テロメア長制御に影響をあたえる否かは機能解析を行わなければならない。などが考えられた。

現在のところDKCや不全型DKC症例のスクリーニング法としては、テロメア長の短縮化を検索することが実用的であると考えられている。本邦ではSouthern blotting法かFlow FISH法を用いて、テロメア長の短縮化を検索しDKCや不全型DKC症例をスクリーニングしている。しかしSouthern blotting法は、DNAが1ug以上は必要で、末梢血や骨髄の細胞数の少ないBMF症例では検体採取が困難な場合がある。Flow FISH法はSouthern blotting法よりは必要な細胞は少ないが、やはり細胞数が少ないと正確な結果を出すことが困難な場合がある。また解析にはコントロールとなる1301細胞株が必要となるため、解析のたびに1301細胞を培養しなくてはならない。

Real time PCR法によるテロメア長測定は、細胞数が少ないBMFが対象であっても簡便で高感度にテロメア長の短縮化を検索することができると考えられた。我々はReal time PCR法によるテロメア長測定の実験系を確立し、従来のSouthern blotting法やFlow FISH法と同様にDKCや不全型DKC症例をスクリーニングすることが可能かを検討した。

B. 研究方法

対象はDKC1症例、不全型DKC2症例、同世代の健常人13人。DNA検体は10ngを使用し、各症例3回の測定を行い、その平均値を結果として用いた。

テロメア長測定のためのReal time PCR用のprimerは、tel1 primerは3'端より6、12、18、24、30、32-37塩基が、tel2 primerは6、12、18、24、30、34-39塩基がヒトテロメアTTAGGG繰り返し配列とミスマッチの配列となっている。このミスマッチによってそれぞれのprimerはヒトテロメア配列にanneling することが可能であるが、tel1 primerとtel2 primerはどの様な形でannelingをしても、3'端の塩基がミスマッチとなりprimer dimmerによる増幅が起こらない様に工夫をした。

検量線はFlow FISH法との比較をすることが容易になるように1301細胞から抽出したDNAを用いた。

(倫理面への配慮)

本研究は当施設遺伝子倫理審査委員会において承認が得られており以下の配慮を予定している。生命倫理上の配慮に関しては、患者、及び健康ボランティアの人権、利益の保護について文書にて十分説明をしたうえで同意を得る。また研究への協力に同意した後であってもその同意を取り消すことができること、更に本研究への同意が得られない場合においても今後の治療などにはなんら不利益を被らないことを説明する。個人情報漏洩に対する取り組みとして研究組織とは別に個人情報管理者をおき連結可能匿名化をはかったうえで解析をおこなう。同意が撤回された場合は、検体、診療情報、遺伝情報はすべて匿名化されたまま焼却により破棄する。得られた結果は学会や論文として発表するが個人情報が出ることはない。遺伝子結果の開示を研究対象者が要求する場合は、倫理的問題を考慮し遺伝子カウンセリングを施行し、結果の告知は臨床遺伝専門医(遺伝カウンセラー)により行う。

C. 研究結果

1. Southern blotting法によるテロメア長測定

DKC症例(22-402)(図1)と不全型DKC症例(J169)(図2)はage machコントロールと比較して明らかにテロメア長の短縮を認めた。またもう一例の不全型DKC症例(32-266)(図3)は、age machコ

ントロールと比較して軽度のテロメア長の短縮を認めた。

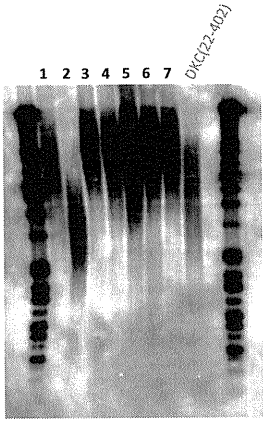


図 1

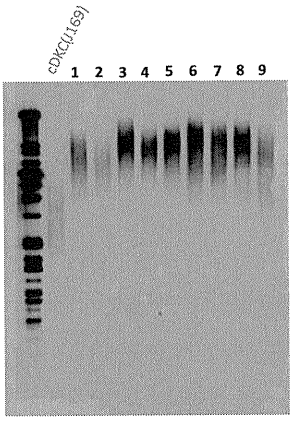


図 2

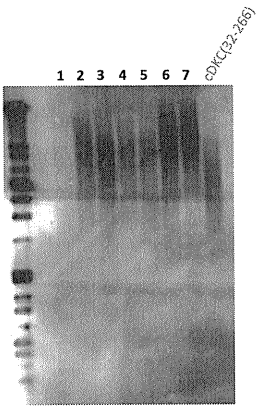


図 3

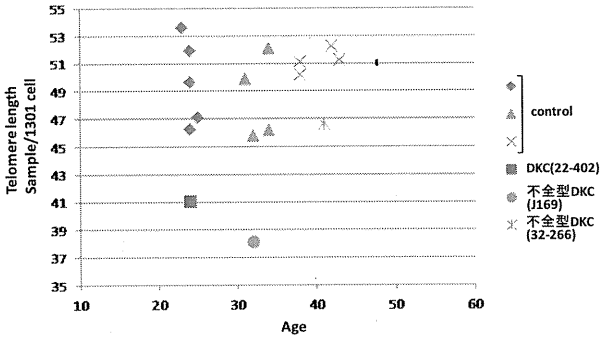
図 1 1, 3-7: age-matched control, 2: テロメア長が短縮したコントロール検体

図 2 1-9: age-matched control

図 3 1-7: age-matched control

2. Real time PCR 法によるテロメア長測定

DKC 症例(22-402)と不全型 DKC 症例(J169)は age mach コントロールと比較して明らかにテロメア長の短縮を認めた(22-402: 41%, J169: 38.1%)。また Southern blotting 法と同様に不全型 DKC 症例(32-266)は、age mach コントロールと比較して軽度のテロメア長の短縮を認めた (32-226: 46.8%)。



D. 考察

Real time PCR 法は、Southern blotting 法や Flow FISH 法と同様にテロメア長の短縮を検索することが可能であった。使用 DNA 量は、テロメア PCR 用に 30ng、補正用の GAPDH の PCR 用に 30ng、計 60ng で、Southern blotting 法の約 1/10、Flow FISH 法の約 1/5 でスクリーニングが可能であった。また今回検索した Southern blotting 法による DKC や不全型 DKC 症例のテロメア長の実測値と Real time PCR 法による 1301 細胞のテロメア長との比較値には関連が認められ、Real time PCR 法は半定量性もあると考えられた。

今後 BMF のテロメア長は、まず Real time PCR 法にてスクリーニングを行い、テロメア長の短縮化が疑われる症例は、Flow FISH 法か Southern blotting 法でテロメア長の短縮化を確定するという方法が良いのではないかと考えられた。

E. 結論

Real time PCR 法は、Southern blotting 法や Flow FISH 法と同様にテロメア長の短縮を検索することが可能であった。検索に必要な DNA 量は、Southern blotting 法や Flow FISH 法に比べ約 1/5~1/10 であり BMF 症例の臨床検査としては有用であった。

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G. 知的財産権の出願・登録状況

(予定を含む。)

特になし。

音受容に関するAdenylate Kinase-2(AK2)の内耳における役割についての研究

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研究要旨

AK2 は免疫学的には骨髄細胞の分化、アポトーシスに関連していることが示唆されている。そこで今回、我々はAK2が音受容機構にどのように関与しているかを検討するために本研究を開始した。齧歯類における AK2 の存在をウエスタンブロット及び免疫組織化学を行い、内耳における AK2 の存在および局在を確認してきた。本年度はモルモットに強大音負荷を行い蝸牛感覚細胞の過酸化を証明しAK2とアポトーシスとの関連を示唆する所見をえた。

A.　研究目的

AK2 の発現が先天的にみられない細網異形成症の患者では免疫不全の他に難聴が高率にみられることが報告されている。難聴のタイプは内耳性難聴であることであることよりAK2が内耳内において聴覚に重要な役割を果たしていることが推察される。本研究は AK2 が音受容機構さらに音響性聴覚障害にどのように関与しているかを検討するために本研究を開始した。

B.　研究方法

モルモットをドミトールとケタラール腹腔内注射にて麻酔後、音響負荷装置を用いて4kHz中心の120dBのオクターブバンドノイズを5時間負荷した。聴覚の測定には聴性脳幹飯能(ABR)を用いた。強大音負荷後 2 時間にて断頭、内耳を取り出し4%パラホルムアルデヒドにて固定後、酸化ストレスマーカーである 8-OHdG に対する免疫組織化学を行った。

(倫理面への配慮)
本研究は動物に過度の苦痛を与えぬよう十分配慮して行った。

C.　研究結果

モルモットの強大音曝露により、永久的な聴力障害を作製した。その内耳の蝸牛感覚上皮は特に外有毛細胞において酸化ストレスのマーカーのひとつである 8-OHdG の強い発現がみられた(図1)。

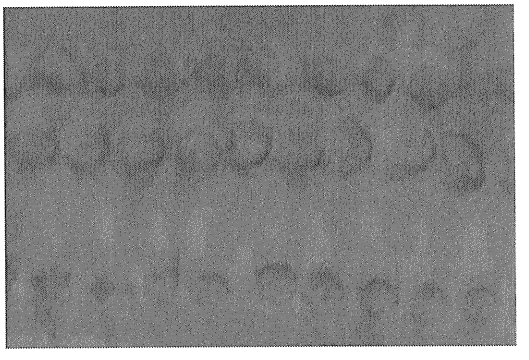

図 1-1　音響負荷なし

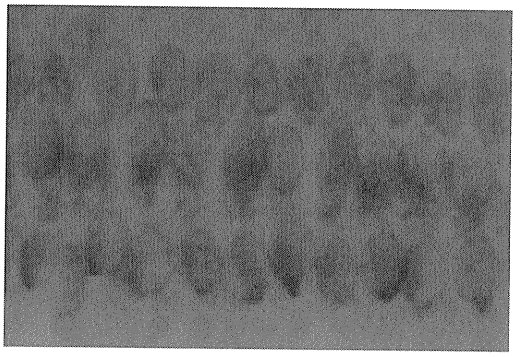

図 1-2　強大音曝露後

D.　考察

AK2 はミトコンドリアの内外膜間に存在し、好中球などにおいて細胞性免疫に大きい役割を果たしている他にいくつかの機能があることが報告されている。本研究ではAK2がマウス内耳組織などに強く発現していることが証明されたが、AK2の機能として(1)ADPをATPとAMPに脱リン酸化するというアデニンヌクレオチドの代謝に関与しているとされる。AK2 の欠陥が内耳障害に関与していると仮定すれば、内耳血管においてADPは内皮細胞の integrity の障害に重要な役割を果たしていることが推察される。これはこれまでにない発見であると考えられる。(2)ミトコンドリアの内外膜間に存在し、FADD (Fas-associated protein with death domain)、 caspase 10 と結合しアポトーシスを誘導するとされる。強大音曝露による聴覚障害では内耳コルチ器の有毛細胞のアポトーシスが起こっていると考えられるが、酸化ストレスによるアポトーシス誘導にAK2が内耳障害の起こるメカニズムにおいても深く関与していることが示唆される。

E.　結論

AK2 が内耳内において聴覚受容や内耳障害の病態に重要な役割を果たしている可能性が推察された。

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G.　知的財産権の出願・登録状況
(予定含む。)

特になし。

Ⅲ　研究成果の刊行に関する一覧

研究成果の刊行に関する一覧

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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Ⅳ　研究成果の刊行に関する一覧　別冊

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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 immunodeficiency diseases, compiled by the *ad hoc* Expert Committee of the International Union of Immunological Societies. As compared to the previous edition, more than 15 novel disease entities have been added in the updated version. For each disorders, the key clinical and laboratory features are provided. This updated classification is meant to help in the diagnostic approach to patients with these diseases.

Keywords: primary immunodeficiency diseases

The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiency met in New York City, May 31–June 1, 2011 to update the classification of human primary immunodeficiencies (PIDs). Novel developments in gene discovery and increased knowledge in the mechanisms that govern immune system development and function have resulted in the identification of several novel PIDs in the last 2 years.

The classification of primary immunodeficiencies (PIDs) provides a framework to help in the diagnostic approach to patients. As in recent classifications, eight major groups of PIDs have been included in the Tables; however the order of the Tables has been changed with **Table 2** now describing the "Well-defined syndromes with immunodeficiency" (previously **Table 3**) to reflect the immunological similarity between the disorders included in this Table and those in **Table 1**, "Combined immunodeficiencies."

Any classification of human disorders is somewhat arbitrary, and the classification of PIDs is no exception. Some disorders might well belong to more than one group. CD40 ligand deficiency, for example, is reported both in **Tables 1** and **3** ("Predominantly antibody deficiencies"), to reflect the facts that failed B cell isotype switching was historically the most prominent feature of this condition (originally named Hyper-IgM syndrome) and that some patients survive into adulthood without significant opportunistic infections and do well with only immunoglobulin replacement therapy. Explanatory notes provided after each Table offer additional information (particularly where a condition appears in more than one Table) and indicate which new disorders have been added to that Table.

Although this updated classification reports on the most typical immunological findings and associated clinical and genetic features for the various PIDs, there is extensive clinical, immunological, and molecular heterogeneity that can not be easily recapitulated in a brief summary. To facilitate a more rigorous analysis of each disease, a column has been added on the right to refer to its catalog number in the Online Mendelian Inheritance in Man (OMIM) publicly accessible database (www.omim.org) of human genetic disorders. It is suggested that the reader consult this regularly updated and fully referenced resource.

The prevalence of the various PIDs varies in different countries. For this reason, in this new classification, we have elected to avoid giving a comment on the relative frequency of PID disorders. However, an asterisk has been placed in the first column, after the disease name, to identify disorders for which fewer than 10 unrelated cases have been reported in the literature. Some of these forms of PID can be considered extremely rare. Others have only recently been identified and it may be that more patients will be detected over time.

Finally, it is increasingly recognized that different mutations in the same gene may result in different phenotypes and may be associated with different patterns of inheritance. This concept of clinical, immunological, and genetic heterogeneity is assuming foremost importance. Notes in the text or in the footnotes identify such heterogeneity, when known.

The scope of the IUIS Expert Committee on Primary Immunodeficiency is to increase awareness, facilitate recognition, and promote optimal treatment for patients with Primary Immunodeficiency disorders worldwide. For this reason, in addition to periodically revising the Classification of PIDs, the Expert Committee is also actively involved in the development of diagnostic criteria and in providing, upon request, advice with regard to therapeutic guidelines.

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. Both of these disorders 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, and granulomas with 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 *SLC19A1* or *PCFT*) and some metabolic disorders, such as methylmalonicaciduria, may present with reversible profound lymphopenia in addition to their characteristic presenting features.

Common Variable Immunodeficiency Disorders (CVID) include several clinical and laboratory phenotypes that may be caused by distinct genetic and/or environmental factors. Some patients with CVID and no known genetic defect have markedly reduced numbers of B cells as well as hypogammaglobulinemia. Alterations? in *TNFRSF13B* (*TACI*) and *TNFRSF13C* (*BAFF-R*) sequences may represent disease modifying mutations rather than disease causing mutations. CD40L and CD40 deficiency are included in **Table 1** as well as this table. A small minority of patients with XLP (**Table 4**), WHIM syndrome (**Table 6**), ICF (**Table 2**), VOD1 (**Table 2**), thymoma with immunodeficiency (Good syndrome) or myelodysplasia are first seen by an immunologist because of recurrent infections, hypogammaglobulinemia, and normal or reduced numbers of B cells. Patients with GATA2 mutations (**Table 5**) may have markedly reduced numbers of B cells, as well as decreased monocytes and NK cells and a predisposition to myelodysplasia but they do not have an antibody deficiency.

XR-EDA-ID is highly heterogeneous clinically, both in terms of developmental features (some patients display osteopetrosis and lymphedema, in addition to EDA, while others do not display any developmental features) and infectious diseases (some display multiple infections, viral, fungal, and bacterial, while others display a single type of infection). The various OMIM entries correspond to these distinct clinical diseases.

Muckle–Wells syndrome, familial cold autoinflammatory syndrome, and neonatal onset multisystem inflammatory disease (NOMID) which is also called chronic infantile neurologic cutaneous and articular syndrome (CINCA) are caused by similar mutations in CIAS1 mutations. The disease phenotype in any individual appears to depend on modifying effects of other genes and environmental factors.

Table 1 | Combined immunodeficiencies.

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
T^-B^+ SEVERE COMBINED IMMUNODEFICIENCY (SCID)							
γc deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells; leaky cases may present with low to normal T and/or NK cells or Omenn syndrome	XL	Defect in γ chain of receptors for IL-2, -4, -7, -9, -15, -21	300400
JAK3 deficiency	Markedly decreased	Normal or increased	Decreased	Markedly decreased NK cells; leaky cases may present with variable T and/or NK cells	AR	Defect in Janus activating kinase 3	600173
IL7Rα deficiency	Markedly decreased	Normal or increased	Decreased	Normal NK cells	AR	Defect in IL-7 receptor α chain	146661
CD45 deficiency*	Markedly decreased	Normal	Decreased	Normal γ/δ T cells	AR	Defect in CD45	151460
CD3δ*/ CD3ε*/CD3ζ* deficiency	Markedly decreased	Normal	Decreased	Normal NK cells Noγ/δT cells	AR	Defect in CD3δ, CD3ε, or CD3ζ chains of T cell antigen receptor complex	186790, 186830, 186740
Coronin-1A deficiency*	Markedly decreased	Normal	Decreased	Detectable thymus	AR	Defective thymic egress of T cells and defective T cell locomotion	605000
T^-B^- SCID							
RAG 1/2 deficiency	Markedly decreased	Markedly decreased	Decreased	May present with Omenn syndrome, expanded γ/δT cells, autoimmunity, and/or granulomas	AR	Defective VDJ recombination; defect of recombinase activating gene (RAG) 1 or 2	601457
DCLRE1C (Artemis) deficiency	Markedly decreased	Markedly decreased	Decreased	Defective VDJ recombination, radiation sensitivity; may present with Omenn syndrome	AR	Defective VDJ recombination; defect in Artemis DNA recombinase repair protein	602450
DNA PKcs deficiency*	Markedly decreased	Markedly decreased	Decreased	(Widely studied *scid* mouse defect)	AR	Defective VDJ recombination; defect in DNAPKcs recombinase repair protein	600899
Reticular dysgenesis, AK2 deficiency	Markedly decreased	Decreased or normal	Decreased	Deficiency of T, B, and NK cells with granulocytopenia, deafness	AR	Defective maturation of lymphoid and myeloid cells (stem cell defect) defect in mitochondrial adenylate kinase 2	103020
Adenosine deaminase (ADA) deficiency	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	AR	Absent ADA activity, elevated lymphotoxic metabolites (dATP, *S*-adenosylhomocysteine)	102700
Omenn syndrome	Present; restricted heterogeneity	Normal or decreased	Decreased, except increased IgE	Erythroderma, eosinophilia, adenopathies, hepatosplenomegaly	AR	Hypomorphic mutations in RAG1/2, Artemis, IL7Rα, RMRP, ADA, DNA Ligase IV, γc, or associated with DiGeorge syndrome; some cases have no defined gene mutation	603554

(Continued)

Table 1 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
DNA ligase IV deficiency	Decreased	Decreased	Decreased	Microcephaly, facial dysmorphisms, radiation sensitivity; may present with Omenn syndrome or with a delayed clinical onset	AR	DNA ligase IV defect, impaired non-homologous end joining (NHEJ)	601837
Cernunnos/ NHEJ1 deficiency*	Decreased	Decreased	Decreased	Microcephaly, *in utero* growth retardation, radiation sensitivity	AR	Cernunnos (NHEJ1) defect, impaired non-homologous end joining	611291
CD40 ligand deficiency	Normal; may progressively decrease	IgM^+ and IgD^+ B cells present, other isotypes absent	IgM increased or normal, other isotypes decreased	Neutropenia, thrombocytopenia; hemolytic anemia, biliary tract, and liver disease, opportunistic infections	XL	Defects in CD40 ligand (CD40L) cause defective isotype switching and impaired dendritic cell signaling	300386
CD40 deficiency*	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	AR	Defects in CD40 cause defective isotype switching and impaired dendritic cell signaling	109535
Purine nucleoside phosphorylase (PNP) deficiency	Progressive decrease	Normal	Normal or decreased	Autoimmune hemolytic anemia, neurological impairment	AR	Absent PNP, T cell, and neurologic defects from elevated toxic metabolites, especially dGTP	164050
CD3γ deficiency*	Normal, but reduced TCR expression	Normal	Normal		AR	Defect in CD3 γ	186740
CD8 deficiency*	Absent CD8, normal CD4 cells	Normal	Normal		AR	Defects of CD8 α chain	186910
ZAP-70 deficiency	Decreased CD8, normal CD4 cells	Normal	Normal		AR	Defects in ZAP-70 signaling kinase	176947
CA^{++} CHANNEL DEFICIENCY							
ORAI-I deficiency*	Normal number, but defective TCR mediated activation	Normal	Normal	Autoimmunity, anhydrotic ectodermic dysplasia, non-progressive myopathy	AR	Defect in ORAI-1, a Ca^{++} release-activated channel (CRAC) modulatory component	610277
STIM-1 deficiency*	Normal number, but defective TCR mediated activation	Normal	Normal	Autoimmunity, anhydrotic ectodermic dysplasia, non-progressive myopathy	AR	Defect in STIM-1, a stromal interaction molecule Ca^{++}sensor	605921
MHC class I deficiency	Decreased CD8, normal CD4	Normal	Normal	Vasculitis	AR	Mutations in *TAP1*, *TAP2* or *TAPBP* (tapasin) genes giving MHC class I deficiency	604571

(Continued)

Table 1 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
MHC class II deficiency	Normal number, decreased CD4 cells	Normal	Normal or decreased	Failure to thrive, diarrhea, respiratory tract infections	AR	Mutation in transcription factors for MHC class II proteins (*CIITA*, *RFX*5, *RFXAP*, *RFXANK* genes)	209920
Winged helix deficiency (nude)*	Markedly decreased	Normal	Decreased	Alopecia, abnormal thymic epithelium, impaired T cell maturation (widely studied nude mouse defect)	AR	Defects in forkhead box N1 transcription factor encoded by *FOXN*1, the gene mutated in nude mice	600838
Complete DiGeorge syndrome	Profoundly decreased	Low to normal	Decreased	Lymphoproliferation (lymphadenopathy, hepatosplenomegaly), autoimmunity (may resemble IPEX syndrome), impaired T cell proliferation	AD	Deletion of chromosome 22q11.2 or in a minority of cases other chromosomal regions, including 10p; heterozygous defects in transcription factor TBX1	188400
Cartilage hair hypoplasia	Decreased or 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	AR	Mutations in *RMRP* (RNase MRP RNA) Involved in processing of mitochondrial RNA and cell cycle control	250250
IKAROS deficiency*	Normal, but impaired lymphocyte proliferation	Absent	Presumably decreased	Anemia, neutropenia, thrombocytopenia	AD *de novo*	Mutation in *IKAROS*	
STAT5b deficiency*	Modestly decreased	Normal	Normal	Growth-hormone insensitive dwarfism, dysmorphic features, eczema, lymphocytic interstitial pneumonitis, autoimmunity	AR	Defects of STAT5b, impaired development and function of γδT cells, Treg, and NK cells, impaired T cell proliferation	604260
ITK deficiency*	Modestly decreased	Normal	Normal or decreased		AR	Defects in ITK, EBV associated lymphoproliferation	613011
MAGT1 deficiency*	Decreased CD4 cells	Normal	Normal	EBV infection, lymphoma; viral infections, respiratory and GI infections	XL	Mutations in MAGT1, impaired Mg^{++} flux leading to impaired TCR signaling	300715
DOCK8 deficiency	Decreased	Decreased	Low IgM, increased IgE	Low NK cells, hypereosinophilia, recurrent infections; severe atopy, extensive cutaneous viral, and bacterial (staph.) infections, susceptibility to cancer	AR	Defect in *DOCK*8	243700

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.

**Ten or fewer unrelated cases reported in the literature.*

*Three disorders have been added to **Table 1**: DOCK8 deficiency, IKAROS deficiency, and MAGT1 deficiency.*

Table 2 | Well-defined syndromes with immunodeficiency.

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
Wiskott–Aldrich syndrome (WAS)	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	XL	Mutations in *WAS*; cytoskeletal and immunologic synapse defect affecting hematopoietic stem cell derivatives	301000
DNA REPAIR DEFECTS (OTHER THAN THOSE IN TABLE 1)							
Ataxia–telangiectasia	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 X-ray sensitivity; chromosomal instability	AR	Mutations in *ATM*; disorder of cell cycle checkpoint and DNA double strand break repair	208900
Ataxia–telangiectasia-like disease (ATLD)*	Progressive decrease	Normal	Antibodies variably decreased	Moderate ataxia; pulmonary infections; severely increased radiosensitivity	AR	Hypomorphic mutations in *MRE*11; disorder of cell cycle checkpoint and DNA double-strand break repair	604391
Nijmegen breakage syndrome	Progressive decrease	Variably reduced	Often decreased IgA, IgE, and IgG subclasses; increased IgM; antibodies variably decreased	Microcephaly; bird like face; lymphomas; solid tumors; ionizing radiation sensitivity; chromosomal instability	AR	Hypomorphic mutations in *NBS*1 (*Nibrin*); disorder of cell cycle checkpoint and DNA double-strand break repair	251260
Bloom syndrome	Normal	Normal	Reduced	Short stature; bird like face; sun-sensitive erythema; marrow failure; leukemia; lymphoma; chromosomal instability	AR	Mutations in *BLM*; RecQ like helicase	210900
Immunodeficiency with centromeric instability and facial anomalies (ICF)	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	AR	Mutations in DNA methyltransferase *DNMT3B* (ICF1) resulting in defective DNA methylation; or in *ZBTB*24 (ICF2)	242860
PMS2 deficiency (class switch recombination deficiency due to impaired mismatch repair)	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	AR	Mutations in *PMS*2, resulting in defective CSR-induced DNA double-strand breaks in Ig switch regions	600259

(Continued)

Table 2 | Continued

Disease	Circulating T cells	Circulating B cells	Serum Ig	Associated features	Inheritance	Genetic defect/ presumed pathogenesis	OMIM number
Riddle syndrome*	Normal	Normal	Low IgG	Mild motor control and learning difficulties, mild facial dysmorphism, and short stature	AR	Mutations in RNF168, resulting in defective DNA double-strand break repair	611943
THYMIC DEFECTS							
DiGeorge anomaly (chromosome 22q11.2 deletion syndrome)	Decreased or normal	Normal	Normal or decreased	Hypoparathyroidism, conotruncal malformation; abnormal facies; large deletion (3 Mb) in 22q11.2 (or rarely a deletion in 10p)	*De novo* defect or AD	Contiguous gene defect in 90% affecting thymic development; mutation in *TBX*1	188400
IMMUNE-OSSEOUS DYSPLASIAS							
Cartilage hair hypoplasia	Decreased or 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	AR	Mutations in *RMRP* (RNase MRP RNA) Involved in processing of mitochondrial RNA and cell cycle control	250250
Schimke syndrome	Decreased	Normal	Normal	Short stature, spondyloepiphyseal dysplasia, intrauterine growth retardation, nephropathy; bacterial, viral, fungal infections; may present as SCID; bone marrow failure	AR	Mutations in *SMARCAL*1 Involved in chromatin remodeling	242900
Comel–Netherton syndrome	Normal	Switched and non-switched B cells are reduced	Elevated IgE and IgA antibody variably decreased	Congenital ichthyosis, bamboo hair, atopic diathesis, increased bacterial infections, failure to thrive	AR	Mutations in *SPINK*5 resulting in lack of the serine protease inhibitor LEKTI, expressed in epithelial cells	256500
HYPER-IGE SYNDROMES (HIES)							
AD-HIES (job syndrome)	Normal Th-17 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, failure/delay of shedding primary teeth, hyperextensible joints, bacterial infections (skin and pulmonary abscesses, pneumatoceles) due to *Staphylococcus aureus*, candidiasis	AD often *de novo* defect	Dominant-negative heterozygous mutations in *STAT*3	
AR-HIES				No skeletal and connective tissue abnormalities; no pneumatoceles	AR		
Tyk2 deficiency*	Normal, but multiple cytokine signaling defect	Normal	(±) Elevated IgE	Susceptibility to intracellular bacteria (mycobacteria, *Salmonella*), fungi, and viruses		Mutation in *TYK*2	243700

(Continued)