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Original Article

The Origins of the First Reported Cases of the Primary Immunodeficiency Diseases

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Abstract

Background: Inborn Errors of Immunity (IEI) or Primary Immunodeficiency Disorders (PID), are heterogeneous diseases with defects on the components of the immune system. We have provided information about the consanguinity and origins of over 400 affected patients for the first time.

Methods: To study the genes, we used the classification tables provided by the IUIS (the International Union of Immunological Societies) in 2020, that documents the key clinical and laboratory features of more than 400 inborn errors of immunity.

Results: We have identified the national origins of 301 cases with a known gene, while national origins' information of the 90 other genes (90 cases) was left incomplete, due to the unavailability of the first case reports or the fail to mention the patients' origin in the article publication of the first report. Among the 301 genes, Asia has the largest geographical dispersion with 103 reported cases. We found that the 101 first case reports, were identified in more than one patient, regardless of the geography they live in. Our survey demonstrated that out of the 165 first reported cases with genetic defects resulted from a consanguineous marriage, 112 cases were identified in Asia.

Conclusion: This report provides valuable information on the geographical data and the prevalence of the various genetic disorders, worldwide. Also, by providing information related to parental consanguinity of the first reported cases with a genetic defect, valuable information about inborn errors of immunity, will be accessible for the researchers, which can be used effectively in future studies.

Keywords: Primary Immune Deficiency; Inborn Errors of Immunity; Consanguinity; Origin

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Introduction

Inborn Errors of Immunity (IEI) or Primary Immunodeficiency Disorders (PIDs) are described as heterogeneous diseases with a shortcoming in the immune system's development and function (1). The use of advanced functional and genetic testing, led to the increased knowledge in the underlying causes of PIDs during the last decades (2). Individuals suffering from PIDs, are more prone to recurrent and chronic infections with several infectious agents, causing a significant morbidity and mortality (3). The prevalence of the PIDs, is estimated to be 1:1200 (4). Since the first report of PID in 1952, scientists have recognized over 400 genetic defects that are related to PIDs (5). The International Union of Immunological Societies (IUIS) PID Expert Committee (EC) defines IEIs based shared pathogenesis and/or clinical consequences and has published classification of these disorders, every other year (6). This classification has been organized in ten tables, as each of which groups IEI sharing given pathogenesis (7). This classification facilitates the clinical researches and comparative studies worldwide, by including new disorders or disease-causing genes in specific categories (8).

The human IEIs are caused by monogenic germline mutations, resulting in loss or gain of the encoded protein function. They can be dominant or recessive, autosomal or X-linked, and with complete or incomplete penetrance (7). IEI (also referred to as PID), manifests increased susceptibility to infectious diseases, autoimmunity, auto-inflammatory diseases, allergy, and/or malignancy (9).

Approximately over 1 billion people currently live in countries where consanguineous marriage is customary, and among them one in every three marriages is between cousins (10). Consanguinity rate in the world is almost 1–9%, on the other hand ,in the Middle East/Northern Africa region this rate increases to 20–56% (11); So that 20% of world populations live in these countries with a preference for consanguineous marriages (12), which results in a higher incidence of autosomal recessive PIDs (13, 14).

Many studies have globally reported the prevalence of the IEI, with information about their origins and parental consanguinity (15-20). Nonetheless, there is not any organized and classified data about parental consanguinity and gene origin status yet. The consanguinity rates vary in different populations with differences in religion, culture and geography (12, 21-25); hence, understanding parental consanguinity status in patients with genetic disorders in different countries, helps us in understanding the relationship between consanguinity and genetic defects and the other causes of the disease. Also, knowing the nationality of the patients with genetic defects, provides useful information to estimate the geographical distribution of genetic defects. This information will be very useful in analyzing the data related to the relevant gene defects.

In this study, our aim is to report the parental consanguinity and gene origin status of the first reported cases of patients with IEI.

Methods

IUIS, divides the genes into 10 categories in terms of clinical and laboratory characteristic, covering more than 400 genes, which is our criterion for the classification and examination of the genes. Based on the IUIS 2020 report, we have searched various databases, including the OMIM, Web of Science, Scopus and PubMed to extract the PID cases from the articles. We have investigated the PID cases with known and unknown genetic defects, based on the IUIS 2020 report. Then, required information, including the parental consanguinity, origins and publish years, were extracted and reported in Table 1.

Results

Among over 400 genes classified according to the IUIS 2020 report, 17 genetic diseases were not directly connected to any specific mutated gene so far. We have identified the national origins of 301 cases with the known gene, while the national origin of the other genes (90 cases) was left incomplete due to the unavailability of the first cases' reports or not mentioning the patients' origin in the publication of the first report.

National Origin data

Due to the widespread prevalence of the genetic diseases, the first reports of the genetic defects on different continents, are unexpected. Among the 301 genes, Asia has the largest geographical

dispersion, with 103 reported cases, in which the cases of concomitant Asia and other continents have been excluded. The percentage of the genetic defect dispersion in different continents is shown in **Figure 1**. We found that, the 101 first case reports, were reported by more than one patient, regardless of their geographical classification. For example, 29 of the first case reports with genetic defects, were simultaneously reported in Asia and Europe, 9 cases with genetic defects within

Table 1. Characteristics of genes involved in primary immunodeficiency diseases.

	Disease	Gene	Origin	Consanguinity	Year	Ref.
1.	**Immunodeficiencies affecting cellular and humoral immunity**					
1.	γc deficiency (common gamma chain SCID, CD132 deficiency)	IL2RG	*unknown*	*unknown*	1993	PMID: 8462096
2.	JAK3 deficiency	JAK3	*unknown*	1	1995	PMID: 7659163
3.	IL7Rα deficiency	IL7R	Sicilian	1	2000	PMID: 11023514
4.	CD45 deficiency	PTPRC	Turkey	1	1997	PMID: 9068311
5.	CD3δ deficiency	CD3D	Mennonite descent (Netherlands)	1	2003	PMID: 14602880
6.	CD3ε deficiency	CD3E	*unknown*	*unknown*	1993	PMID: 8490660
7.	CD3ζ deficiency	CD3Z	Caribbean	*unknown*	2006	PMID: 16672702
8.	Coronin-1A deficiency	CORO1A	*unknown*	0	2009	PMID: 19097825
9.	LAT deficiency	LAT	Arab	1	2016	PMID: 27242165
10.	RAG deficiency	RAG1, RAG2	*unknown*	1	1996	PMID: 8810255
11.	DCLRE1C (Artemis) deficiency	DCLRE1C	American	1	2002	PMID: 12055248
12.	DNA PKcs deficiency	PRKDC	Turkey	1	2009	PMID: 19075392
13.	Cernunnos/XLF deficiency	NHEJ1	France, Turkey, Italy	(France: 0) (Turkey, Italia: 1)	2006	PMID: 16439204
14.	DNA ligase IV deficiency	LIG4	*unknown*	*unknown*	2001	PMID: 11779494
15.	Adenosine deaminase (ADA) deficiency	ADA	Belgium	1	1987	PMID: 3684597
16.	AK2 defect	AK2	Germany	*unknown*	2009	PMID: 19043417
17.	Activated RAC2 defect	RAC2	*unknown*	0	2000	PMID: 10758162
18.	CD40 ligand (CD154) deficiency	CD40LG	*unknown*	*unknown*	1993	PMID: 7679801
19.	CD40 deficiency	CD40	Turkey	1	2007	PMID: 17502893
20.	ICOS deficiency	ICOS	*unknown*	*unknown*	2003	PMID: 12577056
21.	ICOSL deficiency	ICOSLG	*unknown*	*unknown*	*unknown*	*unknown*
22.	CD3γ deficiency	CD3G	Spain	0	1986	PMID: 2872416
23.	CD8 deficiency	CD8A	Spain	1	2001	PMID: 11435463
24.	ZAP-70 deficiency (ZAP70 LOF)	ZAP70	Mennonite families (Netherlands)	*unknown*	1994	PMID: 8124727
25.	ZAP-70 combined hypomorphic and activating mutations	ZAP70	Caucasus	0	2016	PMID: 26783323

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
26.	MHC class I deficiency	TAP1 ,TAP2, TAPBP, B2M	(TAP1: Japan) (TAP2: Morocco)	(TAP1: 1) (TAP2: 1) (TAPBP: 0) (B2M: 1)	(TAP1: 1985) (TAP2:1994) (TAPBP:2002) (B2M: 1969)	(TAP1, PMID: 3891604) (TAP2, PMID: 7517574) (TAPBP, PMID: 12149238) (B2M, PMID: 4186801)
27.	MHC class II deficiency group A, B, C, D	CIITA, RFXANK ,RFX5 , RFXAP	(CIITA: North African)	(CIITA: 1)	(CIITA: 2001)	(CIITA, PMID: 11313409)
28.	IKAROS deficiency	IKZF1	Caucasus	*unknown*	2013	PMID: 21548011
29.	DOCK8 deficiency	DOCK8	Turkey, Mexico	1	2014	PMID: 14722525
30.	DOCK2 deficiency	DOCK2	Lebanon, Finland, turkey, Honduras	1 (in 3 patients) 0 (in 2 patients)	2015	PMID: 26083206
31.	Polymerase and deficiency	POLD1, POLD2	*unknown*	*unknown*	[POLD1:2013]	[POLD1, PMID: 23770608]
32.	RHOH deficiency	RHOH	France	1	2012	PMID: 22850876
33.	STK4 deficiency	STK4	Turkey	1	2012	PMID: 22174160
34.	TCRα deficiency	TRAC	Pakistan	1	2011	PMID: 21206088
35.	LCK deficiency	LCK	France	0	2012	PMID: 22985903
36.	ITK deficiency	ITK	Arab	1	2011	PMID: 21109689
37.	MALT1 deficiency	MALT1	Lebanon	1	2013	PMID: 23727036
38.	CARD11 deficiency	CARD11	Central Europe	1	2013	PMID: 23561803
39.	BCL10 deficiency	BCL10	Ecuador	1	2014	PMID: 25365219
40.	IL-21 deficiency	IL21	Turkey	1	2014	PMID: 24746753
41.	IL-21R deficiency	IL21R	Lebanon	1	2013	
42.	OX40 deficiency	TNFRSF4	Turkey	1	2013	PMID: 23897980
43.	IKBKB deficiency	IKBKB	Canada	*unknown*	2013	PMID: 24369075
44.	NIK deficiency	MAP3K14	Caucasus	*unknown*	2011	PMID: 21257964
45.	RelB deficiency	RELB	Ireland	1	2015	doi.org/10.14785/lpsn-2015-0005
46.	RelA haploinsufficiency	RELA	Massachusetts	*unknown*	2017	PMID: 28600438
47.	Moesin deficiency	MSN	*unknown*	*unknown*	2016	PMID: 27405666
48.	TFRC deficiency	TFRC	Saudi Arabia	1	2016	PMID: 26642240

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
49.	c-Rel deficiency	REL	Arabic	1	2019	PMID: 31103457
50.	FCHO1 deficiency	FCHO1	Italy, Turkey, Algeria	*unknown*	2019	PMID: 30822429
2.	**Combined immunodeficiencies with associated or syndromic features**					
51.	Wiskott-Aldrich syndrome (WAS LOF)	WAS	*unknown*	*unknown*	1994	PMID: 8069912
52.	WIP deficiency	WIPF1	Morocco	1	2012	PMID: 22231303
53.	Arp2/3-mediated filament branching defect	ARPC1B	South Asian descent	1	2017	PMID: 28368018
54.	Ataxia-telangiectasia	ATM	Palestine	*unknown*	1992	PMID: 1551665
55.	Nijmegen breakage syndrome	NBS1	Slavic	1	1998	PMID: 9590180
56.	Bloom syndrome	BLM	Ashkenazi Jewish	0	1995	PMID: 7585968
57.	Immunodeficiency with centromeric instability and facial anomalies (ICF types1, 2, 3, 4)	DNMT3B, ZBTB24, CDCA7, HELLS	(CDCA7: Turkish) (HELLS: Turkish, British)	1	2015	PMID: 26216346
58.	PMS2 deficiency	PMS2	*unknown*	*unknown*	*unknown*	*unknown*
59.	RNF168 deficiency (Radio sensitivity, Immune Deficiency, Dysmorphic features, Learning difficulties [RIDDLE] syndrome)	RNF168	*unknown*	*unknown*	2009	PMID: 19203578
60.	MCM4 deficiency	MCM4	Ireland	1	2012	PMID: 22354167
61.	POLE1 (Polymerase ε subunit 1) deficiency(FILS syndrome)	POLE1	France	1	2012	PMID: 23230001
62.	POLE2 (Polymerase ε subunit 2) deficiency	POLE2	Saudi Arabia	1	2017	PMID: 26365386
63.	Ligase I deficiency	LIG1	Ashkenazi Jewish, japan	*unknown*	1992	PMID: 1581963
64.	NSMCE3 deficiency	NSMCE3	Dutch	*unknown*	2016	PMID: 27427983
65.	ERCC6L2 (Hebo deficiency)	ERCC6L2	Pakistan, French	1	2014	PMID: 24507776
66.	GINS1 deficiency	GINS1	France	*unknown*	2017	PMID: 28414293
67.	DiGeorge/velocardio-facial syndrome Chromosome 22q11.2 deletion syndrome(22q11.2DS)	TBX1	Japan	*unknown*	2003	PMID: 14585638
68.	DiGeorge/velocardio-facial syndrome	Unknown	*unknown*	*unknown*	*unknown*	*unknown*
69.	TBX1 deficiency	TBX1	Japan	*unknown*	2003	PMID: 14585638

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
70.	CHARGE syndrome	CHD7, SEMA3E, Unknown	*unknown*	*unknown*	(CHD7:2006) (SEMA3E:2004)	[CHD7, PMID: 16155193 PMID: 16400610] [SEMA3E, PMID: 15235037]
71.	FOXN1 haploinsufficiency	FOXN1	Italy	0	1996	PMID: 8911612
72.	Chromosome 10p13-p14 deletion syndrome (10p13-p14DS)	***Del10p13-p14***	*unknown*	*unknown*	*unknown*	*unknown*
73.	Chromosome 11q deletion syndrome(Jacobsen syndrome)	***11q23del***	*unknown*	*unknown*	*unknown*	*unknown*
74.	Cartilage hair hypoplasia (CHH)	RMRP	Finland	*unknown*	2001	PMID: 11207361
75.	Schimke immuno-osseous dysplasia	SMARCAL1	People from 22 countries	1	2002	PMID: 11799392
76.	MYSM1 deficiency	MYSM1	Saudi Arabia	1	2013	PMID: 24288411
77.	MOPD1 deficiency (Roifman syndrome)	RNU4ATAC	Lebanese–Australian	0	2011	PMID: 21977988
78.	Immunoskeletal dysplasia with neurodevelopmental abnormalities(EXTL3 deficiency)	EXTL3	Colombia, Portugal, India	(Colombia:1, Portugal:1, India:0)	2017	PMID: 28132690
79.	AD-HIES STAT3 deficiency (Job syndrome)	STAT3	Japan	*unknown*	2007	PMID: 17676033
80.	IL6 receptor deficiency	IL6R	English	0	2019	PMID: 31235509
81.	IL6 signal transducer (IL6ST) deficiency	IL6ST	South Asia	1	2017	PMID: 28747427
82.	ZNF341 deficiency AR-HIES	ZNF341	Arab-Israeli	1	2018	PMID: 29907690
83.	ERBIN deficiency	ERBB2IP	*unknown*	*unknown*	2014	PMID: 24812403
84.	Loeys-Dietz syndrome (TGFBR deficiency)	TGFBR1, TGFBR2	(TGFBR2: Japan, France)	*unknown*	[TGFBR2: 2004]	[TGFBR2PMID: 15235604]
85.	Comel-Netherton syndrome	SPINK5	England, North Ireland, Scotland, France, Italy, Pakistan, Kosovo, Turkey, China, Japan	Italy (1) Pakistan (1) Turkey (1)	2002	PMID: 11841556
86.	PGM3 deficiency	PGM3	Egypt	1	2014	PMID: 24589341
87.	CARD11 deficiency (heterozygous)	CARD11	China	*unknown*	2012	PMID: 23129749
88.	Transcobalamin 2 deficiency	TCN2	Lebanon Turkey	1	2009	PMID: 19373259

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
89.	SLC46A1/PCFT deficiency causing hereditary folate malabsorption	SLC46A1	Tunisia	*unknown*	2001	PMID: 11804211
90.	Methylene-tetrahydrofolate dehydrogenase1 (MTHFD1) deficiency	MTHFD1	Ashkenazi Jewish, Russia	0	2011	PMID: 21813566
91.	EDA-ID due to NEMO/IKBKG deficiency(ectodermal dysplasia, immune deficiency)	IKBKG	*unknown*	*unknown*	2000	PMID: 10839543
92.	EDA-ID due to IKBA GOF mutation	NFKBIA	*unknown*	*unknown*	2003	PMID: 14523047
93.	EDA-ID due to IKBKB GOF mutation	IKBKB	Canada	*unknown*	2013	PMID: 24369075
94.	ORAI-1 deficiency	ORAI1	*unknown*	1	2006	PMID: 16582901
95.	STIM1 deficiency	STIM1	Central Europe	1	2009	PMID: 19420366
96.	Purine nucleoside phosphorylase (PNP) deficiency	PNP	*unknown*	*unknown*	1996	PMID: 8931706
97.	Immunodeficiency with multiple intestinal atresias	TTC7A	French Canadian	*unknown*	2013	PMID: 23423984
98.	Tricho-Hepato-Enteric Syndrome (THES)	TTC37, SKIV2L	(TTC37: India, Dutch, Pakistan, Kurdish, English, Italy, Finland) (SKIV2L: north Africa, France, turkey)	(TTC37:1) (SKIV2L: north africa:1, france:0, turkey:1)	(TTC37:2010) (SKIV2L: 2012)	(TTC37, PMID: 20176027 (SKIV2L, PMID: 22444670)
99.	Hepatic veno-occlusive disease with immunodeficiency (VODI)	SP110	Lebanon	1	2006	PMID: 16648851
100.	BCL11B deficiency	BCL11B	*unknown*	0	2016	PMID: 27959755
101.	EPG5 deficiency (Vici syndrome)	EPG5	Caucasian, Arab, Turkish, Japanese and British-Asian origin	0 and 1	2013	PMID: 23222957
102.	HOIL1 deficiency	RBCK1	France and Italy	France (0) Italy (1)	2012	PMID: 23104095
103.	HOIP deficiency	RNF31	Kuwait	1	2015	PMID: 26008899
104.	Hennekam-lymphangiectasia-lymphedema syndrome	CCBE1, FAT4	[CCBE1: Dutch, Oman, Iraq, Norway]	1	[CCBE; 2009] [FAT4: 2013]	[CCBE1, PMID: 19935664] [FAT4, PMID: 24056717}
105.	Activating de novo mutations in nuclear	NFE2L2	India, Caucasus, USA, Qatar,	India (0) Qatar (0)	2017	PMID: 29018201

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
	factor, erythroid 2- like (NFE2L2)					
106.	STAT5b deficiency	STAT5B	Argentina	1	2003	PMID: 13679528
107.	Kabuki syndrome (type 1 and 2)	KMT2D, KDM6A	[KMT2D: European ancestry, Hispanic ancestry], [KDM6A: Belgium, Italy]	*unknown*	[KMT2D, 2010] [KDM6A, 2012]	[KMT2D, PMID: 20711175] [KDM6A, PMID: 22197486]
108.	KMT2A deficiency (Wiedemann-Steiner syndrome)	KMT2A	Japan Australia	*unknown*	2016	PMID: 25810209
3.	**Predominantly antibody deficiencies**					
109.	BTK deficiency, X-linked agammaglobulinemia (XLA)	BTK	*unknown*	*unknown*	1993	PMID: 8380905
110.	μ heavy chain deficiency	IGHM	Turkey	1	1996	PMID: 8890099
111.	λ5 deficiency	IGLL1	*unknown*	*unknown*	1998	PMID: 9419212
112.	Igα deficiency	CD79A	Turkey	0	1999	PMID: 10525050
113.	Igβ deficiency	CD79B	Georgia	*unknown*	2007	PMID: 17675462
114.	BLNK deficiency	BLNK	*unknown*	*unknown*	1999	PMID: 10583958
115.	p110δ deficiency	PIK3CD	Taiwanese boy of Chinese descent	0	2006	PMID: 16984281
116.	p85 deficiency	PIK3R1	Chinese/Peruvian descent	1	2012	PMID: 22351933
117.	E47 transcription factor deficiency	TCF3	*unknown*	0	2013	PMID: 24216514
118.	SLC39A7 (ZIP7) deficiency	SLC39A7	*unknown*	*unknown*	*unknown*	*unknown*
119.	Hoffman syndrome/TOP2B deficiency	TOP2B	*unknown*	*unknown*	*unknown*	*unknown*
120.	Common variable immune deficiency with no gene defect specified (CVID)	Unknown	*unknown*	*unknown*	*unknown*	*unknown*
121.	Activated p110δ syndrome (APDS)	PIK3CD, PIK3R1	(PIK3CD: Taiwanese boy of Chinese descent) (PIK3R1:Chinese /Peruvian descent)	(PIK3CD:0) (PIK3R1:1)	(PIK3CD:2006) (PIK3R1:2012)	(PIK3CD, PMID: 16984281) (PIK3R1: PMID: 22351933)
122.	PTEN deficiency (LOF)	PTEN	Japan	0	2016	PMID: 27426521
123.	CD19 deficiency	CD19	Turkey	1	2006	PMID: 16672701
124.	CD81 deficiency	CD81	Morocco	1	2010	PMID: 20237408

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
125.	CD20 deficiency	CD20	Turkey	1	2010	PMID: 20038800
126.	CD21 deficiency	CD21	*unknown*	0	2012	PMID: 22035880
127.	TACI deficiency	TNFRSF13B	*unknown*	*unknown*	2005	PMID: 16007086 PMID: 16007087
128.	BAFF receptor deficiency	TNFRSF13C	*unknown*	1	2009	PMID: 19666484
129.	TWEAK deficiency	TNFSF12	*unknown*	*unknown*	2013	PMID: 23493554
130.	TRNT1 deficiency	TRNT1	Pakistan, Caucasus	1	2014	PMID: 25193871
131.	NFKB1 deficiency	NFKB1	Dutch-Australian	*unknown*	2015	PMID: 26279205
132.	NFKB2 deficiency	NFKB2	European descent	0	2013	PMID: 24140114
133.	IKAROS deficiency	IKZF1	Caucasus	*unknown*	2012	PMID: 21548011
134.	IRF2BP2 deficiency	IRF2BP2	*unknown*	*unknown*	2016	PMID: 27016798
135.	ATP6AP1 deficiency	ATP6AP1	Caucasus, Tunisia, Irish, Druze	0 and 1	2016	PMID: 27231034
136.	ARHGEF1 deficiency	ARHGEF1	*unknown*	0	2019	PMID: 30521495
137.	SH3KBP1 (CIN85) deficiency	SH3KBP1	*unknown*	*unknown*	2018	PMID: 29636373
138.	SEC61A1 deficiency	SEC61A1	*unknown*	*unknown*	2016	PMID: 27392076
139.	RAC2 deficiency	RAC2	*unknown*	0	2000	PMID: 10758162
140.	Mannosyl-oligosaccharide glucosidase deficiency	MOGS	*unknown*	1	2000	PMID: 10788335
141.	AID deficiency	AICDA	Morocco, Italy, Turkey	Morocco (0), Italy (0&1), Turkey (1)	2000	PubMed: 11007475
142.	UNG deficiency	UNG	*unknown*	*unknown*	2003	PMID: 12958596
143.	INO80 deficiency	INO80	*unknown*	*unknown*	*unknown*	*unknown*
144.	MSH6 deficiency	MSH6	Japan	*unknown*	1997	PMID: 9354786
145.	Ig heavy chain mutations and deletions	Mutation or chromosomal deletion at 14q32	*unknown*	*unknown*	*unknown*	*unknown*
146.	Kappa chain deficiency	IGKC	*unknown*	*unknown*	1985	PMID: 3931219
147.	Isolated IgG subclass deficiency	Unknown	*unknown*	*unknown*	*unknown*	*unknown*
148.	IgG subclass deficiency with IgA deficiency	Unknown	*unknown*	*unknown*	*unknown*	*unknown*
149.	May be asymptomatic Selective IgA deficiency	Unknown	*unknown*	*unknown*	*unknown*	*unknown*

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
150.	Specific antibody deficiency with normal Ig levels and normal B cells	Unknown	*unknown*	*unknown*	*unknown*	*unknown*
151.	Transient hypogammaglobulinemia of infancy	Unknown	*unknown*	*unknown*	*unknown*	*unknown*
152.	CARD11 GOF	CARD11	Central Europe	1	2015	PMID: 23561803
153.	Selective IgM deficiency	Unknown	*unknown*	*unknown*	*unknown*	*unknown*
4.	**Diseases of immune dysregulation**					
154.	Perforin deficiency (FHL2)	PRF1	North American	0 and 1	2004	PMID: 14757862
155.	UNC13D/Munc13–4 deficiency (FHL3)	UNC13D	Morocco	0 and 1	2003	PMID: 14622600
156.	Syntaxin 11 deficiency(FHL4)	STX11	Kurdish origin	1	2005	PMID: 15703195
157.	STXBP2/Munc18–2 deficiency (FHL5)	STXBP2	Saudi Arabian, Turkish, German, Czech	1	2009	PMID: 19804848
158.	FAAP24 deficiency	FAAP24	*unknown*	*unknown*	*unknown*	*unknown*
159.	SLC7A7 deficiency	SLC7A7	Finland	*unknown*	1999	PMID: 10080182
160.	Chediak-Higashi syndrome	LYST	Kuwait, Turkey	1	1997	PMID: 9215679
161.	Griscelli syndrome, type 2	RAB27A	Turkey	1	2000	PMID: 10835631
162.	Hermansky-Pudlak syndrome, type 2	AP3B1	USA	0	1999	PMID: 10024875
163.	Hermansky-Pudlak syndrome, type 10	AP3D1	Turkey	1	2016	PMID: 26744459
164.	IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked	FOXP3	Japan	*unknown*	2001	PMID: 11137993
165.	CD25 deficiency	IL2RA	Caucasus	0	2007	PMID: 17196245
166.	CD122 deficiency	IL2RB	Tajikistan	1	2018	PMID: 31040184
167.	CTLA4 haploinsufficiency(ALPS-V)	CTLA4	Italy	*unknown*	1996	PMID: 8817351
168.	LRBA deficiency	LRBA	Arab, Sicilian, Iran	1	2012	PMID: 22608502
169.	DEF6 deficiency	DEF6	Pakistan, Iraq	Pakistan (1) Iraq (1)	2019	PMID: 31308374
170.	STAT3 GOF mutation	STAT3	Japan	*unknown*	2007	PMID: 17676033
171.	BACH2 deficiency	BACH2	*unknown*	0	2017	PMID: 28530713
172.	FERMT1 deficiency	FERMT1	North African	1	2003	PMID: 12668616
173.	APECED (APS-1), autoimmune polyendocrinopathy with	AIRE	Finland, Swiss	*unknown*	1997	PMID: 9398839

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
	candidiasis and ectodermal dystrophy					
174.	ITCH deficiency	ITCH	Amish (USA)	1	2010	PMID: 20170897
175.	Tripeptidyl-peptidase II deficiency	TPP2	*unknown*	*unknown*	*unknown*	*unknown*
176.	JAK1 GOF	JAK1	*unknown*	*unknown*	2017	PMID: 28111307
177.	Prolidase deficiency	PEPD	Middle east	0	1990	PMID: 2365824
178.	IL-10 deficiency	IL10	*unknown*	*unknown*	*unknown*	*unknown*
179.	IL-10R deficiency	IL10RA, IL10RB	(IL10RA, Lebanon) (IL10RB, Gambia)	(IL10RA:1)	(IL10RA:2009) (IL10RB:2006)	(IL10RA, PMID: 19890111) (IL10RB, PMID: 16757563)
180.	NFAT5 haploinsufficiency	NFAT5	*unknown*	*unknown*	*unknown*	*unknown*
181.	TGFB1 deficiency	TGFB1	Malaysia, Pakistan	Malaysia: 0 Pakistan: 1	2018	PMID: 29483653
182.	RIPK1	RIPK1	Pakistan	1	2018	PMID: 30026316
183.	ALPS-FAS	TNFRSF6	*unknown*	*unknown*	1999	PMID: 10200300
184.	ALPS-FASLG	TNFSF6	African American	*unknown*	1996	PMID: 8787672
185.	ALPS-Caspase10	CASP10	African American	*unknown*	1999	PMID: 10412980
186.	ALPS-Caspase 8	CASP8	*unknown*	1	2002	PMID: 12353035
187.	FADD deficiency	FADD	Pakistan	1	2010	PMID: 21109225
188.	SAP deficiency (XLP1)	SH2D1A	Canada	*unknown*	1998	PMID: 9771704
189.	XIAP deficiency (XLP2)	XIAP	Caucasus	*unknown*	2006	PMID: 17080092
190.	CD27 deficiency	CD27	Morocco	1	2012	PMID: 22197273
191.	CD70 deficiency	CD70	Egypt, Turkey, Iran	1	2017	PMID: 28011863 PMID: 28011864
192.	CTPS1 deficiency	CTPS1	England	*unknown*	2014	PMID: 24870241
193.	CD137 deficiency(41BB)	TNFRSF9	*unknown*	*unknown*	*unknown*	*unknown*
194.	RASGRP1 deficiency	RASGRP1	Turkey	1	2016	PMID: 27776107
195.	RLTPR deficiency	CARMIL2	Morocco, Tunisia, Turkey	Morocco: 1 Tunisia: 1 Turkey: 0	2016	PMID: 27647349
196.	X-linked magnesium EBV and neoplasia (XMEN)	MAGT1	*unknown*	*unknown*	2011	PMID: 21796205
197.	PRKCD deficiency	PRKCD	Turkey	1	2013	PubMed: 23319571

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
5.	**Congenital defects of phagocyte number or function**					
198.	Elastase deficiency (Severe congenital neutropenia [SCN] 1)	ELANE	*unknown*	*unknown*	2000	PMID: 11001877
199.	GFI 1 deficiency (SCN2)	GFI1	*unknown*	*unknown*	2003	PMID: 12778173
200.	HAX1 deficiency (Kostmann Disease) (SCN3)	HAX1	Kurdish, Turkey, Iran, Lebanon, Sweden	Kurdish (1&0)	2007	PMID: 17187068
201.	G6PC3 deficiency (SCN4)	G6PC3	Turkey	1	2009	PMID: 19118303
202.	VPS45 deficiency (SCN5)	VPS45	Palestine	1	2013	PMID: 23738510
203.	Glycogen storage disease type 1b	G6PT1	Japan	1	1998	PMID: 9675154
204.	X-linked neutropenia/myelodysplasia	WAS	European descent	*unknown*	2001	PMID: 11242115
205.	P14/LAMTOR2 deficiency	LAMTOR2	Caucasus	*unknown*	2007	PMID: 17195838
206.	Barth Syndrome (3-Methylglutaconic aciduria type II)	TAZ	*unknown*	*unknown*	1996	PMID: 8630491
207.	Cohen syndrome	VPS13B	Finland	*unknown*	2003	PMID: 12730828
208.	Clericuzio syndrome (Poikiloderma with neutropenia)	USB1	Italy	1	2010	PMID: 20004881
209.	JAGN1 deficiency	JAGN1	Algeria, Iran, Turkey, Morocco, Albania, Pakistan, Germany, Israel	1	2014	PMID: 25129144
210.	3-Methylglutaconic aciduria	CLPB	Canada, Australia, Germany, Turkey, Italy, Poland, Estonia, Greenland, North American, Cambodia	Cambodia (1)	2015	PMID: 25597510 PMID: 25597511 PMID: 25650066
211.	G-CSF receptor deficiency	CSF3R	Caucasus	0	2009	PMID: 19620628
212.	SMARCD2 deficiency	SMARCD2	Pakistan, Lebanon	1	2017	PMID: 28369036
213.	Specific granule deficiency	CEBPE	*unknown*	*unknown*	*unknown*	*unknown*
214.	Shwachman-Diamond Syndrome	SBDS, DNAJC21, EFL1	(DNAJC21: France, Algeria, Pakistan) (EFL1: Mexico, Palestine)	(DNAJC21: 1) [EFL1: Mexico (0), Palestine (1)]	(SBDS:2003) (DNAJC21: 2016) (EFL1:2017)	(SBDS, PMID: 12496757) (EFL1, PMID: 28331068)
215.	HYOU1 deficiency	HYOU1	*unknown*	0	2017	PMID: 27913302

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
216.	SRP54 deficiency	SRP54	Hispanic (Spain)	0	2017	PMID: 28972538
217.	Leukocyte adhesion deficiency type 1 (LAD1)	ITGB2	*unknown*	*unknown*	1990	PMID: 1968911
218.	Leukocyte adhesion deficiency type 2 (LAD2)	SLC35C1	Turkey, Israeli Arabs	*unknown*	2001	PMID: 11326279
219.	Leukocyte adhesion deficiency type 3 (LAD3)	FERMT3	Turkey	1	2007	PMID: 17185466
220.	Rac2 deficiency	RAC2	*unknown*	0	2000	PMID: 10758162
221.	β actin deficiency	ACTB	Irish-English	*unknown*	2006	PMID: 16685646
222.	Localized juvenile periodontitis	FPR1	*unknown*	*unknown*	2019	PMID: 31534221
223.	Papillon-Lefèvre syndrome	CTSC	Egypt, India, Pakistan, Lebanon	Egypt (1), India (1), Pakistan (1), Lebanon (0)	1999	PMID: 10581027
224.	WDR1 deficiency	WDR1	Qatar	1	2016	PMID: 27557945
225.	Cystic fibrosis	CFTR	*unknown*	*unknown*	*unknown*	*unknown*
226.	Neutropenia with combined immune deficiency due to MKL1 deficiency	MKL1	*unknown*	1	2015	PMID: 26224645
227.	X-linked chronic granulomatous disease (CGD), gp91phox	CYBB	France	0	2011	PMID: 21278736
228.	Autosomal recessive CGD	CYBA, CYBC1, NCF1, NCF2, NCF4	(CYBAC1: Saudi Arabia) (NCF2: Japan)	(CYBA: 1 & 0) (CYBC1: 1 & 0)	(CYBA:1990) (CYBC1:2017) (NCF1:1991) (NCF2:1995) (NCF4:2009)	(CYBA, PMID: 224341) (CYBC1, PMID: 28600779 (NCF1, PMID: 2011585) (NCF2, PMID: 7795241) (NCF4, PMID: 19692703)
229.	G6PD deficiency class I	G6PD	Japan	0	1984	PMID: 6714986
230.	GATA2 deficiency	GATA2	*unknown*	*unknown*	2011	PMID: 21670465
231.	Pulmonary alveolar proteinosis	CSF2RA, CSFR2B	(CSFR2B: Japan)	(CSFR2B:1)	(CSF2RA:2008) (CSF2RB:2011)	(CSF2RA, PMID: 18955567) (CSFR2B, PMID: 21075760)
6.	**Defects in intrinsic and innate immunity**					
232.	IL-12 and IL-23 receptor β1 chain deficiency	IL12RB1	Dutch, Turkey	Dutch (0), Turkey (1)	1998	PMID: 9603733

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
233.	IL-12p40 (IL-12 and IL-23) deficiency	IL12B	Pakistan	1	1998	PMID: 9854038
234.	IL-12Rβ2 deficiency	IL12RB2	*unknown*	*unknown*	*unknown*	*unknown*
235.	IL-23R deficiency	IL23R	non-Jewish European ancestry	*unknown*	2006	PMID: 17068223
236.	IFN-γ receptor 1 deficiency	IFNGR1	Malta	1	1996	PMID: 8960473
237.	IFN-γ receptor 2 deficiency	IFNGR2	English-Portuguese descent	0	1998	PMID: 9616207
238.	STAT1 deficiency	STAT1	American, France	*unknown*	2001	PMID: 11452125
239.	Macrophage gp91 phox deficiency	CYBB	France	0	2011	PMID: 21278736
240.	IRF8 deficiency	IRF8	Italy, Ireland	0	2011	PMID: 21524210
241.	SPPL2a deficiency	SPPL2A	*unknown*	*unknown*	*unknown*	*unknown*
242.	Tyk2 deficiency	TYK2	Japan	1	2006	PMID: 17088085
243.	P1104A TYK2 homozygosity	TYK2	Japan	1	2006	PMID: 17088085
244.	ISG15 deficiency	ISG15	Turkey, Iran	1	2012	PMID: 22859821
245.	RORγt deficiency	RORC	Palestine Saudi Arabia	1	2015	PMID: 26160376
246.	JAK1 deficiency	JAK1	*unknown*	*unknown*	2017	PMID: 28111307
247.	EVER1 deficiency	TMC6	Colombia, Algeria	1	2002	PMID: 12426567
248.	EVER2 deficiency	TMC8	Colombia, Algeria	1	2002	PMID: 12426567
249.	CIB1 deficiency	CIB1	Colombia, France, Iran, Switzerland, and Togo	1	2018	PMID: 30068544
250.	WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome	CXCR4	*unknown*	*unknown*	2003	PMID: 12692554
251.	STAT1 deficiency	STAT1	American, France	*unknown*	2001	PMID: 11452125
252.	STAT2 deficiency	STAT2	*unknown*	1	2013	PMID: 23391734
253.	IRF9 deficiency	IRF9	Algeria	1	2018	PMID: 30143481
254.	IRF7 deficiency	IRF7	France	0	2015	PMID: 25814066
255.	IFNAR1 deficiency	IFNAR1	Iran, Brazil	Iran (1) Brazil (0)	2019	PMID: 31270247
256.	IFNAR2 deficiency	IFNAR2	Gambia	*unknown*	2006	PMID: 16757563
257.	CD16 deficiency	FCGR3A	*unknown*	*unknown*	1996	PMID: 8608639

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
258.	MDA5 deficiency	IFIH1	British, Japan, European descent, White American	British (0), European descent (0), White American (0)	2014	PMID: 25243380 PMID: 24995871 PMID: 24686847
259.	RNA polymerase III deficiency	POLR3A, POLR3C, POLR3F	(POLR3A: French Canadian, Syria, Europe, Guatemala, France, USA)	[POLR3A: French Canadian (1), Syria (1)]	(POLR3A:2011)	(POLR3A, PMID: 21855841)
260.	TLR3 deficiency	TLR3	France	*unknown*	2007	PMID: 17872438
261.	UNC93B1 deficiency	UNC93B1	Portugal	1	2006	PMID: 16973841
262.	TRAF3 deficiency	TRAF3	France	*unknown*	2011	PMID: 20832341
263.	TRIF deficiency	TICAM1	Saudi Arabia French, Portuguese, and Swiss	Saudi Arabia (1)	2011	PMID: 22105173
264.	TBK1 deficiency	TBK1	Sweden, German, France, Denmark, Portugal	*unknown*	2015	PMID: 25803835
265.	IRF3 deficiency	IRF3	Denmark	*unknown*	2015	PMID: 26216125
266.	DBR1 deficiency	DBR1	Arab, Portugal, Japan	Arab (1) Portugal (0) Japan (0)	2018	PMID: 29474921
267.	CARD9 deficiency	CARD9	Iran	1	2009	PMID: 19864672
268.	IL-17RA deficiency	IL17RA	Argentina, France	France (1)	2011	PMID: 21350122
269.	IL-17RC deficiency	IL17RC	Argentina, Turkey	Argentina (0) Turkey (0 & 1)	2015	PMID: 25918342
270.	IL-17F deficiency	IL17F	Argentina, France	France (1)	2011	PMID: 21350122
271.	STAT1 GOF	STAT1	American, France	*unknown*	2001	PMID: 11452125
272.	ACT1 deficiency	TRAF3IP2	Germany, American, Canada, European ancestry	*unknown*	2010	PMID: 20953188
273.	IRAK4 deficiency	IRAK4	Saudi Arabia	1	2003	PMID: 12637671
274.	MyD88 deficiency	MYD88	France, Spain, Portugal, Turkey	0 & 1	2008	PMID: 18669862
275.	IRAK1 deficiency	IRAK1	Italy	0	2017	PMID: 28069966
276.	TIRAP deficiency	TIRAP	United kingdom, Kenia, Gambia, Vietnam, West African (The Gambia, Guinea-	*unknown*	2007	PMID: 17322885

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
			Bissau, Republic of Guinea)			
277.	Isolated congenital asplenia (ICA)	RPSA, HMOX	(RPSA: Congo, Caucasian originally from the United States, Sweden and french)	(HMOX:0)	(RPSA:2013 (HMOX:1999)	(RPSA, PMID: 23579497) (HMOX, PMID: 9884342)
278.	Trypanosomiasis	APOL1	African Americans	*unknown*	2010	PMID: 20647424
279.	Acute liver failure due to NBAS deficiency	NBAS	Yakut (Russia)	*unknown*	2010	PMID: 20577004
280.	Acute necrotizing encephalopathy	RANBP2	European, Asian, African	1	2009	PMID: 19118815
281.	Osteopetrosis	CLCN7, SNX10, OSTM1, PLEKHM1, TCIRG1, TNFRSF11A, TNFSF11	(SNX10: Palestine) (OSTM1: Italy) (TCIRG1: German, Turkish) (TNFRSF11A: Northern Irish, American) [TNFSF11: Tunisian ancestry, Kurdish ancestry, Sikh (India)]	CLCN7 (0) SNX10 (1) TCIRG1 (1) TNFRSF11A (0) [TNFSF11: Tunisian ancestry(1) Kurdish ancestry(1) Sikh (India) (0)]	(CLCN7:2001) (SLX10:2012) (OSTM1:2003) (PLEKHM1: 2007) (TCIRG1:2000) (TNFRSF11A: 2000) (TNFSF11: 2007)	(CLCN7, PMID: 11207362) (SLX10, PMID: 22499339) (OSTM1, PMID: 12627228) (PLEKHM1, PMID: 17404618) (TCIRG1, PMID: 10942435) (TNFRSF11A, PMID: 10615125) (TNFSF11,PMID: 17632511)
282.	Hidradenitis suppurativa	NCSTN, PSEN, PSENEN	China	*unknown*	2010	PMID: 20929727
283.	IRF4 haploinsufficiency	IRF4	European ancestry	*unknown*	2008	PMID: 18483556
284.	IL-18BP deficiency	IL18BP	Algeria	1	2019	PMID: 31213488
7.	**Autoinflammatory disorders**					
285.	STING-associated vasculopathy, infantile-onset (SAVI)	TMEM173	Turkish ancestry European ancestry French-Canadian ancestry Chilean ancestry	*unknown*	2014	PMID: 25029335
286.	ADA2 deficiency	ADA2	European ancestry	0	2014	PMID: 24552284
287.	TREX1 deficiency, Aicardi-Goutieres syndrome 1(AGS1)	TREX1	Dutch, India, Pakistan, British, German, Turkey, Ireland, Mixed European/Afro-Caribbean	Dutch (1&0) India (1) Pakistan (1) British (0) Germany (0) Turkey (1) Ireland (1)	2006	PMID: 16845398

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
				Mixed European/Afro-Caribbean (0)		
288.	RNASEH2B deficiency, AGS2	RNASEH2B	Morocco, Italy, Algeria, Ireland, French Canadian, British, German, Hungary, Tunisian/Algerian	Morocco(1 & 0) Italy(1 & 0) Algeria(1) Ireland(1) French Canadian (0) British (0) Germany (0) Hungary (0) Tunisian/Algerian (0)	2006	PMID: 16845400
289.	RNASEH2C deficiency, AGS3	RNASEH2C	Pakistan, Bangladesh	1	2006	PMID: 16845400
290.	RNASEH2A deficiency, AGS4	RNASEH2A	Spanish	1	2005	PMID: 15870678
291.	SAMHD1 deficiency, AGS5	SAMHD1	Hungarian, French, Fiji, Canada, Pakistan, Morocco, India, Arab, Malta, Ashkenazi	Hungarian(1) French(0) Fiji(0) Canada(0) Pakistan(1) Morocco(1) India(1) Arab(1) Malta(0) Ashkenazi(0)	2009	PMID: 19525956
292.	ADAR1 deficiency, AGS6	ADAR1	Japan	*unknown*	2003	PMID: 12916015
293.	Aicardi-Goutieres syndrome 7(AGS7)	IFIH1	European descent	0	2014	PMID: 24686847
294.	DNAse II deficiency	DNASE2	Japan	*unknown*	1992	PMID: 1586130
295.	Pediatric systemic lupus erythematosus due to DNASE1L3 deficiency	DNASE1L3	Arab	1	2011	PMID: 22019780
296.	Spondyloenchondro-dysplasia with immune dysregulation(SPENCD)	ACP5	Turkish, France, Austria, Pakistan, India, Portugal, Mali, Egypt	Turkish(1) France(0) Austria(0) Pakistan(1) India(1) Portugal(1) Egypt(1)	2011	PMID: 21217755
297.	X-linked reticulate pigmentary disorder	POLA1	Israel, Serbia, china, USA, Spain	*unknown*	2016	PMID: 27019227
298.	USP18 deficiency	USP18	Turkey, German	(turkey: 1) (German: 0)	2016	PMID: 27325888
299.	OAS1 deficiency	OAS1	Japan	0	2018	PMID: 29455859
300.	Familial Mediterranean fever	MEFV	Jewish, Armenian, Druze, Iraq, North African	*unknown*	1997	PMID: 9288758

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
			Jewish, Ashkenazi Jewish			
301.	Mevalonate kinase deficiency (Hyper IgD syndrome)	MVK	British, Czech, Spain, Dutch	*unknown*	2001	PMID: 11313769
302.	Muckle-Wells syndrome Familial cold autoinflammatory syndrome 1	NLRP3	North America	*unknown*	2017	PMID: 28847925
303.	Neonatal onset multisystem inflammatory disease (NOMID) or chronic infantile neurologic cutaneous and articular syndrome (CINCA) Familial cold autoinflammatory syndrome 2	NLRP12	Guadeloupe (in the southern Caribbean Sea)	*unknown*	2008	PMID: 18230725
304.	NLRC4-MAS (macrophage activating syndrome) Familial cold autoinflammatory syndrome 4	NLRC4	Caucasus Japan	0	2014	PMID: 25217960 PMID: 25217959 PMID: 25385754
305.	PLAID (PLCγ2 associated antibody deficiency and immune dysregulation)	PLCG2	European ancestry	*unknown*	2012	PMID: 22236196
306.	NLRP1 deficiency	NLRP1	Algerian, Dutch	Algerian (1)	2016	PMID: 27965258
307.	NLRP1 GOF	NLRP1	Caucasian French	*unknown*	2013	PMID: 23349227
308.	TNF receptor-associated periodic syndrome (TRAPS)	TNFRSF1A	Ireland, Scotland, France, Canada, English, German, Finland, Australia	*unknown*	1999	PMID: 10199409
309.	Pyogenic sterile arthritis, pyoderma gangrenosum, acne (PAPA) syndrome, hyperzincemia and hypercalprotectinemia	PSTPIP1	*unknown*	*unknown*	2002	PMID: 11971877
310.	Blau syndrome	NOD2	Caucasus	0	2010	PMID: 19467619
311.	ADAM17 deficiency	ADAM17	Lebanese origin	1	2011	PMID: 22010916
312.	Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	LPIN2	Jordanian Arab	1	2005	PMID: 15994876
313.	DIRA (Deficiency of the Interleukin 1 Receptor Antagonist)	IL1RN	Canada, Netherlands, Lebanon, Puerto Rico,	Lebanon (1) Puerto Rico (0)	2009	PMID: 19494218

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
314.	DITRA (Deficiency of IL-36 receptor antagonist)	IL36RN	Tunisia	1 & 0	2011	PMID: 21848462
315.	SLC29A3 mutation	SLC29A3	Arab, Bulgaria	Arab (1) Bulgaria (0)	2008	PMID: 18940313
316.	CAMPS (CARD14 mediated psoriasis)	CARD14	European ancestry, Taiwanese family	*unknown*	2012	PMID: 22521418
317.	Cherubism	SH3BP2	African-Brazilian, European Descent, Hispanic (Spain)	0	2001	PMID: 11381256
318.	CANDLE (chronic atypical neutrophilic dermatitis with lipodystrophy)	PSMB8, PSMG2	(PSMB8: Portugal, Mexico, japan)	Portugal (0) Mexico (0) Japan (1)	(PSMB8:2010)	(PSMB8, PMID: 20534754)
319.	COPA defect	COPA	*unknown*	*unknown*	2015	PMID: 25894502
320.	Otulipenia/ORAS	OTULIN	Pakistan	1	2016	PMID: 27523608
321.	A20 deficiency	TNFAIP3	European Canadian, European American, Turkish, Dutch	*unknown*	2016	PMID: 26642243
322.	AP1S3 deficiency	AP1S3	British, Swiss, Ireland, Poland	*unknown*	2014	PMID: 24791904
323.	ALPI deficiency	ALPI	Italy Ashkenazi Jewish	0	2018	PMID: 29567797
324.	TRIM22	TRIM22	African, Asian, American, European	*unknown*	2014	PMID: 24863734
325.	T cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency)	HAVCR2	East Asian, Polynesian, Caucasian, North African	*unknown*	2018	PMID: 30374066
8.	**Complement deficiencies**					
326.	C1q deficiency due to defects	C1QA, C1QB, C1QC	(C1QA: Sweden, Iraq, turkey, Slovak republic, Sudan, Cyprus) (C1QB: morocco, inuit (Canada), Mexico) (C1QC: Germany, India, Saudi Arabia, Caucasian, Arabian, Pakistan, Kosovo, Yugoslavia, England, turkey)	Sudan: 1 Sweden: 0 Arabian: 1 turkey: 1 caucasuse: 1 Pakistan: 1 Asia: 1	2011	PMID: 21654842
327.	C1r deficiency	C1R	USA and Europe (Austria)	*unknown*	2016	PMID: 27745832

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
328.	C1r Periodontal Ehlers-Danlos	C1R	USA and Europe (Austria)	*unknown*	2016	PMID: 27745832
329.	C1s deficiency	C1S	*unknown*	*unknown*	1998	PMID: 9856483
330.	C1s Periodontal Ehlers-Danlos	C1S	USA and Europe	*unknown*	2016	PMID: 27745832
331.	Complete C4 deficiency	C4A + C4B	*unknown*	*unknown*	*unknown*	*unknown*
332.	C2 deficiency	C2	*unknown*	*unknown*	1995	PMID: 8621452
333.	C3 deficiency (LOF)	C3	South Africans	0	1992	PMID: 1350678
334.	C3 GOF	C3	South Africans	0	1992	PMID: 1350678
335.	C5 deficiency	C5	African American	*unknown*	1995	PMID: 7730648
336.	C6 deficiency	C6	South Africa	*unknown*	1995	PMID: 7535801
337.	C7 deficiency	C7	Japan	*unknown*	1996	PMID: 8892662
338.	C8α deficiency	C8A	Japan	*unknown*	1998	PMID: 9759902
339.	C8 γ deficiency	C8G	*unknown*	*unknown*	*unknown*	*unknown*
340.	C8 β deficiency	C8B	Germany, Italy, Swiss, Poland	*unknown*	1993	PMID: 8098723
341.	C9 deficiency	C9	Swiss	*unknown*	1997	PMID: 9144525
342.	MASP2 deficiency	MASP2	*unknown*	*unknown*	2003	PMID: 12904520
343.	Ficolin 3 deficiency	FCN3	Macedonia, Albania	*unknown*	2009	PMID: 19535802
344.	C1 inhibitor deficiency	SERPING1	*unknown*	*unknown*	1995	PMID: 7883978
345.	Factor B GOF	CFB	Spanish	*unknown*	2007	PMID: 17182750
346.	Factor B deficiency	CFB	England, Scotland	0	2013	PMID: 24152280
347.	Factor D deficiency	CFD	Dutch	1	2001	PMID: 11457876
348.	Properdin deficiency	CFP	Dutch	*unknown*	1996	PMID: 8871668
349.	Factor I deficiency	CFI	Scotland	0	1996	PMID: 8613545
350.	Factor H deficiency	CFH	Native American	*unknown*	1997	PMID: 9312129
351.	Factor H-related protein deficiencies	CFHR1, CFHR2, CFHR3, CFHR4, CFHR5	[CFHR5: Cyprus, Northern Ireland, UK (European descent)]	*unknown*	(CFHR5:2010) (CFHR:2006)	(CFHR1, PMID: 16998489) (CFHR5, PMID: 20800271)
352.	Thrombomodulin deficiency	THBD	Hispanic	*unknown*	1995	PMID: 7811989
353.	Membrane Cofactor Protein (CD46) deficiency	CD46	Belgium, German, Turkey	Turkey (1)	2003	PMID: 14566051
354.	Membrane Attack Complex Inhibitor (CD59) deficiency	CD59	Japan	1	1992	PMID: 1382994
355.	CD55 deficiency (CHAPEL disease)	CD55	Turkey, Morocco, Syria, Muslim Arab	1	2017	PMID: 28657829 PMID: 28657861
9.	**Bone marrow failure**					
356.	Fanconi anemia type A	FANCA	Italy	*unknown*	1996	PMID: 8896564
357.	Fanconi anemia type B	FANCB	*unknown*	*unknown*	2004	PMID: 15502827
358.	Fanconi anemia type C	FANCC	Ashkenazi Jewish	*unknown*	1993	PMID: 8348157

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
359.	Fanconi anemia type D1	BRCA2	*unknown*	0 & 1	2002	PMID: 12065746
360.	Fanconi anemia type D2	FANCD2	*unknown*	*unknown*	2001	PMID: 11239453
361.	Fanconi anemia type E	FANCE	Turkey, Bangladesh	*unknown*	2000	PMID: 11001585
362.	Fanconi anemia type F	FANCF	*unknown*	*unknown*	2000	PMID: 10615118
363.	Fanconi anemia type G	XRCC9	German , Arabian	Arabian (1)	1998	PMID: 9806548
364.	Fanconi anemia type I	FANCI	Turkey, India, USA, Hungary, Austria, Germany	Turkey (1) India (1)	2007	PMID: 17452773
365.	Fanconi anemia type J	BRIP1	African-American, European-American and Hispanic (Spain)	*unknown*	2005	PMID: 16116424
366.	Fanconi anemia type L	FANCL	*unknown*	*unknown*	2009	PMID: 19405097
367.	Fanconi anemia type M	FANCM	Finland	1	2017	PMID: 29231814
368.	Fanconi anemia type N	PALB2	Albania, Morocco, German, Hispanic (Spain), North America, African Ancestry, British,	*unknown*	2007	PMID: 17200671
369.	Fanconi anemia type O	RAD51C	Pakistan	1	2010	PMID: 20400963
370.	Fanconi anemia type P	SLX4	Dutch	1	2011	PMID: 21240277
371.	Fanconi anemia type Q	ERCC4	Spain	0	2013	PMID: 23623386
372.	Fanconi anemia type R	RAD51	*unknown*	*unknown*	2015	PMID: 26681308
373.	Fanconi anemia type S	BRCA1	Scotland	*unknown*	1995	PMID: 7791869
374.	Fanconi anemia type T	UBE2T	Japan	*unknown*	2015	PMID: 26046368
375.	Fanconi anemia type U	XRCC2	Saudi Arabian	1	2012	PMID: 22232082
376.	Fanconi anemia type V	MAD2L2	*unknown*	1	2016	PMID: 27500492
377.	Fanconi anemia type W	RFWD3	Germany	*unknown*	2017	PMID: 28691929
378.	MIRAGE (myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, enteropathy)	SAMD9	Japan	*unknown*	2016	PMID: 27182967
379.	Ataxia pancytopenia syndrome	SAMD9L	Irish, German, and Native American ancestry	*unknown*	2016	PMID: 27259050

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
380.	DKCX1	DKC1	Caucasus, English, Ireland, Belgium	*unknown*	1998	PMID: 9590285
381.	DKCA1	TERC	USA	*unknown*	2001	PMID: 11574891
382.	DKCA2	TERT	Hispanic (Spain), Asian, Amerindian (USA)	*unknown*	2005	PMID: 15814878
383.	DKCA3	TINF2	European ancestry	0	2008	PMID: 18252230
384.	DKCA4	RTEL1	European descendants	0	2009	PMID: 19461895
385.	DKCA5	TINF2	European ancestry	0	2008	PMID: 18252230
386.	DKCA6	ACD	*unknown*	0	2014	PMID: 25205116
387.	DKCB1	NOLA3	Saudi Arabia	1	2007	PMID: 17507419
388.	DKCB2	NOLA2	Turkey	1	2008	PMID: 18523010
389.	DKCB3	WRAP53	*unknown*	*unknown*	2011	PMID: 21205863
390.	DKCB4	TERT	Iranian-Jewish, Libya	1	2007	PMID: 17785587
391.	DKCB5	RTEL1	European descendants	0	2009	PMID: 19461895
392.	DKCB6	PARN	Pakistan, England	Pakistan (1) England (0)	2015	PMID: 25893599
393.	DKCB7	ACD	*unknown*	0	2014	PMID: 25205116
394.	BMFS1 (SRP72-deficiency)	SRP72	*unknown*	*unknown*	2012	PMID: 22541560
395.	BMFS5	TP53	*unknown*	*unknown*	2018	PMID: 30146126
396.	Coats plus syndrome	STN1, CTC1	(STN1: Palestinian) (CTC1: Egypt, Norway, England, Scotland, Canada, European-American, Italy, Swiss-French, African and European, Portugal)	(STN1:1)	(STN1:2016) (CTC1:2012)	(STN1, PMID: 27432940) (CTC1, PMID: 22267198)
10.	**Phenocopies of inborn errors of immunity**					
397.	Autoimmune lymphoproliferative syndrome (ALPS–SFAS)	Somatic mutation in *TNFRSF6*	*unknown*	*unknown*	1999	PMID: 10200300
398.	RAS-associated autoimmune	Somatic mutation in *KRAS* (GOF)	Italian ancestry	*unknown*	2010	PMID: 21079152

Table 1. continued

	Disease	Gene	Origin	Consanguinity	Year	Ref.
	leukoproliferative disease (RALD)					
399.	RAS-associated autoimmune leukoproliferative disease (RALD)	Somatic mutation in *NRAS* (GOF)	*unknown*	*unknown*	2007	PMID: 17517660
400.	Cryopyrinopathy, (Muckle-Wells/ CINCA/NOMID-like syndrome)	Somatic mutation in *NLRP3*	North America	*unknown*	2017	PMID: 28847925
401.	Hypereosinophilic syndrome due to somatic mutations in STAT5b	Somatic mutation in *STAT5B* (GOF)	Argentina	1	2003	PMID: 13679528
402.	Chronic mucocutaneous candidiasis	AutoAb to IL-17 and/or IL-22	*unknown*	*unknown*	*unknown*	*unknown*
403.	Adult-onset immunodeficiency with susceptibility to mycobacteria	AutoAb to IFNγ	*unknown*	*unknown*	*unknown*	*unknown*
404.	Recurrent skin infection	AutoAb to IL-6	*unknown*	*unknown*	*unknown*	*unknown*
405.	Pulmonary alveolar proteinosis	AutoAb to GM-CSF	*unknown*	*unknown*	*unknown*	*unknown*
406.	Acquired angioedema	AutoAb to CI inhibitor	*unknown*	*unknown*	*unknown*	*unknown*
407.	Atypical hemolytic uremic syndrome	AutoAb to Complement Factor H	*unknown*	*unknown*	*unknown*	*unknown*
408.	Thymoma with hypogammaglobulinemia (Good syndrome)	AutoAb to various cytokines	*unknown*	*unknown*	*unknown*	*unknown*
0: non-consanguineous marriage						
1: consanguineous marriage						

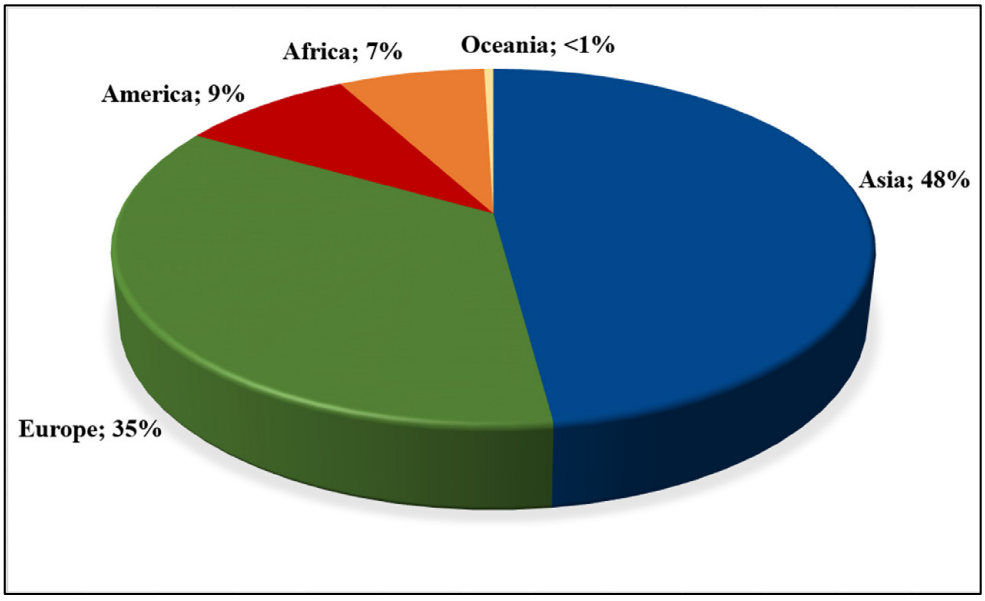

Figure 1. Percentage of the genetic defect's dispersion, based on the first case report. This information excludes genes that have been reported simultaneously in several countries.

Europe and America and 6 cases with a known gene defects, were reported in Asia, Europe and the United States at the same time.

Due to the high prevalence of the known genetic defects in the Middle East, this region is important for evaluating the first report of the genetic defects; As many as 95 of the reported genetic defects, are related to Middle Eastern countries. These cases have been raised either individually or jointly with other countries. In this regard, Turkey has the most first cases reported compared to the other countries in the Middle East.

Consanguinity data

Parental consanguinity is one of the interfering and influential factors on gene dispersion. In this regard, findings show that the highest geographical distribution of patients with genetic defects and parental consanguinity, are observed in Asia. Our survey demonstrated, that out of the 165 first report cases with genetic defects and consanguineous marriage, 112 cases were identified in Asia. Although, these 112 patients are either exclusively in Asia or jointly within non-Asian countries. In the case of patients with genetic defects and no parental consanguinity, the highest dispersion (43 out of 87 cases) is related to Europe. This number may be exclusive to European continent or shared with other countries from other continents.

By studying the first published case reports of the genetic defects, patients with genetic defects and consanguineous parents in the Middle East are more, compared to the patients with unrelated parents. In this regard, the review of the first reports shows that out of the 165 cases registered with consanguineous parents, 71 cases were related to the Middle East, while out of the 87 reported patients with genetic defects and non-consanguineous parents, only 13 cases are related to the Middle East. Consanguinity information is listed in Table 1.

Discussion

In the current study, which investigated the first report of the PID, most reports are related to Asia. Numerous studies have written about the worldwide frequency of the PIDs, demonstrating an estimate of the number of the PID patients. In Asia, they have seen the highest number of people with these diseases in most cases (26-29).

There is a great deal of cultural and ethnic diversity in Asia; therefore, in this continent, the distribution of the first report of the PID is different. Our results show that the Middle East and Southwest Asian countries, have more frequency in reporting the first cases, than the other countries. Approximately, 95 of the reported genetic defects are related to Middle Eastern countries. These cases have raised either individually or jointly with other countries in different continents. In this regard, Turkey has the most first case reports compared to other countries in the Middle East. Other studies also confirmed that a large number of PIDs patients have been observed in Turkey and Iran (17, 18). Various studies were conducted to the prevalence of the PIDs in the Middle East and Southwest Asia (16, 17, 30-38). However, there are comprehensive studies on the genetic defects and PID, in other Asian countries, especially the eastern countries (16, 39-44). Higher prevalence of the first reported cases with PID in these regions, can depend on a variety of reasons. One of these reasons is the consanguineous marriage, which greatly increases the risk of genetic diseases and PID (45-49). Countries with a high percentage of consanguineous marriages, are also important, due to the concentration on identifying patients in these areas, resulting in a major impact on finding the novel genes and the causes of the rare genetic diseases. Of note, in current study, the survey of the first published reports of the genetic defects, shows that out of the 165 cases with an active consanguinity status, 112 are in Asia. Of course, these 112 patients are either exclusively in Asia or jointly with non-Asian countries, also 71 of the cases, were somehow related to the Middle East.

In the meantime, the role of other countries in the development of the novel genes and PIDs should not be overlooked; because in the current study, 131 of the patients were non-Asian and 67 were non-Asians, demonstrating the significant frequency of these areas. Numerous studies were conducted to the prevalence of the PIDs in different parts of the world, which were mostly non-Asian communities (3, 33, 50-53). This shows the importance of geographical dispersion in the

study of PIDs. Many cases are such that in these articles, different patients from several countries are studied simultaneously. Accordingly, in some reports related to the first report of the PID, patients with multiple nationalities, who are often from different continents, have been studied. For example, in the current study, the percentage of the first case reports of the genetic defects simultaneously in Asia-Europe and Europe-America, were reported 7.1% and 2.2%, respectively, and approximately 1.5% of the cases were identified in Asia, Europe and the United States at the same time. However, the expansion of the treatment systems and patient information systems can provide more comprehensive and accurate information on the prevalence of the PID patients, especially in the less developed countries such as Africa.

The rate of the consanguineous marriage is lower in western and American countries than in Asia and the Middle East, due to the less prevalent culture of this tradition. Extensive studies have been conducted to the field of the consanguineous marriage in different countries, all of which indicate the spread of the consanguineous marriage in different continents (17, 25, 54-57). This issue can significantly impact the development and diversity of the rare genetic diseases, including the PID. In this study, 87 cases with PID who have no parental consanguinity, belong to only 13 cases in the Middle East and 43 cases (49.4%) in Europe.

Conclusion

This report provides valuable information on the geographical data and the prevalence of various genetic disorders worldwide. Also, by providing information related to the parental consanguinity about the first reported cases with a genetic defect, valuable information about the inborn errors of immunity, will be provided to researchers, that can be used effectively in the future studies.

Conflict of interest

There is no conflict of interest.

References

1. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. J Allergy Clin Immunol Pract. 2019;7(6):1763-70.
2. Al-Herz W, Chou J, Delmonte OM, Massaad MJ, Bainter W, Castagnoli R, et al. Comprehensive genetic results for primary immunodeficiency disorders in a highly consanguineous population. Front Immunol. 2019;9:3146.
3. Erjaee A, Bagherpour M, Van Rooyen C, Van den Berg S, Kinnear C, Green RJ, et al. Primary immunodeficiency in Africa–a review. S Afr Med J. 2019;109(8, Supplement 1):S4-S12.
4. Modell V, Knaus M, Modell F, Roifman C, Orange J, Notarangelo LD. Global overview of primary immunodeficiencies: a report from Jeffrey Modell Centers worldwide focused on diagnosis, treatment, and discovery. Immunol Res. 2014;60(1):132-44.
5. Abolhassani H, Azizi G, Sharifi L, Yazdani R, Mohsenzadegan M, Delavari S, et al. Global systematic review of primary immunodeficiency registries. Expert Rev Clin Immunol 2020;16(7):717-32.
6. Bousfiha A, Jeddane L, Al-Herz W, Ailal F, Casanova JL, Chatila T, et al. The 2015 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol. 2015;35(8):727-38.
7. Bousfiha A, Jeddane L, Picard C, Al-Herz W, Ailal F, Chatila T, et al. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. J Clin Immunol. 2020:1-16.
8. Bousfiha A, Jeddane L, Picard C, Ailal F, Gaspar HB, Al-Herz W, et al. The 2017 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol. 2018;38(1):129-43.
9. 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.
10. Hamamy H, Antonarakis SE, Cavalli-Sforza LL, Temtamy S, Romeo G, Ten Kate LP, et al. Consanguineous marriages, pearls and perils: Geneva international consanguinity workshop report. Genet Med. 2011;13(9):841-7.
11. Picard C, Al-Herz W, Bousfiha A, Casanova J-L, Chatila T, Conley ME, et al. Primary immunodeficiency diseases: an update on the classification from the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency 2015. J Clin Immunol. 2015;35(8):696-726.

12. Tadmouri GO, Nair P, Obeid T, Al Ali MT, Al Khaja N, Hamamy HA. Consanguinity and reproductive health among Arabs. Reprod Health. 2009;6(1):17.
13. Sorensen R, Etzioni A, Bousfiha AA, Zeiger JB. Collaborating to improve quality of life in primary immunodeficiencies: World PI Week, 2013. Springer; 2013.
14. Barbouche MR, Galal N, Ben-Mustapha I, Jeddane L, Mellouli F, Ailal F, et al. Primary immunodeficiencies in highly consanguineous North African populations. Ann N Y Acad Sci. 2011;1238(1):42-52.
15. Ishimura M, Takada H, Doi T, Imai K, Sasahara Y, Kanegane H, et al. Nationwide survey of patients with primary immunodeficiency diseases in Japan. J Clin Immunol. 2011;31(6):968-76.
16. Pilania RK, Chaudhary H, Jindal AK, Rawat A, Singh S. Current status and prospects of primary immunodeficiency diseases in Asia. Genes Dis. 2020;7(1):3-11.
17. Al-Mousa H, Al-Saud B. Primary immunodeficiency diseases in highly consanguineous populations from Middle East and North Africa: epidemiology, diagnosis, and care. Front Immunol. 2017;8:678.
18. Kilic SS, Ozel M, Hafizoglu D, Karaca NE, Aksu G, Kutukculer N. The prevalances and patient characteristics of primary immunodeficiency diseases in Turkey—two centers study. J Clin Immunol. 2013;33(1):74-83.
19. Liang F-C, Wei Y-C, Jiang T-H, Hsieh M-Y, Wen Y-C, Chiou Y-S, et al. Current classification and status of primary immunodeficiency diseases in Taiwan. Acta Paediatr Taiwan. 2008;49(1):3-8.
20. Choi C, Kim B, Kim E-K, Song ES, Lee JJ. Erratum to Correction of figure legends Incidence of Bronchopulmonary Dysplasia in Korea. J Korean Med Sci 27,(2012) 914-921.
21. Modell B, Darr A. Genetic counselling and customary consanguineous marriage. Nat Rev Genet. 2002;3(3):225-9.
22. Bittles A. A global overview on consanguinity. EGF [en línea]. 2007.
23. Bittles AH, Black ML. Consanguinity, human evolution, and complex diseases. Proc Natl Acad Sci U S A. 2010;107(suppl 1):1779-86.
24. Teebi AS, Teebi SA, Porter CJ, Cuticchia AJ. Arab genetic disease database (AGDDB): A population-specific clinical and mutation database. Hum Mutat. 2002;19(6):615-21.
25. Anwar WA, Khyatti M, Hemminki K. Consanguinity and genetic diseases in North Africa and immigrants to Europe. Eur J Public Health. 2014;24(suppl_1):57-63.
26. Kirkpatrick P, Riminton S. Primary immunodeficiency diseases in Australia and New Zealand. J Clin Immunol. 2007;27(5):517-24.
27. Boyle J, Buckley R. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007;27(5):497-502.
28. Joshi AY, Iyer VN, Hagan JB, Sauver JLS, Boyce TG, editors. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clin Proc; 2009: Elsevier.
29. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova J-L, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol. 2013;33(1):1-7.
30. Al-Herz W. Primary immunodeficiency disorders in Kuwait: first report from Kuwait national primary immunodeficiency registry (2004–2006). J Clin Immunol. 2008;28(2):186-93.
31. Al-Tamemi S, Naseem SUR, Al-Siyabi N, El-Nour I, Al-Rawas A, Dennison D. Primary immunodeficiency diseases in Oman: 10-year experience in a tertiary care hospital. J Clin Immunol. 2016;36(8):785-92.
32. Galal N, Meshaal S, Elhawary R, Abd ElAziz D, Alkady R, Lotfy S, et al. Patterns of primary immunodeficiency disorders among a highly consanguineous population: Cairo University Pediatric Hospital's 5-year experience. J Clin Immunol. 2016;36(7):649-55.
33. Mellouli F, Mustapha IB, Khaled MB, Besbes H, Ouederni M, Mekki N, et al. Report of the Tunisian registry of primary immunodeficiencies: 25-years of experience (1988–2012). J Clin Immunol. 2015;35(8):745-53.
34. Aghamohammadi A, Mohammadinejad P, Abolhassani H, Mirminachi B, Movahedi M, Gharagozlou M, et al. Primary immunodeficiency disorders in Iran: update and new insights from the third report of the national registry. J Clin Immunol. 2014;34(4):478-90.
35. Golan H, Dalal I, Garty B-Z, Schlesinger M, Levy J, Handzel Z, et al. The incidence of primary immunodeficiency syndromes in Israel. IMAJ-RAMAT GAN-. 2002;4(11; SUPP):868-71.
36. Ehlayel MS, Bener A, Laban MA. Primary immunodeficiency diseases in children: 15 year experience in a tertiary care medical center in Qatar. J Clin Immunol. 2013;33(2):317-24.
37. Al-Saud B, Al-Mousa H, Al Gazlan S, Al-Ghonaium A, Arnaout R, Al-Seraihy A, et al. Primary immunodeficiency diseases in Saudi Arabia: a tertiary care hospital experience over a period of three years (2010–2013). J Clin Immunol.

2015;35(7):651-60.
38. Al-Muhsen S, Alsum Z. Primary immunodeficiency diseases in the Middle East. Ann N Y Acad Sci. 2012;1250(1):56-61.
39. Abd Hamid IJ, Zainudeen ZT, Hashim IF. Current perspectives and challenges of primary immunodeficiency diseases in Malaysia. J Paediatr Child Health. 2019;25(2):1-6.
40. Jindal AK, Pilania RK, Rawat A, Singh S. Primary immunodeficiency disorders in India—a situational review. Front Immunol. 2017;8:714.
41. Lee P, Lau Y-L. Endemic infections in Southeast Asia provide new insights to the phenotypic spectrum of primary immunodeficiency disorders. Asian Pac J Allergy Immunol. 2013;31(3):217-26.
42. Lee P-w. Primary immunodeficiency disorders in Southeast Asia: needs, priorities and opportunities. HKU Theses Online (HKUTO). 2014.
43. Abd Hamid IJ, Azman NA, Gennery AR, Mangantig E, Hashim IF, Zainudeen ZT. Systematic Review of Primary Immunodeficiency Diseases in Malaysia: 1979–2020. Front Immunol. 2020;11:1923.
44. Leung D, Chua GT, Mondragon AV, Zhong Y, Nguyen-Ngoc-Quynh L, Imai K, et al. Current Perspectives and Unmet Needs of Primary Immunodeficiency Care in Asia Pacific. Front Immunol. 2020;11:1605.
45. Rezaei N, Pourpak Z, Aghamohammadi A, Farhoudi A, Movahedi M, Gharagozlou M, et al. Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. Am J Reprod Immunol. 2006;56(2):145-51.
46. Al-Herz W, Aldhekri H, Barbouche M-R, Rezaei N. Consanguinity and primary immunodeficiencies. Hum Hered. 2014;77(1-4):138-43.
47. Al-Herz W, Naguib KK, Notarangelo LD, Geha RS, Alwadaani A. Parental consanguinity and the risk of primary immunodeficiency disorders: report from the Kuwait National Primary Immunodeficiency Disorders Registry. Int Arch Allergy Immunol. 2011;154(1):76-80.
48. Broides A, Nahum A, Mandola AB, Rozner L, Pinsk V, Ling G, et al. Incidence of typically severe primary immunodeficiency diseases in consanguineous and non-consanguineous populations. J Clin Immunol. 2017;37(3):295-300.
49. Fareed M, Afzal M. Genetics of consanguinity and inbreeding in health and disease. Ann Hum Biol. 2017;44(2):99-107.
50. Sediva A, Bataneant M, Belevtsev M, Blaziene A, Ciznar P, Förster-Waldl E, et al. Primary immunodeficiencies in Central and Eastern Europe—the power of networking Report on the activity of the Jeffrey Modell Foundation Centers Network in Central and Eastern Europe. Immunol Res. 2019;67(4-5):358-67.
51. Costa-Carvalho B, González-Serrano M, Espinosa-Padilla S, Segundo G. Latin American challenges with the diagnosis and treatment of primary immunodeficiency diseases. Expert Rev Clin Immunol. 2017;13(5):483-9.
52. Rubin Z, Pappalardo A, Schwartz A, Antoon JW. Prevalence and outcomes of primary immunodeficiency in hospitalized children in the United States. J Allergy Clin Immunol Pract. 2018;6(5):1705-10. e1.
53. Ludviksson BR, Sigurdardottir ST, Johannsson JH, Haraldsson A, Hardarson TO. Epidemiology of primary immunodeficiency in Iceland. J Clin Immunol. 2015;35(1):75-9.
54. Reda SM, Afifi HM, Amine MM. Primary immunodeficiency diseases in Egyptian children: a single-center study. J Clin Immunol. 2009;29(3):343-51.
55. Baykara-Krumme H. Consanguineous marriage in Turkish families in Turkey and in Western Europe. International Migration Review. 2016;50(3):568-98.
56. Romeo G, Bittles AH. Consanguinity in the contemporary world. Hum Hered. 2014;77(1/4):6-9.
57. Liascovich R, Rittler M, Castilla EE. Consanguinity in South America: demographic aspects. Hum Hered. 2001;51(1-2):27-34.