アセント（7歳〜12歳）
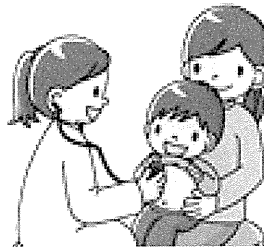
　この　はなしを　よくきいて、「Pierホームページ」を　つかってもいいか　おとうさん　や　おかあさん　と　よくかんがえて　ください。

2.　どんなことをするの？

　＜「Pierホームページ」には　こんなことを　かきます＞

　・あたまや　おなかが　いたい、　きもちがわるい、　ごはんをたべたくない。　そんなとき、「Pierホームページ」に　そのことを　かきます。
おかあさんや　おとうさん、おうちの人に、書いて　もらいましょう。

　・びょういん　に　いったときは、いついったのか、なにをされたのか　を
かきましょう。たとえば、血のけんさ、おしっこのけんさ、レントゲン、先生
に　しんさつ　してもらったときです。

びょういん　で　しんさつ　を　してもらったとき　かきこみます

それらの結果を、おかあさんや、おとうさん、おうちの人に　てつだって　もらいながら、「Pierホームページ」に書いて　もらいましょう。
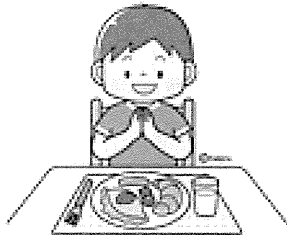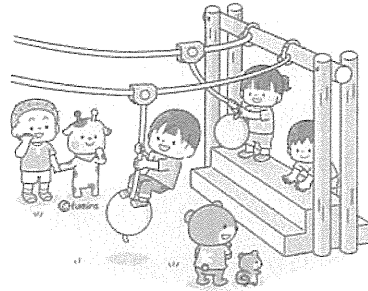

おうちの　人と　いっしょに　かこう

アセント（7歳〜12歳）

3. どんなときにやくにたつの？

先生が ホームページ「Pier」を みることで、しんさつ や ちりょう が
しやすくなります。あなたが げんきになる てだすけをします。

ごはん が おいしい

げんきに あそべる

4. しんぱいなときはそうだんしましょう

あなたや おうちの人が かきこんだ ないよう は、Pierにかきこんでいな
い人や、病院の先生じゃない人は、見ることができないので、あんしん し
てください。
先生や おかあさん、おとうさん、おうちのひとに そうだん して 「Pierホ
ームページ」に かきこむか きめましょう。
とちゅうで、やめることも できます。

Pier

御担当先生　御侍史

拝啓

　時下　益々ご清祥のこととお慶び申し上げます。

　私ども平成24年度厚生労働科学研究費補助金（難治性疾患等克服研究事業）「原発性免疫不全症候群患者支援団体による患者レジストリの構築を通した研究支援体制の構築に関わる研究」班（代表研究者；今井耕輔）では、原発性免疫不全症（PID）患者支援団体 NPO 法人 PID つばさの会により個人電子医療記録機能を持つ患者レジストリ Pier を構築し、患者背景、病歴、治療経過に関する情報収集、分析し、一般医師および PID 専門医によって構築された PIDJ データベースとそれをハブにした PIDJ ネットワークに提供することで、研究を加速し、より効果的な診療に役立て、患者の予後を改善することを目的として研究して参りました。Pier は、患者が電子医療記録としても用いることができ、毎日の体調管理を行えるサイトです。

　しかし、Pier および PIDJ データベースは周知が不十分なこともあり、登録件数が十分ではないことも現実です。

　本研究では、多くの先生方および未診断の患者さんに、PID について知って頂き、PIDJ ネットワークを介した診断から、Pier を用いた QOL の向上につなげたいと考えております。

　そこで、2013年4月22日〜29日が World PI Week（国際先天性免疫不全症週間）であることから、この期間により多くの方に PID について知って頂くためのポスターを作成致しました。外来待合室や医局などに掲示して頂けましたら幸いです。

なお、日本では、PID つばさの会の総会が4月28日に東京医科歯科大学にて行われます。

詳しくは、下記ホームページをご参照いただければ幸いです。

　Pier ホームページ：http://pier.kazusa.or.jp/pier/jsp/

　PID つばさの会ホームページ：http://npo-pidtsubasa.org

　PIDJ ホームページ：http://pidj.rcai.riken.jp

　　　　　　　　　　　　　　　　　　（pier 事務局連絡先：03-5803-4705）

お忙しい中、大変恐縮ではございますが、ご協力のほど宜しくお願い申し上げます。

　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　敬具

　　　平成25月3月吉日

　　　　　　　研究代表者：今井　耕輔

　　　　　　　（東京医科歯科大学　大学院歯学総合研究科　小児・周産期地域医療学

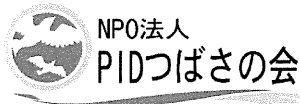　　　　　　　NPO 法人　PID つばさの会理事，Pier 事務局）

国際先天性免疫不全症週間
www.worldpiweek.org
2013 4/22▸29

World PI Week

Test. Diagnose. Treat.

先天性免疫不全症(PID)をご存じですか？
PIDについて知ることで
早期診断と適切な治療につなげましょう！

Test!
Diagnose!
Treat!

NPO法人
PIDつばさの会

Pier

PIDJ

(:) 厚生労働省
Ministry of Health, Labour and Welfare

- 先天性免疫不全症(PID)は、生まれつき免疫系に障害があるために、中耳炎、肺炎、皮膚膿瘍、腸炎などの感染症にかかりやすくなる疾患です。
- 感染症は、しばしば慢性、持続性、反復性であり、重症化し、生命に関わることもあります。こどもだけではなく、おとなになって、はじめて診断される人も少なくありません。
- 国際先天性免疫不全症週間には、医療関係者、教育関係者、保護者のみなさん、そして政府や行政に、この疾患を知ってもらい、患者さんたちに必要な援助を得るための様々なイベントが世界中で企画されています。
- 日本では、患者支援団体であるNPO法人PIDつばさの会が参加しています。
- また、厚生労働省助成金により、一般医の相談サイトであるPIDJ、患者のための電子医療ノートPier：primary immunodeficiency electronic recordも稼働中です。
- 詳しくはwebで→　http://npo-pidtsubasa.org　または　http://pidj.rcai.riken.jp

ASID　CI Society www.cisociety.com　CIS Clinical Immunology Society　EFIS European Federation of Immunological Societies　ESiD　IMMUNE DEFICIENCY FOUNDATION　INGID　IPOPI　jm Jeffrey Modell Foundation　LASID　PPTA Plasma Protein Therapeutics Association

Ⅴ．研究成果の刊行に関する一覧

雑誌

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Letter to the Editor

Common variable immunodeficiency classification by quantifying T-cell receptor and immunoglobulin κ-deleting recombination excision circles

To the Editor:

Common variable immunodeficiency (CVID) is the most frequent primary immunodeficiency associated with hypogammaglobulinemia and other various clinical manifestations. CVID was originally reported to be a disease primarily caused by defective B-cell function, with defective terminal B-cell differentiation rendering B cells unable to produce immunoglobulin. However, combined immunodeficiency (CID) involving both defective B and T cells is often misdiagnosed as CVID.[1] Indeed, one study reported that CD4^{+} T-cell numbers were decreased in 29% of 473 patients with CVID[2]; similarly, another study found that naive T-cell numbers were markedly reduced in 44% (11/25) of patients with CVID.[3] These observations indicated that a subgroup of patients with clinically diagnosed CVID is T-cell deficient. Consistently, some patients with CVID have complications that might be related to T-cell deficiency, including opportunistic infections, autoimmune diseases, and malignancies, which is similar to that observed in patients with CID.[1,4] Therefore identifying novel markers to better classify CVID and distinguish CID from CVID will be required to best manage medical treatment for CVID.

We recently performed real-time PCR-based quantification of T-cell receptor excision circles (TREC) and signal joint immunoglobulin κ-deleting recombination excision circles (KREC) for mass screening of severe combined immunodeficiency (SCID)[5] and B-lymphocyte deficiency[6] in neonates. TREC and KREC are associated with T-cell and B-cell neogenesis, respectively.[7] Here we retrospectively report that TREC and KREC are useful for classifying patients with clinically diagnosed CVID.

Hypogammaglobulinemic patients (n = 113) were referred to our hospital for immunodeficiency from 2005-2011, and the following patients were excluded from the CVID pool by estimating their SCID genes based on clinical manifestations and lymphocyte subset analysis: 18 patients with SCID diagnoses; 14 patients less than 2 years of age (transient infantile hypogammaglobulinemia); 10 patients with IgM levels of greater than 100 mg/dL (hyper-IgM syndrome); 26 patients with diseases other than CVID caused by known gene alterations (10 with X-linked agammaglobulinemia and 11 with hyper-IgM syndrome [*CD40L* or *AICDA* mutated]), (2 with DiGeorge syndrome, and 3 with *FOXP3*, *IKBKG*, or *6p* deletions); and 5 patients with drug-induced hypogammaglobulinemia. The remaining 40 patients with decreased IgG (≥2 SDs below the mean for age), IgM, and/or IgA levels, as well as absent isohemagglutinins, poor response to vaccines, or both were included in this study as patients with CVID and analyzed for TREC/KREC levels, retrospectively.

Ages of patients with CVID ranged from 2 to 52 years (median age, 15.5 years). The sex ratio of the patients was 21 male/19 female patients. Serum IgG, IgA, and IgM levels were 370 ± 33 mg/dL (0-716 mg/dL), 30 ± 7 mg/dL (1-196 mg/dL), and 40 ± 6 mg/dL (2-213 mg/dL), respectively. TREC and KREC quantification was performed by using DNA samples extracted from peripheral blood, as reported previously.[5,6] Clinical symptoms were then assessed
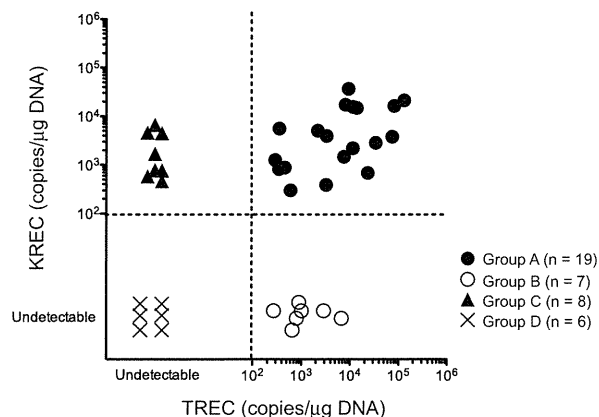

FIG 1. Quantifying TREC and KREC classifies patients with CVID into 4 groups. Patients with CVID were classified as follows: TREC(+)/KREC(+), group A (19 patients); TREC(+)/KREC(−), group B (7 patients); TREC(−)/KREC(+), group C (8 patients); and TREC(−)/KREC(−), group D (6 patients). *Undetectable*, Less than 100 copies/μg DNA.

retrospectively. The study protocol was approved by the National Defense Medical College Institutional Review Board, and written informed consent was obtained from adult patients or parents of minor patients in accordance with the Declaration of Helsinki.

Based on TREC and KREC copy numbers, the 40 patients with CVID were classified into 4 groups (groups A, B, C, and D; Fig 1). Comparing lymphocyte subsets, CD3^{+} T-cell numbers were similar among groups A, B, and D but were significantly lower in group C ($P < .05$; group A, 1806 ± 204 cells/μL; group B, 1665 ± 430 cells/μL; group C, 517 ± 124 cells/μL; and group D, 1425 ± 724 cells/μL; $P = .0019$, Tukey multiple comparison test based on 1-way ANOVA). CD3^{+}CD4^{+}CD45RO^{+} memory T-lymphocyte percentages in groups B, C, and D were significantly higher than those in group A ($P < .0001$; group A, 37% ± 16%; group B, 67% ± 13% [$P = .0006$]; group C, 92% ± 8.2% [$P < .0001$]; and group D: 83% ± 14% [$P < .0001$]; see Fig E1 in this article's Online Repository at www.jacionline.org); additionally, the percentages of these cells in groups C and D were higher than in group B ($P = .0115$). These results indicate that group C and D patients have markedly decreased CD4^{+}CD45RA^{+} naive T-cell counts than group A patients and that counts in group B are also significantly decreased, although less so than in groups C or D, which is consistent with a report showing lower TREC copy numbers in CD4^{+}CD45RO^{+} cells. Some patients in groups B, C, and D exhibited normal CD4^{+}CD45RO^{+} percentages, although TREC levels, KREC levels, or both decreased. This discrepancy indicates that TREC/KREC levels could be independent markers to determine the patient's immunologic status in addition to CD4^{+}CD45RA^{+}; the reasons underlying the discrepancy between CD4^{+}CD45RA^{+} and TREC/KREC levels remain unsolved.

CD19^{+} B-cell numbers in group A were significantly higher ($P < .05$) than those in groups B and D (group A, 269 ± 65 cells/μL; group B, 35 ± 16 cells/μL; group C, 60 ± 11 cells/μL; and group D, 29 ± 16 cells/μL; $P = .0001$). However, B-cell subpopulations, including CD27^{−}, IgD^{+}CD27^{+}, and
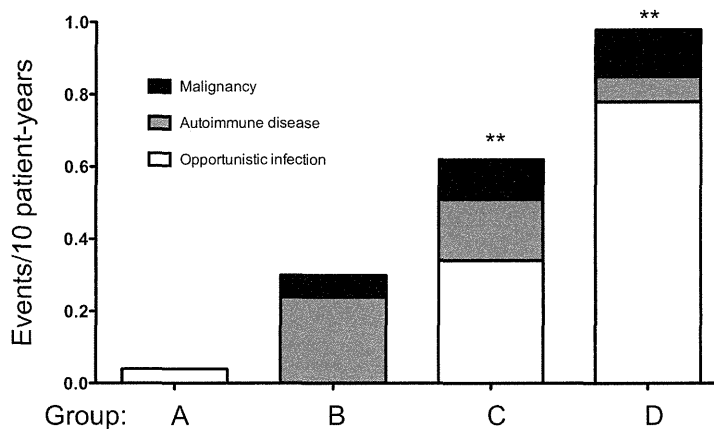
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FIG 2. Cumulative incidence of complication events per 10 patient-years differs among groups. Opportun-istic infections, autoimmune diseases, and malignancies were evaluated for each patient group. Compli-cation incidences in group D (0.98 events/10 patient-years), group C (0.63 events/10 patient-years), and group B (0.30 events/10 patient-years) were higher than in group A (0.04 events/10 patient-years). Group A versus group D: **P = .0022; group A versus C: **P = .0092; group A vs group B: P = .0692.

IgD⁻CD27⁺ cells, were not significantly different among the groups. Standardizing KREC copy numbers for each patient by dividing their CD19⁺ by their CD27⁺ percentages revealed the same patient classification as that shown in Fig 1 (data not shown), indicating that the original classification was independent of CD19⁺ B-cell or CD27⁺ memory B-cell percentages.

Because TREC and KREC levels decrease with age (see Fig E2 in this article's Online Repository at www.jacionline.org)[5,6] and age distribution was wide in this study, we compared patients' ages among groups at the time of analysis to determine whether classification was associated with age. TREC/KREC-based clas-sification was independent of both age and sex because age distri-bution was not significantly different among groups (P > .05; group A, 12.7 ± 2.3 years [2-30 years]; group B, 23.4 ± 4.2 years [6-39 years]; group C, 21.5 ± 6.1 years [4-52 years]; and group D, 25.5 ± 4.4 years [15-46 years]; data not shown) nor was male/fe-male sex ratio (overall, 21/19; group A, 10/9; group B, 2/5; group C, 5/3; and group D, 4/2; P = .4916, χ^2 test; data not shown).

We next evaluated whether any correlation existed between TREC/KREC-based classification and clinical symptoms in each patient group. All patients in the study had been treated with intravenous immunoglobulin (IVIG) substitution at the time of analysis. We found that the cumulative events of complications (opportunistic infections, autoimmune diseases, and malignan-cies) per 10 patient-years were highest in group D (0.98 events/10 patient-years), followed by group C (0.63 events/10 patient-years), group B (0.30 events/10 patient-years), and group A (0.04 events/10 patient-years), where events in groups D and C were significantly higher than group A (group A vs group D, P = .0022; group A vs group C, P = .0092; group A vs group B, P = .0692; Fig 2). Furthermore, we found similar results when evaluating only patients 19 years old or older for group D (1.01 events/10 patient-years), group C (0.56 events/10 patient-years), group B (0.32 events/10 patient-years), and group A (0.06 events/10 patient-years; group A vs group D, P = .0074; group A vs group C, P = .0407; group A vs group B, P = .1492; data not shown). Categorizing patients by using several different previously reported CVID classifications (focused primarily on separating patients based on levels of circulating B-cell subsets), we found

that no classification scheme showed any significant event increases in any particular group (see Fig E3 in this article's On-line Repository at www.jacionline.org). Assessing longitudinal cumulative opportunistic infection incidence among the groups, group D and C values were significantly higher than in group A (see Fig E4, A, in this article's Online Repository at www.jacionline.org; P = .0059). Autoimmune and malignant diseases (P = .5168 and P = .6900, respectively) were observed in groups B and D but not in group A (see Fig E4, B and C). Cumulative events were significantly different between groups (P = .0313, log-rank test; group A, 5.3% and 5.3%; group B, 14.3% and 57.1%; group C, 27.1% and 63.5%; and group D, 33.3% and 83.3% at 10 and 30 years of age, respectively; see Fig E4, D). One patient in group D died of Pneumocystis jirovecii pneumonia, and 2 other patients in the same group received hematopoietic stem cell transplantation after complications caused by EBV-related lymphoproliferative disorder.

Assessing these data, TREC/KREC-based classification matches clinical outcomes. Because group D patients exhibited the most frequent complications (opportunistic infections, auto-immune diseases, and malignancies), they could receive a diag-nosis of CID based on these symptoms. If they are indeed determined to have CID, then TREC/KREC analysis is helpful to distinguish between CID and CVID. Their TREC(−)/KREC(−) phenotype might relate to defective V(D)J recombination in T- and B-cell development[8] because patients with B-negative SCID (RAG1, RAG2, Artemis, and LIG4), as well as patients with ataxia-telangiectasia (AT) and Nijmegen breakage syndrome (NBS; see Fig E5 in this article's Online Repository at www.jacionline.org)[5,6] were also negative for both TREC and KREC; it is intriguing to speculate that an unknown V(D)J recombination gene or genes is responsible. As for treatment, hematopoietic stem cell transplantation should be considered the preferred treatment to "cure" group D patients, as reported in patients with severe CVID/CID, because event-free survival is poor.[9]

In contrast to group D patients, TREC(+)/KREC(+) group A patients treated with IVIG substitution therapy remained healthy. One possible explanation is that these patients harbor

defects only in terminal B-cell differentiation, but not in T cells, and represent typical patients with CVID, as originally reported.

Group C patients had a high frequency of both opportunistic infections and malignancies, suggesting that these TREC(−) patients have T-cell defects. Although group C patients had a similar TREC/KREC pattern to patients with SCID with B cells (*IL2RG* and *JAK3*; see Fig E5, *A*), they do not fulfill the European Society for Immunodeficiencies criteria for SCID, and no mutation was identified in the SCID genes estimated from clinical manifestation and lymphocyte subset analysis. However, from our data, they would likely benefit from undergoing similar treatment to patients with SCID or CID to prevent these complications.

Although opportunistic infections were rare in group B patients, autoimmune diseases were often observed. This is consistent with this group being TREC(+)/KREC(−) and the idea that balance between T and B cells is important to prevent autoimmune diseases in patients with CVID.[1] Intriguingly, a group of patients with AT and NBS were also TREC(+)/KREC(−) (see Fig E4, *B*), which is similar to group B patients. Additionally, CD45RA$^+$CD4$^+$ naive T-cell numbers were reduced in most group B patients, which is similar to the phenotype exhibited by patients with AT and NBS. This finding raises the possibility that although some group B patients are also T-cell deficient, as well as B-cell deficient, and should be treated similarly to patients with CID, other patients have only B-cell deficiency and are effectively treated with IVIG substitution therapy.

By analyzing a large CVID patient cohort, the overall survival rate of patients with more than 1 complication was worse than that for patients without other complications.[4] Our findings indicate that low TREC levels, KREC levels, or both are useful markers that correlate well with the overall survival rate in patients with CVID. Therefore we conclude that TREC and KREC are useful markers to assess the clinical severity and pathogenesis of each patient with CVID and to distinguish CID from CVID. Thus patient classification based on TREC/KREC levels would provide a helpful tool for deciding on an effective treatment plan for each patient with CVID.

Chikako Kamae, MD^a
Noriko Nakagawa, MD, PhD^a

Hiroki Sato, MS^b
Kenichi Honma, MD^a
Noriko Mitsuiki, MD^{c,d}
Osamu Ohara, PhD^c
Hirokazu Kanegane, MD, PhD^e
Srdjan Pasic, MD, PhD^f
Qiang Pan-Hammarström, MD, PhD^g
Menno C. van Zelm, PhD^h
Tomohiro Morio, MD, PhD^d
Kohsuke Imai, MD, PhD^b
Shigeaki Nonoyama, MD, PhD^a

From the Departments of ^{a}Pediatrics and ^{b}Preventive Medicine and Public Health, National Defense Medical College, Saitama, Japan; ^{c}the Department of Human Genome Research, Kazusa DNA Research Institute, Chiba, Japan; ^{d}the Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan; ^{e}the Department of Pediatrics, University of Toyama, Toyama, Japan; ^{f}the Department of Immunology, Mother and Child Health Institute, Medical Faculty, University of Belgrade, Belgrade, Serbia; ^{g}the Department of Laboratory Medicine, Karolinska Institute, Karolinska University Hospital, Huddinge, Stockholm, Sweden; and ^{h}the Department of Immunology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands. E-mail: kimai.ped@tmd.ac.jp.

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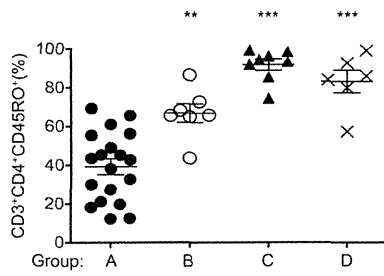
FIG E1. CD45RO$^+$CD3$^+$CD4$^+$ T-cell frequency within CD4$^+$CD3$^+$ lymphocytes was analyzed among groups. CD45RO$^+$CD3$^+$CD4$^+$ lymphocyte counts were significantly higher in groups B, C, and D compared with those in group A ($P < .0001$). Group A: 37% ± 16%; group B: 67% ± 13% (**$P < .01$); group C: 92% ± 8.2% (***$P < .001$); and group D: 83% ± 14% (***$P < .001$).

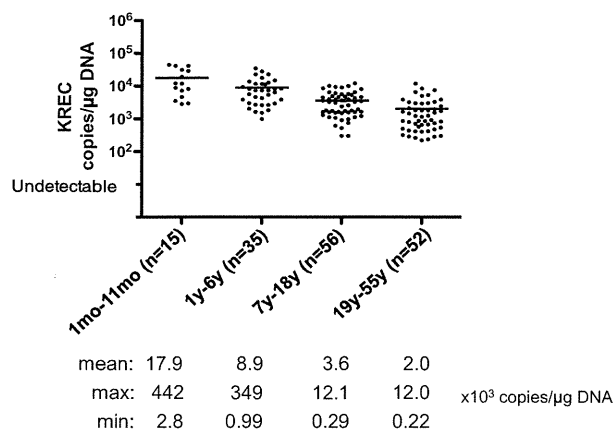| mean:	17.9	8.9	3.6	2.0	
max:	442	349	12.1	12.0	$\times 10^3$ copies/μg DNA
min:	2.8	0.99	0.29	0.22	

FIG E2. KREC levels were analyzed in genomic DNA samples extracted from peripheral blood of control subjects at different age groups (n = 158; age range, 1 month to 55 years). KREC levels were significantly higher in infants (17.9 $\pm$ 3.9 $\times$ 10^3 copies/μg DNA) compared with other children's age groups (8.9 $\pm$ 1.3 $\times$ 10^3 copies/μg DNA in the 1- to 6-year-old group and 3.6 $\pm$ 3.8 $\times$ 10^3 copies/μg DNA in the 7- to 18-year-old group) and adults (2.0 $\pm$ 3.3 $\times$ 10^3 copies/μg DNA; P < .0001).
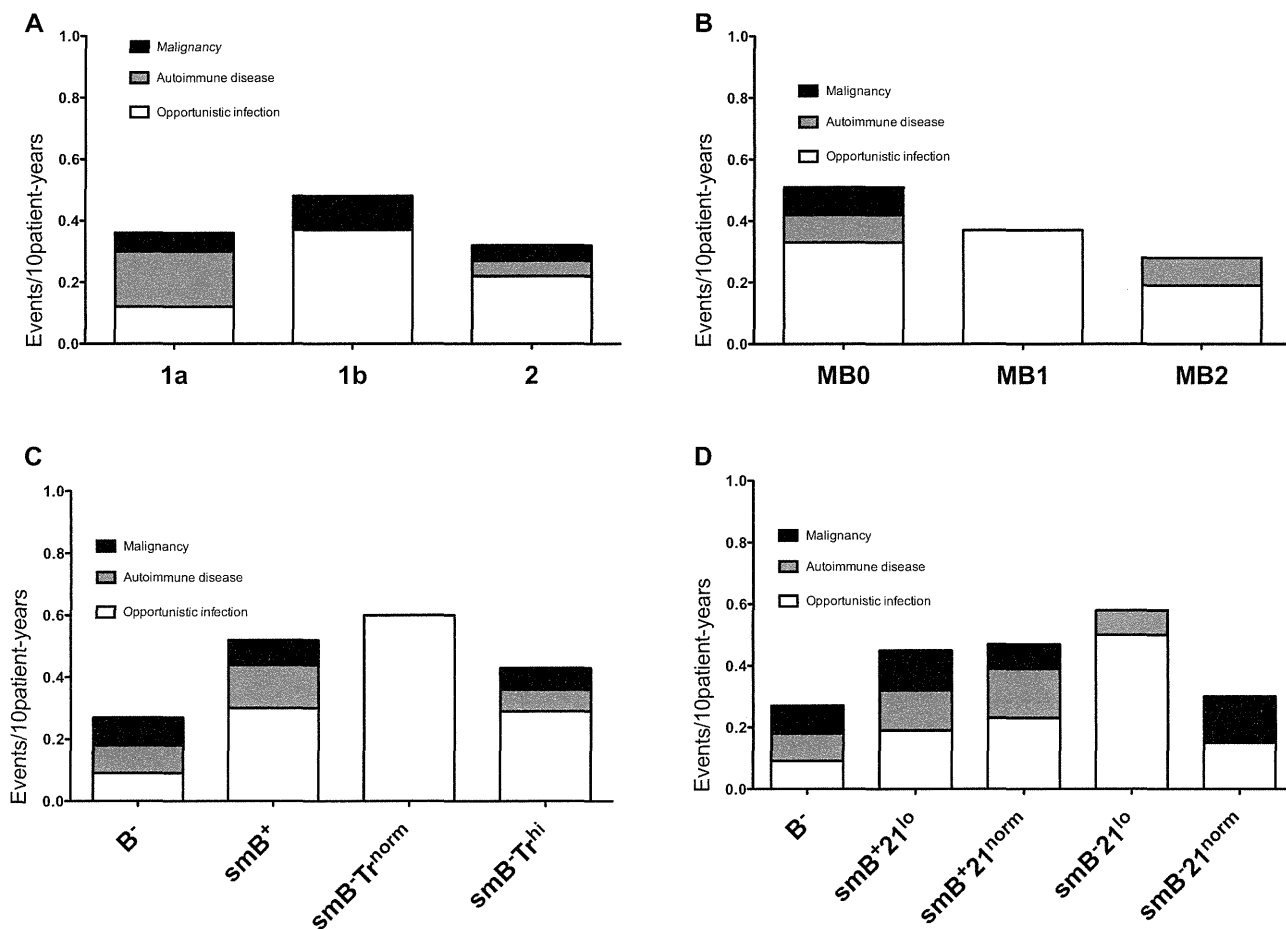
FIG E3. Patients were classified in the following way and analyzed for cumulative incidence of complications: **A,** Freiburg; **B,** Paris; and **C,** EUROclass classifications, according to $CD38^{hi}IgM^{hi}$ transitional B cells (Fig E3, *A-C*) or $CD21^{low}$ B cells **(D).** Five patients were excluded from the Freiburg and Paris classifications because of decreased B-cell numbers (<1%). Additionally, we excluded 4 patients in the Freiburg classification, 1 patient in the Paris classification, and 4 patients in the EUROclass classification for transitional B cells and 8 in the EUROclass classification for $CD21^{low}$ B cells because of lack of data. The following cumulative events/10 patient-years were found. Freiburg classification: 1a, 0.36; 1b, 0.48; 2, 0.32. Paris classification: MB0, 0.50; MB1, 0.37; MB2, 0.28. EUROclass classification according to transitional B cells: B^-, 0.27; smB^+, 0.52; smB^-Tr^{norm}, 0.60; smB^-Tr^{high}, 0.43. EUROclass classification according to $CD21^{lo}$ B cells: B^-, 0.27; smB^+21^{lo}, 0.45; smB^+21^{norm}, 0.47; smB^-21^{lo}, 0.58; smB^-21^{norm}, 0.30. No classification showed any significantly increased events in any particular group according to calculated *P* values, as follows—Freiburg classification: 1a vs 2 = .898, 1b vs 2 = .479, 1a vs 1b = .838; Paris classification: MB0 vs MB2 = .179, MB1 vs MB2 = .654, MB0 vs MB1 = .764; EUROclass classification according to transitional B cells: B^- vs smB^+ = .298, smB^-Tr^{norm} vs smB^+ = .809, smB^-Tr^{hi} vs smB^+ = .702, smB^-Tr^{hi} vs smB^-Tr^{norm} = .641, smB^-Tr^{norm} vs B^- = .329, smB^-Tr^{hi} vs B^- = .508; EUROclass classification according to $CD21^{lo}$ B cells: B^- vs smB^+21^{norm} = .443, smB^+21^{lo} vs smB^+21^{norm} = .930, smB^-21^{lo} vs smB^+21^{norm} = .695, smB^-21^{norm} vs smB^+21^{norm} = .575, B^- vs smB^-21^{norm} = .926, smB^+21^{lo} vs smB^-21^{norm} = .609, smB^-21^{lo} vs smB^-21^{norm} = .399, B^- vs smB^+21^{lo} = 0.474, B^- vs smB^-21^{lo} = 0.270, smB^+21^{lo} vs smB^-21^{lo} = 0.618.
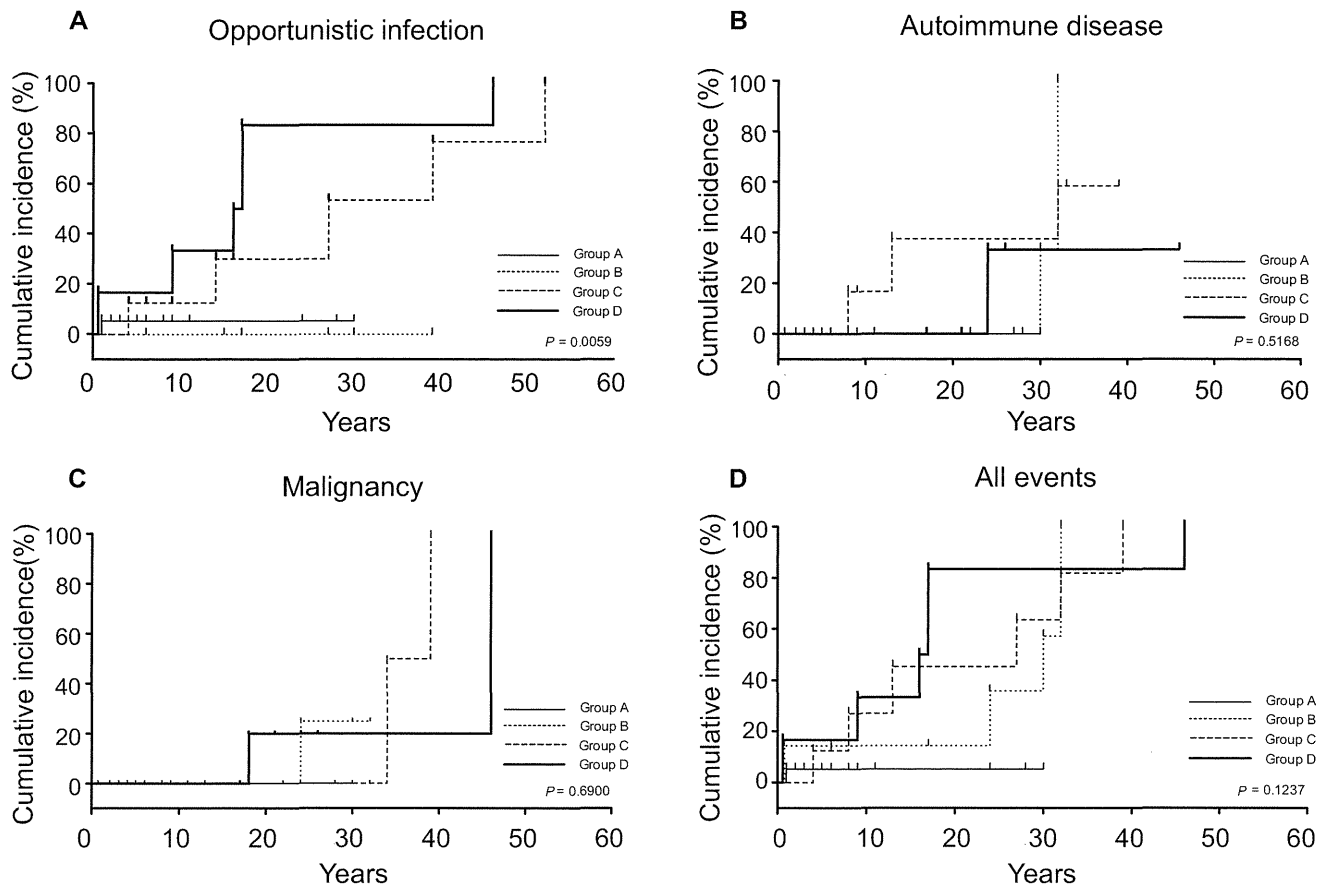
FIG E4. Comparing longitudinal cumulative incidence of complication events among groups. Cumulative incidence was estimated separately and longitudinally by using the Kaplan-Meier method and statistically compared between groups by using the log-rank test. The cumulative incidence of opportunistic infections **(A)**, autoimmune diseases **(B)**, malignancies **(C)**, and all events **(D)** is shown.
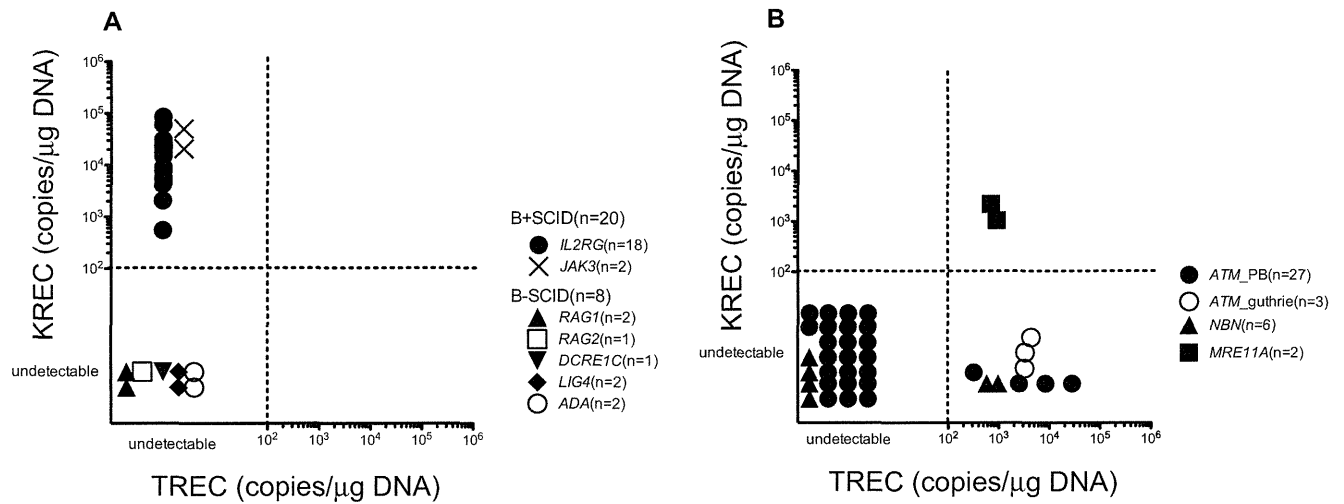
FIG E5. TREC and KREC quantification classifies patients with SCID, AT, NBS, or ataxia-telangiectasia–like disease *(ATLD)* into 4 groups. **A,** Patients with B⁺SCID (n = 20) were classified as group C, and patients with B⁻SCID (n = 8) were classified as group D; these patients were included in the previous studies.[5,6] **B,** Although most patients with AT (n = 23) and patients with NBS (n = 4) were classified as group D, TRECs were detected in peripheral blood samples (n = 4 in patients with AT and n = 2 in patients with NBS) and neonatal Guthrie cards (n = 3) of some patients with AT, who were classified as group B. Patients with ATLD with *MRE11A* mutations were classified as group A.

原発性免疫不全症の最新国際分類*

今 井 耕 輔**

Key Words : primary immunodeficiency(PID), classification

原発性免疫不全症
(primary immunodeficiency；PID)の分類

　PIDの分類は, 1970年に世界保健機関の専門委員会から発表され, 1999年からは, 国際免疫学会連合の専門家委員会で2年ごとに改訂され, その間に原因遺伝子が同定されたり, 新しい記載がなされた疾患が追加されている. 本稿では, 2011年に発表された最新国際分類[1]について, 紹介したい.

　今回の分類も以前までと同様に, その障害細胞, 分子により, 大きく8つに分類しているが, 今回から表の順番が一部変わっている. 免疫不全症を伴う症候群が表2になり, 抗体産生不全症が表3になった. これは, 免疫不全症を伴う免疫不全症の多くが, 複合免疫不全症を伴っており, 表1の疾患と類似しているからである.

　免疫系を, 自然免疫, 獲得免疫の軸と, 細胞性免疫, 液性免疫の軸に分け, PIDの各分類を配置すると, 図1のようになる. 各構成細胞(好中球, T細胞, B細胞), 機能分子(抗体, 補体)の数的, 量的異常は, 50年以上前からPIDとして記載されている(図1-上段：古典的免疫不全症).

　一方, 貪食細胞の中でもマクロファージの機能異常による非定型抗酸菌やBCGへの易感染性を示す疾患〔メンデル遺伝型マイコバクテリア易感染症候群(mendelian susceptibility of mycobacterial disease；MSMD)〕, Toll like receptor (TLR)などの病原体を認識する受容体のシグナル伝達に異常をきたす狭義の自然免疫不全症などは, 限られた病原体に対して易感染性を示す新しい免疫不全症である(図1-下段).

　さらに, 先天性自己免疫疾患などの免疫制御異常症, 周期性発熱症候群などの自己炎症性疾患, 補体抑制因子欠損による非典型溶血性尿毒症性症候群などは, 易感染性を示さない新しい免疫不全症(免疫制御不全症)も, しだいにその記載が増え, 原因遺伝子も判明しつつある.

　各分類別の同定された原因遺伝子数とその割合について, 図2に示す. 個々の分類の疾患について, 以下に概説する.

複合免疫不全症(表1)

　特異的液性免疫, すなわち抗体の産生にはT細胞の存在が不可欠であるため, T細胞の数的, 機能的異常をきたす場合, 細胞性免疫不全症と抗体産生不全症を生じる. そのため, T細胞の数的, 機能的不全症を複合免疫不全症と呼ぶ. なかでも, 重篤な複合免疫不全症をきたし, 無治療の場合, 乳児期に致死的である一群を重症複合免疫不全症(severe combined immunodeficiency；SCID)と呼ぶ.

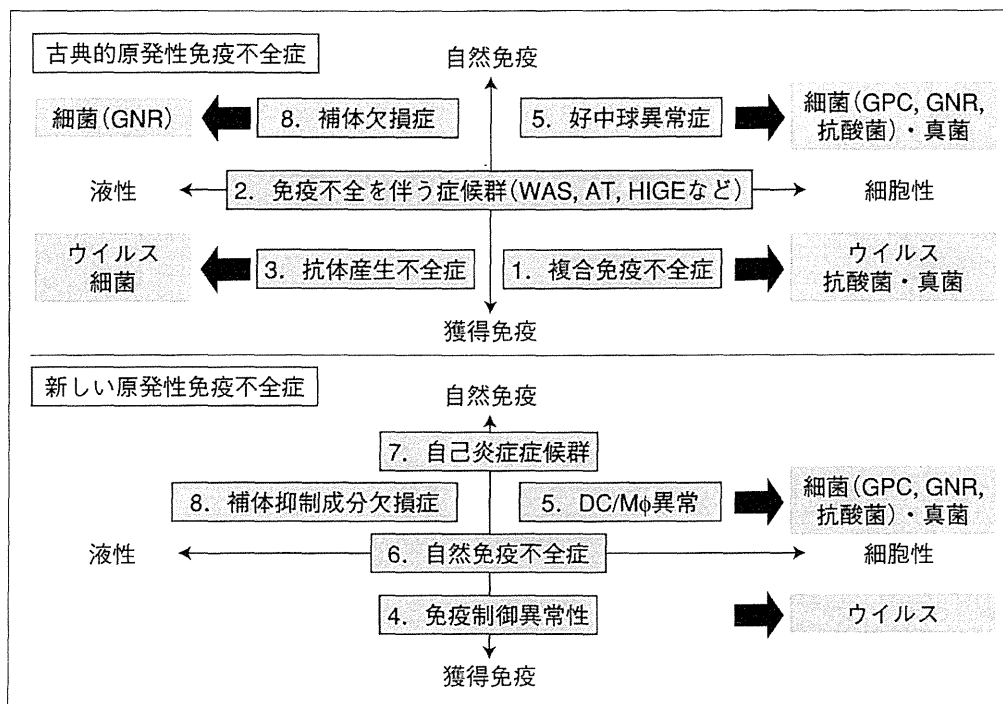　SCIDは, その障害部位によっていくつかの病型に分けることができる. 通常最も患者数の多いのは, 伴性劣性遺伝を示す*IL2RG*遺伝子異常症である. *IL2RG*遺伝子はIL2, 4, 7, 9, 15, 21に

図 1　原発性免疫不全症の分類
上段：古典的原発性免疫不全症，下段：新しい原発性免疫不全症．数字は，分類の表番号を示す．

共通するγ鎖（γc鎖）をコードしており，IL7シグナル異常によりT細胞の発生が，IL15シグナル異常によりNK細胞の発生がみられず，$B^+T^-NK^-$の表現型をとる．γcの下流分子である*JAK3*遺伝子異常の場合は，常染色体劣性の遺伝形式を取るが，表現型は*IL2RG*遺伝子異常症と同じである．また，*IL7R*遺伝子の異常の場合は，T細胞のみを欠損し，$B^+T^-NK^+$の表現型をとる．

次に患者数の多いのは，V(D)J再構成の異常のため$B^-T^-NK^+$の表現型をとる遺伝子異常の一群で，*RAG1/2, Artemis, Cernunnos, DNAPKcs, LIG4*の異常症がその中に含まれる．遺伝子変異によっては，酵素活性などの分子機能が若干残存し，T細胞が残存し，乳児期以降に複合免疫不全症として診断される例や，オリゴクローナルなT細胞，B細胞の活性化によるOmenn症候群（発熱，紅皮症，リンパ節腫脹，肝脾腫，好酸球増多症）を呈する場合もある．

細網異形成症は，好中球系細胞とリンパ球系細胞の両方の異常をきたし，最重症のSCIDの病型を取る．*AK2*遺伝子の異常によることが示されているが，その機序は明らかではない．感音性難聴を伴うのが特徴である．
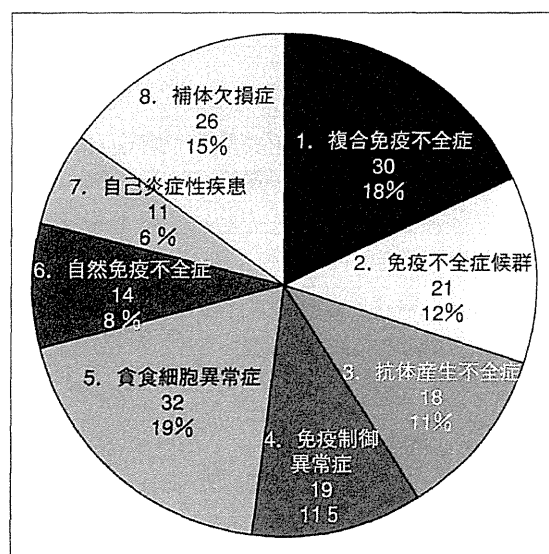

図 2　各分類別の同定された原因遺伝子数（2011年分類による）

T細胞受容体，preT細胞受容体の構成成分や，シグナル伝達分子に異常をきたすと，T細胞のみに異常をきたす複合免疫不全症となる．CD3γ/ε/δ/ζ, CD8, CD45分子の異常に伴うのがその例である．

最近では，Ca^{++}チャンネル（ORAI1, STIM1）や，Mg^{++}チャンネル（MAGT1）異常によるT細胞活

表1　複合免疫

疾患名	末梢血T細胞数	末梢血B細胞数	血清免疫グロブリン
1.　B細胞存在型重症複合（T$^-$B$^+$SCID）			
(a)γc欠損症	著減	正常または増加	低下
(b)JAK3欠損症	著減	正常または増加	低下
(c)IL7R欠損症	著減	正常または増加	低下
(d)CD45欠損症*	著減	正常	低下
(e)CD3δ*/CD3ε*/CD3ζ*欠損症	著減	正常	低下
(f)Coronin1A 欠損症*	著減	正常	低下
2.　B細胞欠損型重症複合免疫不全症（T$^-$B$^-$SCID）			
(a)RAG1/2欠損症	著減	著減	低下
(b)アルテミス/DCLRE1C欠損症	著減	著減	低下
(c)DNA-PKcs欠損症*	著減	著減	低下
(d)アデノシンデアミナーゼ(ADA)欠損症	出生時から欠損(機能喪失変異)または進行性減少	出生時から欠損(機能喪失変異)または進行性減少	進行性低下
(e)細網異形成症(AK2 欠損症)	著減	減少または正常	低下
3.　Omenn症候群	存在(多様性の低下)	正常または減少	IgG, IgA, IgM, IgD低下, IgE増加
4.　DNAリガーゼIV欠損症	減少	減少	低下
5.　セルヌノス/NHEJ1欠損症*	減少	減少	低下
6.　CD40リガンド欠損症	正常, おそらく進行性減少	IgM$^+$IgD$^+$B細胞は存在するが, 他のアイソタイプB細胞は欠損	IgM上昇または正常, 他のアイソタイプは低下
7.　CD40欠損症*	正常	IgM$^+$IgD$^+$B細胞は存在するが, 他のアイソタイプB細胞は欠損	IgM上昇または正常, 他のアイソタイプは低下
8.　プリンヌクレオシドホスホリラーゼ(PNP)欠損症	進行性減少	正常	正常または低下
9.　CD3γ鎖欠損症*	正常だが, T細胞受容体(TCR)発現低下	正常	正常
10.　CD8欠損症*	CD8$^+$T欠損, CD4$^+$T細胞正常	正常	正常
11.　ZAP-70欠損症	CD8$^+$T細胞減少, CD4$^+$T細胞正常	正常	正常
12.　カルシウムチャンネル欠損症			
(a)ORAI-I欠損症*	正常(T細胞受容体経由活性化欠損)	正常	正常
(b)STIM-1欠損症*	正常(T細胞受容体経由活性化欠損)	正常	正常
13.　MHC class I 欠損症	CD8$^+$T細胞減少, CD4$^+$T細胞正常	正常	正常
14.　MHC class II 欠損症	CD4$^+$T細胞低下, CD8$^+$T細胞正常	正常	正常または低下
15.　Winged helix 欠損症(Nude)*	著減	正常	低下
16.　完全DiGeorge症候群	著減	減少から正常	低下
17.　STAT5b欠損症*	中等度減少	正常	正常
18.　ITK欠損症*	中等度減少	正常	正常または低下
19.　MAGT1欠損症*	CD4$^+$T細胞減少	正常	正常
20.　DOCK8欠損症	減少	減少	IgM低下, IgE上昇

*10例以下の報告しかない稀な疾患

不全症

合併所見	遺伝形式	遺伝子変異	OMIM
NK細胞著減．T・NK細胞数減少〜正常の軽症例またはOmenn症候群を呈しうる	XL	*IL2RG*	300400
NK細胞著減．さまざまな数のT・NK細胞数を持つ軽症例を呈しうる	AR	*JAK3*	600173
NK細胞数正常	AR	*IL7R*	146661
γ/δT細胞正常	AR	*CD45*	151460
NK細胞正常 γ/δT細胞欠損	AR	*CD3D/CD3E/CD3Z*	186790, 186830, 186740
胸腺を認める	AR	*CORO1A*	605000
Omenn症候群あるいはγ/δT細胞増多自己免疫・肉芽腫症候群を呈しうる	AR	*RAG1/RAG2*	601457
VDJ再構成障害，放射線感受性，Omenn症候群を呈しうる	AR	*DCLRE1C*	602450
scidマウスと同じ表現型	AR	*PRKDC*	600899
NK細胞数減少，肋軟骨移行部のフレア，神経学的症状，聴力障害，肺疾患，肝疾患；部分欠損の場合遅発性あるいは軽症	AR	*ADA*	102700
T, B, NK細胞欠損症 および顆粒球減少症，難聴	AR	*AK2*	103020
紅皮症，好酸球増多症，リンパ節腫脹，肝脾腫	AR	*RAG1/2, DCLRE1C, IL7R, RMRP, ADA, LIG4, IL2RG*	603554
小頭症，顔面小奇形，放射線感受性，Omenn症候群または遅発性を呈することあり	AR	*LIG4*	601837
小頭症，子宮内発育不全，放射線感受性	AR	*NHEJ1*	611291
好中球減少症，血小板減少症，溶血性貧血，胆管，肝疾患，日和見感染症	XL	*CD40LG*	300386
好中球減少症，消化管，胆管，肝疾患，日和見感染症	AR	*CD40*	109535
自己免疫性溶血性貧血，神経学的障害	AR	*PNP*	164050
	AR	*CD3G*	186740
	AR	*CD8A*	186910
	AR	*ZAP70*	176947
自己免疫疾患，無汗性外胚葉形成異常症，非進行性ミオパチー	AR	*ORAI1*	610277
自己免疫疾患，無汗性外胚葉形成異常症，非進行性ミオパチー	AR	*STIM1*	605921
血管炎	AR	*TAP1, TAP2, TAPBP*	604571
成長障害，下痢症，呼吸器感染証	AR	*CIITA, RFX5, RFXAP, RFXANK*	209920
白子症，胸腺上皮異常，T細胞成熟障害(ヌードマウス様)	AR	*FOXN1*	600838
リンパ増殖症候群(リンパ節腫脹，肝脾腫)，自己免疫疾患(IPEX症候群類似の場合もあり T細胞増殖不良	AD	22q11.2または10p欠失, *TBX1*	188400
成長ホルモン不応性小人症，小奇形，湿疹，リンパ性間質性肺炎，自己免疫疾患	AR	*STAT5B*	604260
	AR	*ITK*	613011
EBV感染症，リンパ腫，ウイルス感染症，呼吸器，消化器感染症	XL	*MAGT1*	300715
NK細胞減少，好酸球増多症，反復性感染症，重症アトピー性皮膚炎，重症ウイルス性・細菌性(ブドウ球菌性)皮膚感染症，発癌感受性	AR	*DOCK8*	243700

表2　特徴的な症状を

疾患名	末梢血 T 細胞数	末梢血 B 細胞数	血清免疫グロブリン
1．Wiskott-Aldrich症候群（WAS）	進行性減少．抗CD3抗体に対するリンパ球反応の異常	正常	IgM低下：特に抗多糖体抗体低下；しばしばIgA，IgE上昇
2．DNA修復異常症（表1以外の疾患）			
（a）毛細血管拡張性運動失調症	進行性減少	正常	IgA, IgE, IgGサブクラスしばしば低下，IgMモノマー増加；抗体産生能低下の程度はさまざま
（b）毛細血管拡張性運動失調症様疾患（ATLD）＊	進行性減少	正常	抗体産生能低下の程度はさまざま
（c）Nijmegen症候群	進行性減少	さまざまに減少	IgA, IgE, IgGサブクラスしばしば低下，IgM上昇；抗体産生能低下の程度はさまざま
（d）Bloom症候群	正常	正常	低下
（e）ICF症候群（セントロメア不安定性と顔面奇形を伴う免疫不全症）	減少または正常；PHA芽球化反応は低下していることもある	減少または正常	低γグロブリン血症，抗体産生能低下の程度はさまざま
（f）PMS2欠損症（ミスマッチ修復障害によるクラススイッチ再構成障害による）	正常	B 細胞減少	IgG, IgA低下，IgM上昇，抗体産生能異常
（g）Riddle症候群＊	正常	正常	IgG低下
3．胸腺欠損症			
DiGeorge症候群（22q11.2欠失症候群）	減少または正常	正常	正常または低下
4．免疫骨異形成症			
（a）軟骨毛髪低形成症	減少または正常．リンパ球増殖障害	正常	正常または低下，抗体産生能低下の程度はさまざま
（b）Schimke症候群	減少	正常	正常
5．Comel-Netherton症候群	正常	クラススイッチ陽性，陰性メモリー B 細胞減少	IgE, IgAの上昇，抗体産生能低下の程度はさまざま
6．高IgE症候群（HIES）			
（a）常染色体優性型高IgE症候群（Job症候群）	正常Th-17細胞減少	正常（クラススイッチ陽性，陰性メモリー B 細胞減少，BAFFレベルの低下）	IgE上昇，特異抗体産生低下
（b）常染色体劣性型高IgE症候群			
（i）Tyk2 欠損症＊	正常であるが多系統のサイトカインシグナル伝達障害を伴う	正常	IgE上昇（＋／−）
（ii）DOCK8 欠損症	減少	減少	IgE上昇（＋／−），IgM低下
（iii）原因不明型	正常	正常	IgE上昇
7．肝中心静脈閉塞症を伴う免疫不全症（VODI）	正常（メモリー T 細胞減少）	正常（減少memory B 細胞）	IgG, IgA, IgM低下，胚中心欠損，組織形質細胞欠損
8．先天性角化異常症（DKC）			
（a）X 連鎖性先天性角化異常症（Hoyeraal-Hreidarsson症候群）	進行性減少	進行性減少	さまざま
（b）常染色体劣性型先天性角化異常症	異常	さまざま	さまざま
（c）常染色体優性型先天性角化異常症	さまざま	さまざま	さまざま
9．IKAROS欠損症＊	正常であるがリンパ球増殖反応は不良	欠損	おそらく低下

＊10例以下の報告しかない稀な疾患