Chapter 11
Genetic Syndromes with Associated Immunodeficiencies

Rebecca A. Marsh and Andrew W. Lindsley

Introduction

There are a variety of genetic syndromes that are associated with defects in the immune system. They are sometimes collectively referred to as "syndromic primary immunodeficiencies" (PIDs) or "syndromic immunodeficiencies" [1, 2]. Syndromic PIDs are usually considered to encompass diseases which feature *prominent* non-immune system problems that form a recognizable syndrome. The immunodeficiencies associated with these syndromes can be highly variable, and not all patients may have immunodeficiency.

The International Union of Immunological Societies (IUIS) primary immunodeficiency expert committee regularly publishes a classification of inborn errors of immunity. The 2019 update on the classification included over 400 inborn errors of immunity [3]. More than 60 genetic diseases with associated immunodeficiencies are classified as "combined immunodeficiencies with associated or syndromic features," and additional inborn errors of immunity with syndromic features can be found elsewhere in the IUIS Classification. For instance, DNA ligase IV deficiency due to mutations in *LIG4*, which is characterized by microcephaly, is classified with the severe combined immune deficiencies, and several pigmentary syndromes are classified with the diseases of immune dysregulation because they also cause hemophagocytic lymphohistiocytosis (HLH).

Genetic syndromes with associated immunodeficiencies can be caused by known single-gene defects or complex chromosomal abnormalities, or the cause of disease

R. A. Marsh (✉)
Bone Marrow Transplantation and Immune Deficiency, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: Rebecca.Marsh@cchmc.org

A. W. Lindsley
Department of Allergy and Immunology, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

J. A. Bernstein (ed.), *Primary and Secondary Immunodeficiency*,
https://doi.org/10.1007/978-3-030-57157-3_11

may be unknown. The spectrum of immunologic defects varies from severe and life-threatening to relatively mild. Even within the same disorder the clinical spectrum of immunologic disease may be wide. A good example of this clinical heterogeneity is DiGeorge syndrome. A patient with DiGeorge syndrome may have a complete athymia and absence of T cells (complete DiGeorge syndrome) which will result in life-threatening infections and a high likelihood of death without correction, or may manifest with only very mild/subtle immune abnormalities which can be asymptomatic [4]. While a complete review of all genetic syndromes associated with syndromic immunodeficiency is outside the scope of this chapter, we present two representative cases to illustrate their complexity and discuss additional generalities.

Case Presentation 1

A 10-year-old female was referred to immunology clinic for a history of recurrent upper respiratory infections, otitis media, and two episodes of pneumonia. She had a history of developmental delay and dysmorphism. The patient did not walk until 2.5 years of age, and speech development was also delayed. She is below grade level at school and has been in special reading and math classes. She wears hearing aids. She has not been fully vaccinated due to parental concern for association with developmental delay.

Physical examination revealed a well-nourished but short pre-pubertal female whose height and weight were <3rd percentile and 40th percentile, respectively. Facial abnormalities were noted and included long palpebral fissures, eversion of the lower lateral eyelids, long eyelashes, arched eyebrows, flattened tip of nose, and large ears (Fig. 11.1). A close inspection of the hands revealed that the fifth fingers bilaterally appeared abnormally shorter than the other digits.

Given the characteristic facial features and developmental delay, Kabuki syndrome, an autosomal dominant congenital epigenetic disease, was suspected. Laboratory evaluations were notable for low levels of IgG (240 mg/dL), IgA (13 mg/dL), and IgM (24 mg/dL). Lymphocyte subset analysis was normal. Mitogen-stimulated proliferation studies were normal. Complete blood count revealed a mildly low platelet count of 97×10^3/mcL. Genetic testing revealed a de novo heterozygous pathologic variant in the *KMT2D* gene, which is the most common cause of Kabuki syndrome (also known as type 1 Kabuki syndrome). *KMT2D* encodes lysine-specific methyltransferase 2D, part of a family of proteins that function as histone methyltransferases [5]. In contrast, type 2 Kabuki syndrome is caused by pathologic variants in *KDM6A* which encodes lysine-specific demethylase 6A, a histone demethylase located in the pseudoautosomal region of the X chromosome [5]. Defects in either enzyme lead to abnormal histone methylation and are thought to disrupt normal regulation of genes important in developmental and other processes [5].

Fig. 11.1 Typical facial features of a patient with Kabuki syndrome

Following the diagnosis, the patient was started on immunoglobulin replacement for treatment of humoral deficiency [6]. Additional screening evaluations were undertaken to look for clinical abnormalities associated with Kabuki syndrome (Table 11.1) such as renal/urinary tract and cardiac malformations which can be observed in approximately 30–40% and 40–50% of patients, respectively [7]. An abdominal ultrasound was normal. A cardiac echo revealed an atrial septal defect, and the patient was referred to cardiology. Skeletal X-rays were normal. An endocrinology referral was made for evaluation of short stature, and the patient was found to be growth hormone deficient, another complication of Kabuki syndrome [7]. A hematology referral was made and a diagnosis of immune thrombocytopenia was made after testing for platelet autoantibodies. The patient was also referred to genetics and developmental clinics.

Case Presentation 2

A 15-month-old female was referred to immunology clinic for a history of recurrent severe infections. At 3 months of age, she required hospitalization for diarrhea and respiratory distress requiring oxygen. She was found to have enterovirus and rhinovirus infections. At 4 months of age, she was hospitalized with enterovirus meningitis. At that time, she was noted to have a low IgG and was started on intravenous immunoglobulin replacement. At 6 months of age, she developed *Pneumocystis jirovecii* pneumonia. She also had a history of failure to thrive.

Table 11.1 Selected non-immune features that may be present in a number of genetic syndromes with associated immunodeficiencies

Disease	Molecular defect	Selected non-immune features which may be present	OMIM	Reference(s)
3-Methylglutaconic aciduria type VII	*CLPB*	Progressive encephalopathy, movement abnormalities, microcephaly, developmental delay, cataracts, seizures	616254	[17]
Ataxia telangiectasia	*ATM*	Radiation sensitivity; cerebellar ataxia, telangiectasia, dysarthric speech, oculomotor apraxia, predisposition to malignancy	607585	[18]
Ataxia telangiectasia-like disease	*MRE11*	Radiation sensitivity; cerebellar degeneration, ataxia	600814	[19–21]
Barth syndrome (3-methylglutaconic aciduria type II)	*TAZ*	Cardiomyopathy, dysmorphism, growth retardation, cognitive impairment	300394	[22]
BCL11B deficiency	*BCL11B*	Developmental delays, intellectual disability, dysmorphism	606558	[23, 24]
Bloom syndrome	*BLM*	Microcephaly, intrauterine and postnatal growth retardation, telangiectatic erythema, cancer predisposition, endocrine abnormalities	604610	[25]
Ca2+ channel deficiency	*STIM1, ORA11*	Hypotonia, abnormal dental enamel, anhidrotic ectodermal dysplasia	605921, 610277	[26]
Cartilage-hair hypoplasia	*RMRP*	Sparse hair, short-limbed dwarfism, ligamentous laxity, anemia, Hirschsprung's disease, cancer predisposition	157660	[27]
Cernunnos deficiency	*NHEJ1*	Radiation sensitivity; microcephaly, intrauterine and postnatal growth retardation	611290	[28]

Table 11.1 (continued)

Disease	Molecular defect	Selected non-immune features which may be present	OMIM	Reference(s)
CHARGE syndrome	*CHD7*	Colobomas, congenital heart malformations, choanal atresia, growth retardation, genital anomalies, ear anomalies, tracheoesophageal fistula, dysmorphism	608892	[29]
Chediak-Higashi syndrome	*LYST*	Partial albinism, neurologic problems	606897	[30]
Cohen syndrome	*VPS13B*	Developmental delay, microcephaly, facial dysmorphism, truncal obesity, joint hypermobility, neutropenia	607817	[31, 32]
Netherton syndrome	*SPINK5*	Congenital ichthyosiform erythroderma, trichorrhexis invaginata, atopy	605010	[33, 34]
DiGeorge syndrome	*22q11.2 deletion*	Congenital heart malformations, hypocalcemia, palatal abnormalities, developmental delay, behavioral problems, learning disabilities, renal abnormalities	602054	[35]
DNA ligase IV deficiency	*LIG4*	Radiation sensitivity; microcephaly, dysmorphism, bone abnormalities, growth retardation	601837	[36]
Dyskeratosis congenita	*DKC1*, *TERC*, *TERT*, *TINF2*, *RTEL1*, *ACD*, *NOP10*, *NHP2*, *WRAP53*, *PARN*	Short telomeres, marrow failure, pulmonary fibrosis, nail dystrophy, oral leukoplakia	300126, 602322, 187270, 604319, 608833, 609377, 606471, 606470, 612661, 604212	[37]
ERCC6L2 deficiency	*ERCC6L2*	Marrow failure, learning disabilities, microcephaly	615667	[38, 39]

(continued)

Table 11.1 (continued)

Disease	Molecular defect	Selected non-immune features which may be present	OMIM	Reference(s)
EXTL3 deficiency	*EXTL3*	Platyspondyly, cervical malformations, short stature, developmental delay, intellectual disabilities	605744	[40, 41]
G6PC3 deficiency (SCN4)	*G6PC3*	Congenital heart malformations, prominent superficial venous pattern, uro-genital anomalies	611045	[42]
GINS1 deficiency	*GINS1*	Prenatal and postnatal growth retardation, facial dysmorphism	610608	[43]
Griscelli syndrome	*RAB27A*	Partial albinism	603868	[44]
Hennekam-lymphangiectasia-lymphedema syndrome	*CCBE1*	Lymphedema, lymphangiectasia, dysmorphism, developmental delay	612753	[45]
Hepatic veno-occlusive disease with immunodeficiency	*SP110*	Hepatic veno-occlusive disease	604457	[46]
Hyper IgE syndrome AD	*STAT3*	Distinctive/coarse facial features, eczema, retained primary teeth, joint hyperflexibility, scoliosis, bone fractures	102582	[47]
ICF syndrome	*DNMT3B*, *ZBTB24*, *CDCA7*, *HELLS*	Dysmorphism, centromeric instability	602900, 614064, 609937, 603946	[9, 48–50]
Immune deficiency with multiple intestinal atresias	*TTC7A*	Intestinal atresia	609332	[51, 52]
IκBα (ectodermal dysplasia and immunodeficiency 2)	*IκBα*	Anhidrotic ectodermal dysplasia	164008	[53]
JAGN1 deficiency	*JAGN1*	Bone and dental abnormalities	616012	[54]

Table 11.1 (continued)

Disease	Molecular defect	Selected non-immune features which may be present	OMIM	Reference(s)
Kabuki syndrome	*KMT2D*, *KDM6A*	Distinctive facial features, growth delay, intellectual disability, skeletal abnormalities, short stature, cardiac abnormalities, renal abnormalities, autoimmunity	602113, 300128	[5, 7]
Leukocyte adhesion deficiency type II	*SLC35C1*	Dysmorphism, developmental delay, short stature	605881	[55]
Leukocyte adhesion deficiency type III	*FERMT3*	Bleeding tendency	607901	[56, 57]
MCM4 deficiency	*MCM4*	Glucocorticoid deficiency/ adrenal failure, failure to thrive, short stature	602638	[58]
MOPD1 deficiency (Roifman syndrome)	*RNU4ATAC*	Dysmorphism, growth retardation, cognitive delay, spondyloepiphyseal dysplasia	601428	[59]
NEMO	*NEMO*	Ectodermal dysplasia, conical or missing teeth, hypohydrosis	300248	[60]
Nijmegen breakage syndrome	*NBS1*	Radiation sensitivity; microcephaly, bird-like facies, growth retardation, intellectual disability	602667	[61]
NSMCE3 deficiency	*NSMCE3*	Dysmorphism, failure to thrive, psychomotor retardation	608243	[62]
PNP (purine nucleoside phosphorylase) deficiency	*PNP*	Neurologic problems such as spasticity, ataxia, developmental delay, intellectual disability	164050	[63]
RAD50 deficiency	*RAD50*	Radiation sensitivity; dysmorphism, microcephaly, growth retardation	604040	[64]
Schimke immuno-osseous dysplasia	*SMARCAL1*	Spondyloepiphyseal dysplasia, short stature, nephropathy, dysmorphism, cerebral infarcts	606622	[65]

(continued)

Table 11.1 (continued)

Disease	Molecular defect	Selected non-immune features which may be present	OMIM	Reference(s)
Shwachman-Diamond syndrome	*SBDS*, *DNAJC21*, *EFL1*	Marrow failure, exocrine pancreatic insufficiency, skeletal abnormalities, intellectual disability	607444, 617052, 617941	[66]
SMARCD2 deficiency	*SMARCD2*	Dysmorphism, developmental delay, bone marrow fibrosis, dysplasia	601736	[67]
STAT5b deficiency	*STAT5b*	Poor growth due to growth hormone insensitivity	604260	[68]
Vici syndrome	*EPG5*	Agenesis of the corpus callosum, cataracts, pigmentary defects, cardiomyopathy	615068	[69]
VPS45 deficiency (SCN5)	*VPS45*	Bone marrow fibrosis	610035	[70, 71]
WHIM	*CXCR4*	Warts (though related to the immune deficiency), myelokathexis	162643	[72]
Wiskott-Aldrich syndrome	*WAS*	Small platelets, eczema, predisposition to malignancy	300392	[73]

On examination, the patient was noted to be thin with a protuberant abdomen. Facial features were notable for mild hypertelorism and low-set ears. Immunologic evaluations were notable for undetectable IgA and IgM, normal lymphocyte subset analysis, lack of class-switched memory B cells, normal distribution of naïve and memory T cells, and normal mitogen-stimulated proliferation studies.

A syndromic immune deficiency was suspected based on the facial features. A large commercially available genetic panel for primary immunodeficiencies was ordered and resulted with one likely pathologic and one variant of uncertain clinical significance in the *DNMT3B* gene which is associated with immunodeficiency, centromeric instability, and facial dysmorphism (ICF) syndrome [1]. ICF syndrome is caused by defective chromosomal methylation. Metaphase chromosomes from phytohemagglutinin-stimulated blood cultures that are performed during routine clinical chromosome analysis can exhibit several anomalies such as whole-arm deletions and pericentromeric breaks of chromosomes 1, 9 and 16, and multiradial configurations containing three or more arms of these chromosomes are striking [8–12]. A routine chromosome analysis was performed and revealed the typical multi-radial configurations involving chromosome 1, which confirmed the clinical diagnosis (Fig. 11.2) [13]. Due to the severity of the primary immunodeficiency, the patient ultimately underwent successful allogeneic hematopoietic cell transplantation.

Fig. 11.2 Radial figures identified for chromosome 1 after phytohemagglutinin stimulation of a blood sample collected from a patient with ICF syndrome. (Image courtesy of Teresa Smolarek, PhD)

General Considerations in Genetic Syndromes with Associated Immunodeficiencies

The immune evaluation for patients suspected to have a primary immunodeficiency component of their syndromic disease is essentially the same as for other patients suspected to have primary immunodeficiencies. Evaluations can be tailored or emphasized depending on the underlying disorder if it is known. For example, a patient with Barth syndrome should have a complete blood count to screen for neutropenia, and a patient with GINS1 deficiency should be screened for neutropenia as well as NK-cell deficiency. A known Kabuki syndrome patient should have careful humoral deficiency evaluations [14, 15]. A patient with DiGeorge syndrome should have careful T-cell deficiency evaluations since the syndrome is associated with athymia and partial athymia but should also have humoral deficiency evaluations since a small percentage of patients have evidence of humoral deficiency [16]. Beyond disease-specific evaluations, most patients should have broad immunologic screening tests performed as suggested in Table 11.2.

In patients who lack a known genetic syndrome diagnosis, immunologic testing and genetic testing should be performed in tandem when appropriate. Routine chromosome analysis and microarray should be considered in patients who lack a known underlying genetic diagnosis. Additionally, targeted sequencing of any genes linked to suspected genetic disorders should be performed. Alternatively, a primary immunodeficiency panel or whole-exome sequencing should be pursued in appropriate patients with a clear immune phenotype, syndromic features, but no obvious unifying genetic diagnosis. Collaboration with a clinical geneticist should be considered during the evaluation of complex patients so that newly described, emerging, or very rare genetic syndromes that are not common to the immunologist are not overlooked.

After a thorough immune evaluation, any needed interventions can be instigated as appropriate. Treatment is highly variable depending on the underlying disorder

Table 11.2 Suggested initial screening immunologic evaluations to consider in patients suspected of having a genetic syndrome with associated immunodeficiency

Clinical test	To evaluate
Complete blood count	Neutrophil, lymphocyte, eosinophil, and monocyte percentages and numbers, hemoglobin/hematocrit, platelet count
Lymphocyte subset enumeration	CD4+ T-cell, CD8+ T-cell, NK-cell, and B-cell percentages and numbers
T-cell phenotyping and/or TREC testing	Presence of naive and memory T-cell subsets, recent thymic emigrants
Mitogen and/or antigen-stimulated proliferation assays	Proliferative responses
B-cell phenotyping	Presence of memory B cells and class-switched memory B cells
Vaccine titers (if appropriately vaccinated)	Antibody responses to vaccinations
Vaccine challenge (if indicated)	Antibody responses to vaccinations

More limited, expanded, or alternative testing may be indicated based on clinical scenario

and the extent of immune deficiency, as observed in the two example cases above. Patients with humoral deficiency should be started on immunoglobulin replacement. Patients with significant T-cell deficiencies may require prophylaxis against *Pneumocystis jirovecii* and other pathogens. Patients with severe neutropenia may need antifungal and other appropriate antimicrobial prophylaxis or treatment with granulocyte-colony stimulating factor. These interventions can significantly improve the quality of life for patients and prevent life-threatening infections. Some patients with severe disorders are optimally treated with allogeneic hematopoietic cell transplantation.

Importantly, many patients will require multi-specialty evaluations and care. Obvious problems such as a cleft lip or palate will be easy to recognize and more straightforward to treat. Some syndromic complications are not obvious, and thoughtful consideration should be given to screening evaluations when appropriate if they have not been performed prior to referral to immunology clinic. For example, patients with CHARGE syndrome should be examined/evaluated for many associated problems such as colobomas, heart malformations, kidney malformations, choanal atresia, cleft lip, cleft palate, tracheoesophageal fistula, growth problems, ear malformations, hearing problems, genital abnormalities, problems with the digits or limbs, cognitive abnormalities or learning disabilities, and other problems. Selected associated complications of other syndromic PID disorders are listed in Table 11.2. Patients may need consultation and/or care with specialists in clinical genetics, neurology, cardiology, developmental pediatrics, gastroenterology, nutrition, nephrology, urology, pulmonology, otolaryngology, orthopedics, general and specialty surgery, and psychiatry and other specialists along with a variety of physical, occupational, and speech therapy services. Appropriate placements in schools and individualized education program (IEP) development may be needed as children progress through school. Multi-subspecialty care clinics can be helpful when available.

Conclusion

The evaluation and treatment of patients with genetic syndromes with associated immunodeficiencies can be complex. There are a large number of phenotypically heterogeneous disorders, many with overlapping non-immune features and a wide spectrum of immunologic defects. Some disorders are common in the primary immunodeficiency clinic and are simple to manage. For syndromes that are ill-defined or complex, evaluations and treatments can be undertaken in collaboration with clinical geneticists and multi-disciplinary specialists as appropriate. Immunologists are often able to have a significant positive impact on the quality of life of patients with syndromic PIDs through the recognition and treatment of the associated immunodeficiencies in these patients.

Clinical Pearls and Pitfalls

- Genetic syndromes with associated immunodeficiencies are diverse.
- Most patients suspected to have a syndromic immunodeficiency should have broad immunologic and genetic testing performed to quantify the degree of immunodeficiency and determine the underlying genetic disorder.
- Patients may need multi-subspecialty evaluations and care.
- Treatment interventions for immunodeficiency depend on the underlying disorder and extent of immunodeficiency.

References

1. Kersseboom R, Brooks A, Weemaes C. Educational paper: syndromic forms of primary immunodeficiency. Eur J Pediatr. 2011;170(3):295–308.
2. Ming JE, Stiehm ER. Genetic syndromic immunodeficiencies with antibody defects. Immunol Allergy Clin N Am. 2008;28(4):715–36, vii.
3. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human inborn errors of immunity: 2019 update on the classification from the international union of immunological societies expert committee. J Clin Immunol. 2020;40(1):24–64.
4. Davies EG. Immunodeficiency in DiGeorge syndrome and options for treating cases with complete athymia. Front Immunol. 2013;4:322.
5. Lavery WJ, Barski A, Wiley S, Schorry EK, Lindsley AW. KMT2C/D COMPASS complex-associated diseases [KCDCOM-ADs]: an emerging class of congenital regulopathies. Clin Epigenetics. 2020;12(1):10.
6. Lindsley AW, Saal HM, Burrow TA, Hopkin RJ, Shchelochkov O, Khandelwal P, et al. Defects of B-cell terminal differentiation in patients with type-1 Kabuki syndrome. J Allergy Clin Immunol. 2016;137(1):179–87. e110.
7. Bogershausen N, Wollnik B. Unmasking Kabuki syndrome. Clin Genet. 2013;83(3):201–11.
8. Ehrlich M, Jackson K, Weemaes C. Immunodeficiency, centromeric region instability, facial anomalies syndrome (ICF). Orphanet J Rare Dis. 2006;1:2.
9. Maraschio P, Zuffardi O, Dalla Fior T, Tiepolo L. Immunodeficiency, centromeric heterochromatin instability of chromosomes 1, 9, and 16, and facial anomalies: the ICF syndrome. J Med Genet. 1988;25(3):173–80.

10. Tiepolo L, Maraschio P, Gimelli G, Cuoco C, Gargani GF, Romano C. Multibranched chromosomes 1, 9, and 16 in a patient with combined IgA and IgE deficiency. Hum Genet. 1979;51(2):127–37.
11. Carpenter NJ, Filipovich A, Blaese RM, Carey TL, Berkel AI. Variable immunodeficiency with abnormal condensation of the heterochromatin of chromosomes 1, 9, and 16. J Pediatr. 1988;112(5):757–60.
12. Tuck-Muller CM, Narayan A, Tsien F, Smeets DF, Sawyer J, Fiala ES, et al. DNA hypomethylation and unusual chromosome instability in cell lines from ICF syndrome patients. Cytogenet Cell Genet. 2000;89(1–2):121–8.
13. Kellner ES, Rathbun PA, Marshall GS, Tolusso LK, Smolarek TA, Sun M, et al. The value of chromosome analysis to interrogate variants in DNMT3B causing immunodeficiency, centromeric instability, and facial anomaly syndrome type I (ICF1). J Clin Immunol. 2019;39(8):857–9.
14. Hoffman JD, Ciprero KL, Sullivan KE, Kaplan PB, McDonald-McGinn DM, Zackai EH, et al. Immune abnormalities are a frequent manifestation of Kabuki syndrome. Am J Med Genet A. 2005;135(3):278–81.
15. Adam MP, Banka S, Bjornsson HT, Bodamer O, Chudley AE, Harris J, et al. Kabuki syndrome: international consensus diagnostic criteria. J Med Genet. 2019;56(2):89–95.
16. Patel K, Akhter J, Kobrynski L, Benjamin Gathmann MA, Davis O, Sullivan KE, et al. Immunoglobulin deficiencies: the B-lymphocyte side of DiGeorge Syndrome. J Pediatr. 2012;161(5):950–3.
17. Wortmann SB, Zietkiewicz S, Kousi M, Szklarczyk R, Haack TB, Gersting SW, et al. CLPB mutations cause 3-methylglutaconic aciduria, progressive brain atrophy, intellectual disability, congenital neutropenia, cataracts, movement disorder. Am J Hum Genet. 2015;96(2):245–57.
18. Chun HH, Gatti RA. Ataxia-telangiectasia, an evolving phenotype. DNA Repair (Amst). 2004;3(8–9):1187–96.
19. Stewart GS, Maser RS, Stankovic T, Bressan DA, Kaplan MI, Jaspers NG, et al. The DNA double-strand break repair gene hMRE11 is mutated in individuals with an ataxia-telangiectasia-like disorder. Cell. 1999;99(6):577–87.
20. Delia D, Piane M, Buscemi G, Savio C, Palmeri S, Lulli P, et al. MRE11 mutations and impaired ATM-dependent responses in an Italian family with ataxia-telangiectasia-like disorder. Hum Mol Genet. 2004;13(18):2155–63.
21. Fernet M, Gribaa M, Salih MA, Seidahmed MZ, Hall J, Koenig M. Identification and functional consequences of a novel MRE11 mutation affecting 10 Saudi Arabian patients with the ataxia telangiectasia-like disorder. Hum Mol Genet. 2005;14(2):307–18.
22. Finsterer J. Barth syndrome: mechanisms and management. Appl Clin Genet. 2019;12:95–106.
23. Lessel D, Gehbauer C, Bramswig NC, Schluth-Bolard C, Venkataramanappa S, van Gassen KLI, et al. BCL11B mutations in patients affected by a neurodevelopmental disorder with reduced type 2 innate lymphoid cells. Brain. 2018;141(8):2299–311.
24. Punwani D, Zhang Y, Yu J, Cowan MJ, Rana S, Kwan A, et al. Multisystem anomalies in severe combined immunodeficiency with mutant BCL11B. N Engl J Med. 2016;375(22):2165–76.
25. Cunniff C, Bassetti JA, Ellis NA. Bloom's syndrome: clinical spectrum, molecular pathogenesis, and cancer predisposition. Mol Syndromol. 2017;8(1):4–23.
26. Feske S, Picard C, Fischer A. Immunodeficiency due to mutations in ORAI1 and STIM1. Clin Immunol. 2010;135(2):169–82.
27. Ridanpaa M, van Eenennaam H, Pelin K, Chadwick R, Johnson C, Yuan B, et al. Mutations in the RNA component of RNase MRP cause a pleiotropic human disease, cartilage-hair hypoplasia. Cell. 2001;104(2):195–203.
28. Buck D, Malivert L, de Chasseval R, Barraud A, Fondanèche M-C, Sanal O, et al. Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. Cell. 2006;124(2):287–99.
29. Hsu P, Ma A, Wilson M, Williams G, Curotta J, Munns CF, et al. CHARGE syndrome: a review. J Paediatr Child Health. 2014;50(7):504–11.

30. Kaplan J, De Domenico I, Ward DM. Chediak-Higashi syndrome. Curr Opin Hematol. 2008;15(1):22–9.
31. Kolehmainen J, Black GC, Saarinen A, Chandler K, Clayton-Smith J, Träskelin A-L, et al. Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport. Am J Hum Genet. 2003;72(6):1359–69.
32. Chandler KE, Kidd A, Al-Gazali L, Kolehmainen J, Lehesjoki A-E, Black GCM, et al. Diagnostic criteria, clinical characteristics, and natural history of Cohen syndrome. J Med Genet. 2003;40(4):233–41.
33. Chavanas S, Bodemer C, Rochat A, Hamel-Teillac D, Ali M, Irvine AD, et al. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. Nat Genet. 2000;25(2):141–2.
34. Bitoun E, Chavanas S, Irvine AD, Lonie L, Bodemer C, Paradisi M, et al. Netherton syndrome: disease expression and spectrum of SPINK5 mutations in 21 families. J Invest Dermatol. 2002;118(2):352–61.
35. Sullivan KE. Chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. Immunol Rev. 2019;287(1):186–201.
36. Altmann T, Gennery AR. DNA ligase IV syndrome; a review. Orphanet J Rare Dis. 2016;11(1):137.
37. Niewisch MR, Savage SA. An update on the biology and management of dyskeratosis congenita and related telomere biology disorders. Expert Rev Hematol. 2019;12(12):1037–52.
38. Tummala H, Kirwan M, Walne AJ, Hossain U, Jackson N, Pondarre C, et al. ERCC6L2 mutations link a distinct bone-marrow-failure syndrome to DNA repair and mitochondrial function. Am J Hum Genet. 2014;94(2):246–56.
39. Zhang S, Pondarre C, Pennarun G, Labussiere-Wallet H, Vera G, France B, et al. A nonsense mutation in the DNA repair factor Hebo causes mild bone marrow failure and microcephaly. J Exp Med. 2016;213(6):1011–28.
40. Oud MM, Tuijnenburg P, Hempel M, van Vlies N, Ren Z, Ferdinandusse S, et al. Mutations in EXTL3 cause Neuro-immuno-skeletal dysplasia syndrome. Am J Hum Genet. 2017;100(2):281–96.
41. Volpi S, Yamazaki Y, Brauer PM, van Rooijen E, Hayashida A, Slavotinek A, et al. EXTL3 mutations cause skeletal dysplasia, immune deficiency, and developmental delay. J Exp Med. 2017;214(3):623–37.
42. Banka S, Newman WG. A clinical and molecular review of ubiquitous glucose-6-phosphatase deficiency caused by G6PC3 mutations. Orphanet J Rare Dis. 2013;8:84.
43. Cottineau J, Kottemann MC, Lach FP, Kang Y-H, Vély F, Deenick EK, et al. Inherited GINS1 deficiency underlies growth retardation along with neutropenia and NK cell deficiency. J Clin Invest. 2017;127(5):1991–2006.
44. Ménasché G, Pastural E, Feldmann J, Certain S, Ersoy F, Dupuis S, et al. Mutations in RAB27A cause Griscelli syndrome associated with hemophagocytic syndrome. Nat Genet. 2000;25:173–6.
45. Alders M, Hogan BM, Gjini E, Salehi F, Al-Gazali L, Hennekam EA, et al. Mutations in CCBE1 cause generalized lymph vessel dysplasia in humans. Nat Genet. 2009;41(12):1272–4.
46. Roscioli T, Cliffe ST, Bloch DB, Bell CG, Mullan G, Taylor PJ, et al. Mutations in the gene encoding the PML nuclear body protein Sp110 are associated with immunodeficiency and hepatic veno-occlusive disease. Nat Genet. 2006;38(6):620–2.
47. Yong PF, Freeman AF, Engelhardt KR, Holland S, Puck JM, Grimbacher B. An update on the hyper-IgE syndromes. Arthritis Res Ther. 2012;14(6):228.
48. Sterlin D, Velasco G, Moshous D, Touzot F, Mahlaoui N, Fischer A, et al. Genetic, cellular and clinical features of ICF syndrome: a French National Survey. J Clin Immunol. 2016;36(2):149–59.
49. de Greef JC, Wang J, Balog J, den Dunnen JT, Frants RR, Straasheijm KR, et al. Mutations in ZBTB24 are associated with immunodeficiency, centromeric instability, and facial anomalies syndrome type 2. Am J Hum Genet. 2011;88(6):796–804.

50. Thijssen PE, Ito Y, Grillo G, Wang J, Velasco G, Nitta H, et al. Mutations in CDCA7 and HELLS cause immunodeficiency-centromeric instability-facial anomalies syndrome. Nat Commun. 2015;6:7870.
51. Chen R, Giliani S, Lanzi G, Mias GI, Lonardi S, Dobbs K, et al. Whole-exome sequencing identifies tetratricopeptide repeat domain 7A (TTC7A) mutations for combined immunodeficiency with intestinal atresias. J Allergy Clin Immunol. 2013;132(3):656–64. e617.
52. Samuels ME, Majewski J, Alirezaie N, Fernandez I, Casals F, Patey N, et al. Exome sequencing identifies mutations in the gene TTC7A in French-Canadian cases with hereditary multiple intestinal atresia. J Med Genet. 2013;50(5):324–9.
53. Boisson B, Puel A, Picard C, Casanova JL. Human IκBα gain of function: a severe and syndromic immunodeficiency. J Clin Immunol. 2017;37(5):397–412.
54. Boztug K, Jarvinen PM, Salzer E, Racek T, Mönch S, Garncarz W, et al. JAGN1 deficiency causes aberrant myeloid cell homeostasis and congenital neutropenia. Nat Genet. 2014;46(9):1021–7.
55. Etzioni A, Frydman M, Pollack S, Avidor I, Phillips ML, Paulson JC, et al. Brief report: recurrent severe infections caused by a novel leukocyte adhesion deficiency. N Engl J Med. 1992;327(25):1789–92.
56. Kuijpers TW, van Bruggen R, Kamerbeek N, Tool ATJ, Hicsonmez G, Gurgey A, et al. Natural history and early diagnosis of LAD-1/variant syndrome. Blood. 2007;109(8):3529–37.
57. Svensson L, Howarth K, McDowall A, Patzak I, Evans R, Ussar S, et al. Leukocyte adhesion deficiency-III is caused by mutations in KINDLIN3 affecting integrin activation. Nat Med. 2009;15(3):306–12.
58. Hughes CR, Guasti L, Meimaridou E, Chuang C-H, Schimenti JC, King PJ, et al. MCM4 mutation causes adrenal failure, short stature, and natural killer cell deficiency in humans. J Clin Invest. 2012;122(3):814–20.
59. Merico D, Roifman M, Braunschweig U, Yuen RKC, Alexandrova R, Bates A, et al. Compound heterozygous mutations in the noncoding RNU4ATAC cause Roifman Syndrome by disrupting minor intron splicing. Nat Commun. 2015;6:8718.
60. Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA. The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. J Allergy Clin Immunol. 2004;113(4):725–33.
61. Chrzanowska KH, Gregorek H, Dembowska-Baginska B, Kalina MA, Digweed M. Nijmegen breakage syndrome (NBS). Orphanet J Rare Dis. 2012;7:13.
62. van der Crabben SN, Hennus MP, McGregor GA, Ritter DI, Nagamani SCS, Wells OS, et al. Destabilized SMC5/6 complex leads to chromosome breakage syndrome with severe lung disease. J Clin Invest. 2016;126(8):2881–92.
63. Markert ML. Purine nucleoside phosphorylase deficiency. Immunodefic Rev. 1991;3(1):45–81.
64. Waltes R, Kalb R, Gatei M, Kijas AW, Stumm M, Sobeck A, et al. Human RAD50 deficiency in a Nijmegen breakage syndrome-like disorder. Am J Hum Genet. 2009;84(5):605–16.
65. Boerkoel CF, O'Neill S, Andre JL, Benke PJ, Bogdanović R, Bulla M, et al. Manifestations and treatment of Schimke immuno-osseous dysplasia: 14 new cases and a review of the literature. Eur J Pediatr. 2000;159(1–2):1–7.
66. Nelson AS, Myers KC. Diagnosis, treatment, and molecular pathology of Shwachman-Diamond syndrome. Hematol Oncol Clin North Am. 2018;32(4):687–700.
67. Witzel M, Petersheim D, Fan Y, Bahrami E, Racek T, Rohlfs M, et al. Chromatin-remodeling factor SMARCD2 regulates transcriptional networks controlling differentiation of neutrophil granulocytes. Nat Genet. 2017;49(5):742–52.
68. Kofoed EM, Hwa V, Little B, Woods KA, Buckway CK, Tsubaki J, et al. Growth hormone insensitivity associated with a STAT5b mutation. N Engl J Med. 2003;349(12):1139–47.
69. Finocchi A, Angelino G, Cantarutti N, Corbari M, Bevivino E, Cascioli S, et al. Immunodeficiency in Vici syndrome: a heterogeneous phenotype. Am J Med Genet A. 2012;158A(2):434–9.
70. Stepensky P, Saada A, Cowan M, Tabib A, Fischer U, Berkun Y, et al. The Thr224Asn mutation in the VPS45 gene is associated with the congenital neutropenia and primary myelofibrosis of infancy. Blood. 2013;121(25):5078–87.

71. Vilboux T, Lev A, Malicdan MC, Simon AJ, Järvinen P, Racek T, et al. A congenital neutrophil defect syndrome associated with mutations in VPS45. N Engl J Med. 2013;369(1):54–65.
72. McDermott DH, Murphy PM. WHIM syndrome: immunopathogenesis, treatment and cure strategies. Immunol Rev. 2019;287(1):91–102.
73. Massaad MJ, Ramesh N, Geha RS. Wiskott-Aldrich syndrome: a comprehensive review. Ann N Y Acad Sci. 2013;1285:26–43.