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UPDATE

Primary immunodeficiency diseases: an update

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The last full report of the IUIS Scientific Committee for Primary Immunodeficiencies [PIDs] was published in *Clinical and Experimental Immunology* over 3 years ago [1]. This covered the relevant basic immunological principles, cellular, genetic, humoral (including cytokine) and induction aspects of immune responses to those microbial antigens involved in human infections. All primary immunodeficiencies (and the investigations required for diagnosis) are discussed in turn, ranging from combined deficiencies of T and B cells, predominantly humoral defects, T cell defects (including those of cytokine and cytokine receptor production), complement and phagocyte deficiencies and those immunodeficiencies associated with genetic defects in related systems. A section on therapies and brief descriptions of causes of secondary immunodeficiencies completed the knowledge of ID known at that time.

The report was timely and has been much quoted in the literature as a reference point for papers on mechanisms of both PID diseases and their treatments. The citation index must be substantial.

The most recent meeting of this committee took place in July 2001. During the intervening 2 years there were few new types of PID; most of the newly described diseases were extensions of current phenotypes such as:

- recently described enzymes in established pathways (e.g. in VDJ recombination (Artemis), STAT1 in interferon:IL-12 pathways);
- another immunoglobulin isotype switch defect enzyme (AID) presenting as autosomal hyper IgM;
- a new DNA repair enzyme resulting in another ataxia-like syndrome;
- an interaction where previously only one of a pair of ligands had been identified as missing (e.g. CD40).

Thus a major review was not necessary.

The logical progression through the various ways in which parts of the immune system fail make these tables a useful starting point for newcomers to this field. This has also enabled new diseases and those illustrating some newer concepts to be fitted in easily to the existing format.

There are some new concepts, such as:

- selective loss of $CD8^+$ cells (CD8 deficiency), which may/may not turn out to be a lineage differentiation problem;
- finding a human corollary of a known mouse defect (Winged Helix Nude);
- another X-linked disease, explaining one form of ectodermal dysplasia; perhaps there may be more?
- two new forms of leucocyte adhesion defect, with new receptor/pathways to be explored.

There are insufficient advances to reconfigure the tables or to subdivide in a more meaningful way at this stage. The revised tables below (Tables 1–3 and 5) should be read in conjunction with the text published previously. This update provides an excellent opportunity to re-emphasize that many developments in basic immunology have been suggested by/discovered alongside newly described PIDs. This is due to extensive investigation of patients in whom a diagnosis of one of the current 90 or so PIDs is not possible. Such patients provide a rich resource for identifying new genes that turn out to be important in normal immune responses. Hence new pathways are discovered and this results in the wider interest of basic immunologists, completing a longstanding and fruitful collaboration between clinical and basic science. Scientists are hugely important in studying those patients recognized by physicians to have an immune defect (due to the nature and frequency of infections), but in whom there is no clear diagnosis. This is especially relevant in those patients with a family history of the same disease phenotype or from consanguineous marriages, in whom autosomal recessive diseases are most common.

It is encouraging to note the increasing prevalence of many PIDs. This may be due partly to improved techniques for diagnosis, but the collaborative development of definitions and simple 'diagnostic criteria' for use worldwide has undoubtedly played a role [2]. The production of a new major text devoted to PIDs (now in a second edition) has emphasized that the study of PIDs has come of age. The role of these diseases in the successful application of gene therapy helps to underline this.

The next meeting of the IUIS Scientific Committee for Primary Immunodeficiencies is to be held in June 2003. There will be a detailed review of known PIDs at that time and we can look forward to more excitement in the form of new diseases and increased knowledge of immune pathways relevant to protection against infection in humans. Each advance is accompanied by improved diagnostic tests and new technologies result in improvements in therapy. There has never been a better time to enter this exciting and rapidly moving field of immunobiology.

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Table 1. Combined immunodeficiencies

Designation	Serum Ig	Circulating B cells	Circulating T cells	Presumed pathogenesis	Inheritance	Associated features
1. T-B + SCID*						
(a) X-linked (γc deficiency)	Decreased	Normal or increased	Markedly decreased	Mutations in γ chain of IL-2,4,7,9,15, 21 receptors	XL	Markedly decreased NK
(b) Autosomal recessive (Jak3 deficiency)	Decreased	Normal or increased	Markedly decreased	Mutation in Jak3	AR	Markedly decreased NK
(c) IL7R deficiency	Decreased	Normal or increased	Markedly decreased	Mutation in IL7Rα gene	AR	Normal NK
(d) CD45 deficiency	Decreased	Normal	Markedly decreased	Mutations in CD45 gene	AR	Normal $\gamma\delta$T cells
2. T-B-SCID						
(a) RAG 1/2 deficiency	Decreased	Markedly decreased	Markedly decreased	Mutation in RAG1 or 2 genes	AR	
(b) Artemis deficiency	Decreased	Decreased	Decreased	Defective VDJ recombination	AR	Radiation sensitivity
(c) Adenosine deaminase (ADA) deficiency	Decreased	Progressive decrease	Progressive decrease	T-cell and B-cell defects from toxic metabolites (e.g. dATP, S-adenosyl homocysteine) due to enzyme deficiency	AR	
(d) Reticular dysgenesis	Decreased	Markedly decreased	Markedly decreased	Defective maturation of T and B cells and myeloid cells (stem cell defect)	AR	Granulocytopenia; Thrombocytopenia
3. Omenn syndrome	Decreased; but increased IgE	Normal or decreased	Present; restricted heterogeneity	Missense mutations in RAG1 or 2 genes	AR	Erythroderma; Eosinophilia; Hepatosplenomegaly
4. X-linked hyper IgM syndrome	IgM increased or normal; other isotypes decreased	IgM & IgD bearing cells present but others absent	Normal	Mutations in CD40 ligand gene	XL	Neutropenia; Thrombocytopenia; Haemolytic anaemia; Gastrointestinal & liver involvement; opportunistic infections
5. CD40 deficiency	IgM increased or normal; other isotypes decreased	IgM & IgD bearing cells present but others absent	Normal	Mutations in CD40 gene	AR	Neutropenia

Table 1. *Continued*

6. Purine nucleoside phosphorylase (PNP) deficiency	Normal or decreased	Normal	Progressive decrease	T-cell defect from toxic metabolites (e.g. dGTP) due to enzyme deficiency	AR	Autoimmune haemolytic anaemia: neurological symptoms
7. MHC class II deficiency	Normal or decreased	Normal	Normal, decreased CD4 numbers	Mutation in transcription factors (CIITA or RFX5, RFXAP, RFXANK genes) for MHC class II molecules	AR	
8. CD3γor CD3ε deficiency	Normal	Normal	Normal	Defective transcription of CD3γor CD3ε chain	AR	
9. CD8 deficiency	Normal	Normal	Absent CD8, normal CD4	Mutations of CD8α gene	AR	
10. ZAP-70 deficiency	Normal	Normal	Decreased CD8, normal CD4	Mutations in Zap-70 kinase gene	AR	
11. TAP-1 deficiency	Normal	Normal	Decreased CD8, normal CD4	Mutations in TAP-1 gene	AR	MHC class I deficiency
12. TAP-2 deficiency	Normal	Normal	Decreased CD8, normal CD4	Mutations in TAP-2 gene	AR	MHC class I deficiency
13. Winged Helix Nude (WHN)-deficiency	Decreased	Normal	Markedly decreased	Mutation in WHN gene	AR	Alopecia; thymic epithelium abnormal

New defects: A T-B-autosomal recessive SCID has been shown to result from a defect in a novel gene Artemis that encodes an enzyme involved in VDJ recombination. There is a founder effect of this gene defect among Athabascan Indians who have a very high incidence of SCID.

A new autosomal recessive hyper-IgM syndrome has been added where clinical manifestations are similar to the X-linked form of the disease; it has been shown to result from mutations in the gene encoding CD40.

A case of CD8 deficiency has been found to be due to a mutation in the CD8α gene. The patient has absent $CD8^+$ cells, but normal $CD4^+$ cells.

The defect in nude mice has been shown to result from mutations in a transcription factor called Winged Helix Nude (WHN). This defect has now been discovered in human infants who display alopecia and abnormalities of the thymic epithelium.

*Atypical cases of γc or Jak3 deficiency may present with T cells.

Abbreviations: SCID, severe combined immune deficiencies; XL, X-linked inheritance; AR, autosomal recessive inheritance; NK, natural killer cells.

Table 2. Predominantly antibody deficiencies

Associated designation	Serum Ig	Circulating B cells	Presumed pathogenesis	Inheritance	Associated features
1. X-linked agammaglobulinaemia	All isotypes decreased	Profoundly decreased	Mutations in *btk*	XL	Severe bacterial infections
2. Autosomal recessive agammaglobulinaemia	All isotypes decreased	Profoundly decreased	Mutations in μ Igα, Igβ, λ5, Vpreβ genes; or BLNK and syk genes	AR	Severe bacterial infections
3. Ig heavy-chain gene deletions	IgG1 or IgG2, IgG4 absent and in some cases IgE and IgA1 or IgA2 absent	Normal or decreased	Chromosomal deletion at 14q32	AR	Not always symptomatic
4. κ Chain deficiency mutations at AR	Ig(K) decreased: antibody response normal or decreased	Normal or decreased κ-bearing cells	Point mutations at chromosome 2p11 in some patients	AR	–
5. Selective Ig deficiency					Not always symptomatic
(a) IgG subclass deficiency	Decrease in one or more IgG isotypes	Normal or immature	Defects of isotype differentiation	Unknown	
(b) IgA deficiency	Decrease in IgA1 and IgA2	Normal or decreased sIgA+	Failure of terminal differentiation in IgA+ve B cells	Variable	Autoimmune or allergic disorders; some have infections
6. Antibody deficiency with normal or elevated Igs	Normal	Normal	Unknown	Unknown	Selective inability to make antibody to polysaccharides See below[a]
7. Common variable immunodeficiency	Decrease in IgG and usually IgA, ± IgM	Normal or decreased	Variable; undetermined	Variable	
8. Transient hypogammaglobulinaemia of infancy	IgG and IgA decreased	Normal	Differentiation defect: delayed maturation of helper function	Unknown	Frequent in families with other Ids
9. AID deficiency	IgG and IgA decreased	Normal	Mutation in activation-induced cytidine deaminase gene	AR	Enlarged lymph nodes and germinal centres

New defect: A deficiency of activation induced cytidine deaminse (AID) presents as a form of the hyper-IgM syndrome but differs from CD40L and CD40 deficiencies in that the patients have large lymph nodes with germinal centres and are not susceptible to opportunistic infections.

[a] Common variable immunodeficiency: there are several different clinical phenotypes, probably representing distinguishable diseases with differing immunopathogeneses.

Abbreviations: As for Table 1; Ig(K), immunoglobulin of kappa light-chain type; *btk*, Bruton's tyrosine kinase gene.

Table 3. Other well-defined immunodeficiency syndromes

Designation	Serum Ig and antibodies	Circulating B cells	Circulating T cells	Genetic defect	Inheritance	Associated features
1. Wiskott–Aldrich syndrome	Decreased IgM: antibody to polysaccharides particularly decreased; often increased IgA and IgE	Normal	Progressive decrease	Mutations in WASp gene; cytoskeletal defect affecting haematopoietic stem cell derivatives	XL	Thrombocytopenia; small defective platelets; eczema; lymphomas; autoimmune disease
2. Ataxia-telangiectasia	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Normal	Decreased	Mutation in A-T gene (*ATM*); disorder of cell cycle check-point pathway leading to chromosomal instability	AR	Ataxia; telangiectasia; increased alpha fetoprotein; lympho-reticular and other malignancies; increased X-ray sensitivity
(a) Ataxia-like syndrome	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Normal	Decreased	Mutation in Mre 11	AR	Moderate ataxia; severely increased radiosensitivity
3. Nijmegen breakage syndrome	Often decreased IgA, IgE and IgG subclasses; increased IgM monomers; antibodies variably decreased	Normal	Decreased	Defect in *NBS1* (*Nibrin*); disorder of cell cycle checkpoint and DNA double-strand break repair	AR	Microcephaly lymphomas; ionizing radiation sensitivity; chromosomal instability
4. DiGeorge anomaly	Normal or decreased	Normal	Decreased or normal	Contiguous gene defect in 90% affecting thymic development	*De novo* defect or AD	Hypoparathyroidism: conotruncal malformation; abnormal facies; partial monosomy of 22q11-pter or 10p in some patients

Table 3. *Continued*

Designation	Serum Ig and antibodies	Circulating B cells	Circulating T cells	Genetic defect	Inheritance	Associated features
5. Imunodeficiency with albinism						
(a) Chediak Higashi syndrome	Normal	Normal	Normal	Defect in *Lyst*	AR	Albinism; acute phase reaction; low NK and CTL activities; giant lysosomes
(b) Griscelli syndrome	Normal	Normal	Normal	Defect in *myosin 5a,* or RAB27A	AR	Albinism; acute phase reaction; low NK and CTL activities; progressive encephalopathy in severe cases
6. X-linked lympho-proliferative syndrome	Normal or rarely hypogammaglobulinaemia	Normal or reduced	Normal	Defect in *SAP*/SH2DRA	XL	Clinical and immunological manifestations induced by EBV infection; hepatitis; aplastic anaemia; lymphomas
7. Familial haemaphagocytic lymphohistiocytosis	Normal	Normal	Normal	Mutation in perforin gene	AR	Decreased NK and CTL activities
8. Immune dysregulation, polyendocrinopathy, enteropathy, X–linked syndrome (IPEX)	Normal or increased	Normal	Normal, activated phenotype	Mutation in FOXP3	XL	Severe skin involvement; early onset IDDM
9. Autoimmune polyendocrinopathy and ectodermal dysplasia	Normal	Normal	Normal	Mutation in AIRE	AR	Chronic mucocutaneous candidiasis
10. X-linked immunodeficiency and ectodermal dysplasia	Often low IgG and IgA with normal or high IgM	Normal	Normal	Mutation in NEMO/IKKγ	XL	Conical teeth and sparse hair

New defects: an ataxia telangiectasia-like syndrome is due to mutations in the gene encoding Mre11, an enzyme involved in DNA repair.

Another X-linked immunodeficiency associated with ectodermal dysplasia has been found to be due to a mutation in the scaffolding γ subunit of the NF-κB activator (IKK*k*/NEMO). These patients have sparse hair, conical malformed teeth and defects in activation of monocytes, NK cells, T cells and B cells.

Abbreviations: As for Table 1; CTL, cytotoxic T lymphocytes; EBV, Epstein Barr Virus; IDDM, insulin-dependent diabetes mellitus.

Table 5. Congenital defects of phagocytic number and/or function

Disease	Affected cells	Functional defects	Genetic defect	Inheritance	Features
Severe congenital neutropenia (Kostmann)	N	–	Elastase 2	AD	Subgroup with myelodysplasia
Cyclic neutropenia	Mainly N	–	Elastase 2	AD	Oscillations of other leucocytes, reticulocytes and platelets
X-linked neutropenia	N + M	–	WASP	XL	–
Leucocyte adhesion defect 1	N + M + L + NK	Chemotaxis, adherence, endocytosis	CD18 (of LFA-1, Mac 1, p 150,95)	AR	Delayed cord separation, chronic skin ulcers, periodontitis, leucocytosis, defective T +NK cell cytotoxicity
Leucocyte adhesion defect 2	Mainly N + M	Chemotaxis, rolling	GDP-fucose-transporter	AR	Delayed wound healing, chronic skin ulcers, periodontitis, leucocytosis, Bombay blood group, mental retardation
Rac-2 GTPase-defect	N	Chemotaxis, adherence	GTPase Rac2	AD	Delayed wound healing, leucocytosis
Localized juvenile periodontitis	N	Formyl peptide-induced chemotaxis	Formyl peptide receptor	AR	Periodontitis
Specific granule defect	N	Chemotaxis	CCAAT/enhancer binding protein ε	AR	N with bi-lobed nuclei
Shwachman–Diamond syndrome	N	Chemotaxis	Unknown	AR	Pancytopenia, pancreatic insufficiency, chondrodysplasia
Chronic granulomatous disease					
(a) X-linked CGD	N + M	Killing (faulty production of superoxide metabolites)	gp 91 phox	XL	McLeod phenotype*
(b) Autosomal CGDs	N + M	Killing – as above	p22 phox; p47 phox; p67 phox	AR	
Neutrophil G-6 PD defect	N + M	Killing	Glucose-6-P-dehydrogenase	XL	Haemolytic anaemia
Myeloperoxidase deficiency	N	Killing	MPO	AR	This deficiency may be found in normal people
Leucocyte mycobactericidal defects:		Killing – failure of			Susceptibility to mycobacteria and salmonella
(a) IFN-γ receptor defects	M	upregulation of interferon	IFN-γR1; IFN-γR2	AR/AD; AR	
(b) STAT-1-defect	M	production	STAT-1	AD	
(c) Interleukin-12-receptor defect	L + NK		IL12Rβ1	AR	
(d) Interleukin-12-defect	M		IL12p40	AR	

New defects: a new form of leucocyte adhesion defect is due to a mutation in the small GTPase Rac2. There is defective chemotaxis and poor adherence of neutrophils in affected patients who display delayed wound healing.

Another form of LAD has been found in children with localized periodontitis caused by mutations in the formyl peptide receptor.

Another leucocyte mycobactericidal defect has been found in patients with mutations in the STAT1 gene, which encodes the transcription factor that is activated by the interferon-γ receptor.

*Some patients have deletions in the short arm of the X-chromosome; in these patients additional features, including McLeod phenotype, retinitis pigmentosa and Duchenne muscular dystrophy, may be found.

Abbreviations: As for Table 1; N, neutrophils; M, monocytes/macrophages; L, lymphocytes; NK, natural killer cells; AD, autosomal dominant inheritance.