoliosis, delay of shedding primary teeth, hyperextensible joints, bacterial infections (skin and pulmonary abscesses, pneumatoceles) due to *Staphylococcus aureus*, candidiasis, aneurysm formation	147060
(i) Tyk2 deficiency[a]	Mutation in *TYK2*	AR	Normal, but multiple cytokine signaling defect	Normal	(±) Elevated IgE	Susceptibility to intracellular bacteria (*Mycobacteria, Salmonella*), fungi, and viruses	611521

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