Original Article

DOI: 10.5582/irdr.2024.01061

Classification and epidemiologic analysis of 86 diseases in *China's* Second List of Rare Diseases

Junfeng Li¹, Meilin Liu^{1,§}, Han Li^{2,§}, Xin Zhang^{3,§}, Xufei Xiang^{1,§}, Yiping Wang^{1,§}, Shuyi Wang^{1,§}, Jinxiang Han^{1,4}, Yanqin Lu^{1,4,*}

²Shandong Experimental High School, Ji'nan, China;

³Digestive Diseases Hospital of Shandong First Medical University, Ji'ning, China;

⁴ Department of Endocrinology and Metabology, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, Ji'nan, China.

SUMMARY Following the release of China's First List of Rare Diseases in May 2018, the Chinese government officially published China's Second List of Rare Diseases in September 2023. To date, there is no unified standard and international consensus for rare diseases, and epidemiologic data for most rare diseases in China are lacking. We investigated 86 rare diseases on the second list using Orphanet and other databases to clarify the classification, nomenclature, and epidemiologic data for these diseases, and we summarized the genotype and phenotype of hereditary diseases. The results showed that most of 86 rare diseases were coded in the database of Unified Medical Language System (UMLS), Orphanet, Medical Subject Headings (MeSH) and International Classification of Diseases, Eleventh Revision (ICD-11). Some rare diseases are composed by group of different disorders, in which multiple identifiers existed. Meanwhile, some rare diseases have different subtypes, which correspond to different identifiers. This increases the actual number of rare diseases in the second list. Over 50% of rare diseases are genetic rare diseases and they are mainly classified into neoplastic diseases, transplant-related disorders and neurological diseases. Epidemiologic data indicated that these rare diseases had a broad prevalence spectrum and over 20 rare diseases had a prevalence of over 1/10,000, these rare diseases in the China's Second List of Rare Diseases expanded the number and scope of rare diseases according to the China's official definition of rare diseases.

Keywords China's Second List of Rare Diseases, classification, nomenclature, epidemiology, incidence, prevalence

1. Introduction

A rare disease is a health condition with low prevalence and incidence compared with other more prevalent diseases in the general population. Although these diseases are individually rare, over 7,000 conditions have been identified, which affect 3.5%-5.9% of individuals worldwide or an estimated 263-446 million individuals collectively (1). Rare diseases are a global public health issue. Patients with rare diseases face challenges regarding diagnosis, treatment, and care. Great advances have been made in the diagnosis, treatment, care, and epidemiology of rare diseases in China, and several polices have been enacted to ensure progress in the area of rare diseases (2,3). Before China's official definition of rare diseases in 2021, five bodies including the National Health Commission of the People's Republic of China and the National Medical Products Administration issued *China's First List of Rare Diseases* in May 2018 (4,5). Five years later, *China's Second List of Rare Diseases* was officially released on 21 September 2023 by six bodies. Until now, 207 rare diseases have been included on this list. In September 2021, China defined rare diseases as a condition with at least one of the following three criteria: an incidence among newborns of less than 1/10,000, a prevalence of less than 1/10,000, and an affected population of less than 140,000 (6). Thus, the rare diseases list and this definition have now been simultaneously adopted in China.

¹ Key Laboratory for Biotech-Drugs of National Health Commission, Key Laboratory for Rare & Uncommon Diseases of Shandong Province, Biomedical Sciences College & Shandong Medicinal Biotechnology Centre, Shandong First Medical University & Shandong Academy of Medical Sciences, Ji'nan, China;

There is no unified international standard and consensus to date on how rare diseases should generally be named and classified. The nomenclature of rare diseases is recorded using international terminologies in different reference databases. In this study, we investigated the classification, genetic information, incidence, and prevalence of 86 conditions in *China's Second List of Rare Diseases* using Orphanet, OMIM, and other databases.

2. Methods

The nomenclature of 86 conditions in *China's Second List of Rare Diseases* was retrieved using international terminologies in different reference databases, including ICD-10 (7) and ICD-11 (8) (*https://icd.who.int/en*), Online Mendelian Inheritance in Man (OMIM) (*www. omim.org*), Orphanet (*https://www.orpha.net/consor/ cgi-bin/index.php*), UMLS (9) (*https://www.nlm.nih. gov/research/umls/index.html*), MeSH (*https://www. nlm.nih.gov/mesh/meshhome.html*), Medical Dictionary for Regulatory Activities Terminology (MedDRA) (*10*) (*https://www.meddra.org/*), and Genetic and Rare Diseases (GARD) (*https://rarediseases.info.nih.gov/*). The classification and epidemiology of 86 rare diseases were analyzed through Orphanet database. The genetic information was summarized using OMIM database.

3. Results

3.1. Nomenclature of 86 diseases in *China's Second List* of Rare Diseases

Rare diseases in China's Second List of Rare Diseases were mapped to seven different reference databases (Table 1). UMLS coded the most rare diseases (n =78, 90.70%) with a unique identifier, followed by 77 diseases (89.53%) in ORPHAcode, 74 diseases (86.05%) in MeSH, 66 diseases (76.74%) in ICD-11, and 64 diseases (74.42%) in ICD-10, 59 diseases (68.60%) in GARD and 57 diseases (66.28%) in MedDRA (Supplemental Table S1, https://www.irdrjournal.com/ action/getSupplementalData.php?ID=220). In ICD-10, identifier C49.9 encodes both dermatofibrosarcoma protuberans and epithelioid sarcoma, Lennox-Gastaut syndrome and West syndrome were classified into other generalized epilepsy and epileptic syndromes (G40.4). Bardet-Biedl syndrome and IGF1 deficiency were classified into hypopituitarism in ICD-11 (5A61.0). Except MeSH, melanoma and pemphigus were coded by at least two different codes in all other 6 nomenclature systems. PIK3CA related overgrowth syndrome and was multiple coded in 5 different nomenclature systems.

In Orphanet database, acquired hemophilia, congenital biliary atresia, malignant hyperthermia, melanoma, pemphigus and thalassemia major were coded using more than two different codes. ORPHA163596 and 231214 coded alpha-thalassemia major and betathalassemia major, respectively. Syndrome with alphathalassemia as a major feature (ORPHA 232288) was a group of disorders consisting of alpha-thalassemiaintellectual disability syndrome linked to chromosome 16 (ORPHA 98791), alpha-thalassemia-myelodysplastic syndrome (ORPHA 231401) and X-linked alphathalassemia-intellectual disability syndrome (ORPHA 847). Code 182095 represents a group of disorders of interstitial lung disease (ILD), including interstitial lung disease in childhood and adulthood ORPHA (264757), interstitial lung disease specific to adulthood (ORPHA 264735) and interstitial lung disease specific to childhood (ORPHA 264656).

In ICD-10, nine different diseases were non-coded. Cutaneous neuroendocrine carcinoma, melanoma, pemphigus, pheochromocytoma, PIK3CA related overgrowth syndrome and thalassemia major were coded using more than three different codes. In ICD-11, five diseases were non-coded. Thirteen types of rare tumor were coded using at least two different identifiers. A total of 26 diseases were coded using more than two different identifiers and 13 of them were tumor diseases. In UMLS, gastroenteropancreatic neuroendocrine neoplasm was non-coded. In the databases of MeSH, GARD and MeDRA, a total of 11, 24 and 26 rare diseases were non-coded, respectively (Table 1, Supplemental Table S1, https://www.irdrjournal.com/action/ getSupplementalData.php?ID=220).

3.2. Classification of 86 diseases in *China's Second List* of *Rare Diseases*

In the Orphanet classification system of rare diseases, 83 diseases with ORPHAcodes in *China's Second List of Rare Diseases* were mapped (Supplemental Table S2, *https://www.irdrjournal.com/action/ getSupplementalData.php?ID=221*). Of these, 45 are genetic rare diseases, accounting for 53.49%. These were followed by 28 (32.56%) neoplastic diseases and transplant-related disorders, respectively; 24 neurological diseases (27.91%), 15 skin diseases (17.44%), 13 renal diseases (15.12%), 12 developmental anomalies during embryogenesis, hepatic diseases, hematological diseases, endocrine diseases, ophthalmic disorders and systemic and rheumatological diseases, each accounting for 13.95% (Table 2).

3.3. Group of rare disorders and genotypic heterozygosity of rare diseases

Some rare diseases are groups of disorders and others have different subtypes according to classification, leading to a higher number of rare diseases in *China's Second List of Rare Diseases* than the actual number (Supplemental Table S3, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=222*). As an

			m manag fa mana					
#	Rare disease	ORPHA	ICD-10	ICD-11	NMLS	MeSH	GARD	MedDRA
1	Achondroplasia	15	Q77.4	LD24.00	C0001080	D000130	8173	C0001080
7	Acquired hemophilia	599480	D66.	3B22	C0272325	C536392	6405	10082745
		955485	X01		C0398609			10082747
б	Acromegaly	963	E22.0	5A60.0	C0001206	D000172	5725	10000599
4	Adult-onset Still disease	829	M06.1	FA23	C0085253	D016706	436	10064056
5	Alagille syndrome	52	Q44.7	LB20.0Y	C0085280	D016738	804	10053870
9	Alpha-1-antitrypsin deficiency	09	E88.0	5C5A	C0221757	D019896	5784	10001806
7	ANCA-associated vasculitis	156152		4A44.A	C2717865	D056648	·	·
8	Bardet-Biedl syndrome	110	Q87.8	5A61.0	C0752166	D020788	6866	10056715
6	Behçet's disease	117	M35.2	4A62	C0004943	D001528	848	10004213
10	Blue rubber bleb nevus	1059	Q27.8	LC51	C0346072	C536240	5940	
11	CDKL5-deficiency disorder	505652		8A62.Y	C4750718	C564064	·	10083005
12	Choroideremia	180	H31.2	9B61	C0008525	D015794	6061	10008791
13	Chronic inflammatory demyelinating polyneuropathy	2932	G61.8	8C01.3	C0393819	D020277	6102	10057645
14	Clear cell sarcoma of kidney	457246	C64	XH0765	C0334488			10009253
15	Cold agglutinin disease	56425	D59.1	3A20.1	C0175816	D000744	6130	ı
16	Congenital biliary atresia	498345	Q44.2	LB20.21	C5680082	D001656		ı
		30391						
17	Congenital factor VII deficiency	327	D68.2	3B14.7	C0015503	D005168	2238	10016079
18	Cryopyrin associated periodic syndrome/ NLRP3-associated	208650		4A60.1	C2316212	D056587	10927	10068850
	systemic autoinflammatory disease							
19	Cutaneous neuroendocrine carcinoma (Merkel cell carcinoma)	79140	C44.3	2C34	C0007129	D015266	9266	·
			C44.6	XH8IN8				
			C44.7					
20	Cutaneous T-cell lymphomas	178551	C84.8	XH1951	C5680497	D016410	ı	ı
			C86.3	2B0Y				
			C86.6	2B0Z				
				2B03.0				
				XH84A5				
				XH5SC3				
				XH7S84				
				XH2513				
21	Cystinosis	213	E72.0	5C60.1	C4316899	D003554	6236	10011777
22	Dermatofibrosarcoma protuberans	31112	C49.9	2B53.Y	C0392784	D018223	9569	10057070
				XH4QZ8				
				XH5CT4 VH0V02				
23	Eosinophilic gastroenteritis	2070	K52.8	DA94.21	C1262481	C535952		10017902

Intractable & Rare Diseases Research. 2024; 13(4):213-226.

Tab	ole 1. Identifiers of 86 rare diseases in <i>China's Second L</i>	ist of Rare Diseases en	coded by seven dif	ferent reference data	ibases (continued)			
#	Rare disease	ORPHA	ICD-10	ICD-11	NMLS	MeSH	GARD	MedDRA
24	Epithelioid sarcoma	293202	C49.9	2B5F.2 XH4F96 XH92Y0 XH4BT2 XH13Z6	C0205944	D012509	10181	10015099
25 26	Facioscapulohumeral muscular dystrophy Familial hemophagocytic lymphohistiocytosis	269 540	G71.0 D76.1	8C70.3 4A01.23	C0238288 C0272199	D020391 -	9941 6589	10064087 10070904
27	Familial adenomatous polyposis Eibroducelosio ossificone morenessivo	733 337	D12.6 M61-1	2B90.Y FB31.1	C0032580 C0016037	D011125	6408 6445	10056981
29	r rorocyptasia ossiricans progressiva Fragile X syndrome	806 806	Q99.2	LD55	C0016667	D005600	6464	10017324
30	Gangliosidosis	309144	E75.0	00.90.00	C001/083	D005/33	01621	·
31	Gastroenteropancreatic neuroendocrine neoplasm	100092				ı	2437	·
75	Gastrointestinal stromal tumor	44890	C20.3	2B5B 2B5B.0 2B5B.1 2B5B.Y 2B5B.Z 2E87 XH9H01 XH9H01	C0238198	2C10400	8600	9901 0001
33	Generalized pustular psoriasis	247353	L40.1	EA90.40	C0343055	ı	12819	
34	Genetic hypoparathyroidism	208593			C5680825	ı		
35	Giant cell arteritis Giant cell tumor of home	397 363976	M31.6 D48.0	4A44.2 2F7R	C0039483 C0206638	D013700 D018212	9615 -	10018250 -
2				2F9B XH0492 XH4TC2				
37	Glanzmann thrombasthenia Gliobhaetoma	849 360	D69.1	3B62.0Y 2 A 00 00	C0040015	D013915	2478 2401	- 10018236
0	CIDDIASOILLA			ZAV02.00 XH17J4 XH17J4 XH2BA5 XH49K9 XH4FN3 XH4FN3 XH4FN3 XH4FN3 XH4FN3 XH4FN3 XH4FN3 XH4FN3 XH4FN3 XH4FN3 ZH0200	000170170		1647	
39	Gorlin syndrome	377	C44.9	LD2D.4	C0004779	D001478	7166	10062804
40 41	Hidradenitis suppurativa Hutchinson-Gilford progeria syndrome	- 740	L73.2 E34.8	ED92.0 LD2B	C0162836 C0033300	D017497 D011371	- 7467	- 10036794

216

www.irdrjournal.com

Tal	ble 1. Identifiers of 86 rare diseases in <i>China's Second List of</i>	f Rare Diseases end	oded by seven diff	erent reference data	abases (continued)			
#	Rare disease	ORPHA	ICD-10	ICD-11	NMLS	MeSH	GARD	MedDRA
42	Inflammatory myofibroblastic tumor	178342	D48.7	2E92.1 2F30.Y XH66Z0	C0334121		7146	10067917
43	Leber congenital amaurosis	65	H35.5	9B70	C0339527	D057130	634	10070667
44	Lennox-Gastaut syndrome	2382	G40.4	8A62.1	C0238111	D065768	9912	10048816
45	Limbal stem cell deficiency	171673	H18.7	ı	C1561989	D000092423		10072138
46	Malignant hyperthermia	423	T88.3	8C78	C0024591	D008305	·	·
		46650		NE86	C2930828			
47	Malignant pleural mesothelioma	50251	C45.0	2C26.0	C1377913	D000086002	7026	10059518
48	Melanoma	617910	C43.001	XH4846	C0206651	D008545	8621	10061252
		252031	C43.101	XH25M1	C0220633		120161	10066384
		404560	C43.151	2C00.1	C0346360			
		618	C43.201	2C22.3	C1512419			
		293822	C43.251	2C30	C2314896			
		168999	C43.301	2C30.0	C4749348			
		97338	C43.302	2C30.1	C4749577			
		252050	C43.351	2C30.2	C5191057			
		39044	C43.352	2C30.3				
			C43.401	2C30.Y				
			C43.402	2C30.Z				
			C43.501	2C70.1				
			C43.551	2C71.1				
			C43.552	2C81.1				
			C43.553	2D00.0				
			C43.601	2D01.0				
			C43.602	2E63				
			C43.651	2E63.0				
			C43.701	2E63.0Z				
			C43.751	2E63.1				
			C43.752	2E63.Y				
			C43.851	2E63.Z				
			C43.901	9B71.40				
			C43.902					
49	Metachromatic leukodystrophy	512	E75.2	5C56.02	C0023522	D007966	3230	10067609
50	Monogenic non-syndromic obesity-Genetic non-syndromic obesity	98267	E66.8	5B81.Y	C5680229	ı	·	ı

Note: "- "indicates no records are available.

217

www.irdrjournal.com

Tat	ole 1. Identifiers of 86 rare diseases in <i>China's Secon</i> .	d List of Rare Diseases en	ncoded by seven diff	erent reference dat	abases (continued)			
#	Rare disease	ORPHA	ICD-10	ICD-11	NMLS	MeSH	GARD	MedDRA
51 52	Multiple endocrine neoplasia Narcolepsy	276161 619284	D44.8 -	2F7A.Y 7A20 7A20.0 7A20.1 7A20.1	C0027662 C0027404	D009377 D009290		10061299 10028713
53	Neuroblastoma	635	C74.9	VV01 2A00.11	C0027819	D009447	7185	10029260
54 55	Neurofibromatosis Neuronal ceroid linofuscinosis	634518 216	Q85.001 E75.4	XH8520 LD2D.1 5C56.1	C5816781 C0027877	D017253 D009472	- 10739	- 1 00 7 46 0 7
56	Neurotrophic keratitis Oerocorroma	137596	H16.2	1F00.10 2B50	C0339296 C0029463	- - D012516	-	10069732
ò		0000		2B50.0 2B50.0 2B50.1			107	1/71/001
				2B50.2 2B50 V				
				2B50.7				
				6M90HX				
				XH0 Y 34 XH1 S32				
				XH1XF3				
				XH1Y90 XH23T4				
				XH29N8				
				XH2CD6				
				XH3T03 VH40A0				
				АП40А9 ХН4ЕZ4				
				XH5CL5				
				XH5FH4				
				XH6LT5				
				XH6TL0				
				XH7N84				
				XH7XB9				
				XH8HG5 VH8H72				
				XH8X47 XH8X47				
				XH9119				
				XH9344 XH9LS2				

Tab	ole 1. Identifiers of 86 rare diseases in <i>China's Second 1</i>	List of Rare Diseases en	coded by seven diff	erent reference data	bases (continued)			
#	Rare disease	ORPHA	ICD-10	ICD-11	NMLS	MeSH	GARD	MedDRA
58	Pemphigus	704	L10.0	EB40.0	C0030809	D010392	6559	10052802
		2841 16495	L10.1	EB40.0Y ED40.1	C0085106		1354	10057056
		63455	L10.2	EB40.1	C0263313		<i>(())</i>	10057069
		79479	L10.4	EB40.1	C0263314			10058917
		79480	L10.8	EB40.2	C0263316			
		79481	L10.8	EB40.Y	C1112570			
		208524	L10.8	EC20.2	C1274167			
		555905	Q82.8		C4749730			
		636955			C5681323			
59	Persistent pulmonary hypertension of the newborn	·	P29.3	KB42	C0031190	D010547	ı	ı
60	Pheochromocytoma	ı	C74.101	5A75	C0031511	D010673	ı	·
			D35.051	XH3854	C0334419			
				XH9K97	C1302282			
				2D11.1				
61	PIK3CA related overgrowth syndrome	530313	Q04.5	EF02.1	C0431391	C536142	6950	10081236
			Q74.0	LA05.1	C1865285	C567763	10939	
			Q74.2	LB97.1	C2751313	C567863	2637	
			Q87.3	LD2C	C2752042	D065705		
				LD2F.1Y	C4749904			
				Q74.0	C5192432			
					C5679987			
					C5679988			
62	Polycythaemia vera	977	D45	2A204	C0032463	D011087	7422	10036057
63	Primary biliary cholangitis	186	K74.3	DB96.1	C0008312	D008105	7459	10080429
)			DB96.10				
				DB96.1Y				
				DB96.1Z				
64	Primary ciliary dyskinesia	244	Q34.8	LA75.Y	C4551720	D002925	4484	10069713
65	Primary IGF1 deficiency	73272	E34.3	5A61.0	C1837475	C563867	10627	ı
99	Primary immunodeficiency	101997		L1-4A0	C0398686	D000081207	,	10064859
67	Primary myelofibrosis	824	D47.4	2A20.2	C0001815	D055728	8618	10077161
				XH7GG7				
68	Primary sclerosing cholangitis	171	K83.0	DB96.20 DR96.2V	C0566602	D015209	1280	10036732
				DB96.2Z				

Intractable & Rare Diseases Research. 2024; 13(4):213-226.

219

ם מי	UC I. IUCILIIICIS UI UU LAIC UISCASUS III VIIIII S DEVVIN ZUSI UJ A		חחבת הל שבירוו תווור	Lelle feice und	Dases (commucu)			
#	Rare disease	ORPHA	ICD-10	ICD-11	NMLS	MeSH	GARD	MedDRA
69	Progressive fibrosing interstitial lung disease	182095	J84.9 J84.1	CB03.6 CB04.Y CB04.Z CB05.1 CB05.1 CB05.2 CB05.3 CB05.4 CB05.4 CB05.7	C0206062	D017563	1	10022611
70 71 72 73	Recurrent pericarditis Retinopathy of prematurity Rett syndrome Short bowel syndrome	251307 90050 778 104008	109.2 H35.1 F84.2 -	CB05.Z - 9B71.3 LD90.4 DA96.04	C4707790 C0035344 C0035372 C0036992	- D012178 D015518 D012778	- 5695 5696 1502	- 10038933 10039000 10049416
75 75	Systemic juvenile idiopathic arthritis Systemic mastocytosis	85414 2467	M08.2 C96.2	FA24.4 FA21.0 2A21.0 2A21.0 2A21.0 ZA21.0 ZA21.0Z XH10N1 XH10N1 XH2Y59 XH2Y59	C0087031 C0221013	- D034721	10966 8616	1 0042061 1 0042949
76 77 78	Takayasu arteritis Tenosynovial giant cell tumor/Pigmented villonodular synovitis Thalassemia major	3287 66627 66627 163596 231214 231214 231401 231401	M31.4 M12.2 D46.7 D56.0 D56.1	4444.1 XH6911 XH6911 XH52J9 XH5AQ9 3A50.03 3A50.03 3A50.1 3A50.1 3A50.1	C0039263 C1318543 C5680928 C0002875 C0022875 C02585216	D013625 D000070779 D017086	7730 7396 5864	10043097 - -
79 80 81 82 83 83	Thrombotic thrombocytopenic purpura Transthyretin amyloidosis Tumor necrosis factor receptor associated periodic syndrome Tumor-induced osteomalacia Von Hippel-Lindau syndrome Von Willebrand disease type3	847 54057 271861 32960 352540 892 166096	M31.1 - E85.0 M83.8 Q85.8 D68.0	D56.0 3B64.14 5D00.20 BC43.20 4A60.2 5A75 3B12	C0795917 C1845055 C0034155 C5679761 C1275126 C1274103 C0019562 C1264041	D011697 C567782 - C537751 D006623 D056729	- - 8457 9652 7855	10043648 - - 10047716

220

	fedDR∕	04780	0021750	system in Orphanet database	number	Percentage (%)
	2	=	1		number	Tereentage (70)
				genetic diseases	45	52.35
				neoplastic diseases	28	32.56
	Ð	10	5	transplant-related disorders	28	32.56
	ìΑR	787	788	neurological diseases	24	27.91
	10			renal diseases	13	15.12
				developmental anomalies during embryogenesis	12	13.95
		58	36	hematological diseases	12	13.95
	[eS]	082	130	endocrine diseases	12	13.95
	Z	D0	D0	ophthalmic disorders	12	13.95
				systemic and rheumatological diseases	12	13.95
				bolic diseases	7	8.14 8.14
(pa				systemic or rheumatologic diseases of	7	8 14
nu	0	.19	69	childhood	,	0.11
nti	Ţ	244	377	hepatic diseases	5	5.81
c 0	5	00	000	circulatory system diseases	5	5.81
es (0	inborn errors of metabolism	5	5.81
Jas				gastroenterological diseases	5	5.81
tal				immunological diseases	4	4.65
da				infertility disorders	3	3.45
nce		2 + 5	<i>y</i>	abdominal surgical diseases	2	2.33
ere	-1-	GV 85.4	2.2	cardiac mailormations	1	1.16
ıt ref	P	XH 2/2	48			
viseases encoded by seven	A ICD-1	C88.(G40.	immunodeficiency owing to a del (ORPHA 101988). The former gr T- and B-cell immunodeficience immune dysregulation disease w (ORPHA 169361), immunodefi affecting antibody production ()	ect in in oup inclu cy (ORP vith imm ciency p	nate immunity ides combined PHA 101972), unodeficiency predominantly 101977) and
of Rare Dise	ORPH/	33226	3451	combined immunodeficiency (C latter group includes autoinfl with immune deficiency (ORP	ORPHA ammato HA 290	331217). The ry syndrome 839), genetic
Second List		lasmacytic		(ORPHA 183710), immunod a complement cascade protei 101992), other immunodeficienc	to partic deficien n anom y syndro	ular pathogens icy owing to aly (ORPHA omes owing to
in <i>China's</i>		/ Lymphof	ome	defects in innate immunity (ORI immunodeficiency with predisp infection (ORPHA 431156), a	PHA 331 osition t and quan	193), primary o severe viral ntitative and/
diseases	re disease	ulinemia.	sms syndro	or qualitative congenital phage 101985). Genetic rare diseases in	the sec	tect (ORPHA cond list are
ure	Rai	lob	spa:	summarized in Supplementa	l Table	S4 (https://
5 r8		80 0	tile	www.irdriournal.com/action/g	etSupple	ementalData.
ers of 80		öm macı	me/Infant	php?ID=223). Inheritance, phen genes are included in the table a	otype, a as data c	nd pathogenic collected from
tifi		stri	Idro	the OMIM database. Some rar	e diseas	es are caused
1. Iden		Walden: ymphorr	West syn	by mutation of single genes a by mutation in multiple genes.	nd othe A total c	rs are caused of 53 different
Table	#	85	86	phenotypes with 49 pathogenic g	genes ex autosoi	ist in primary nal recessive

(AR), autosomal dominant (AD) or X-linked recessive inheritance format. Bardet-Biedl syndrome (BBS) is inherited mainly in the form of AR with 22 different phenotypes and 24 genes. Phenotype BBS1 corresponds to three different pathogenic genes CCDC28B, ARL6, and BBS1, with AD or AR inheritance patterns. The phenotype BBS14 corresponds to the TMEM67 and CEP290 genes inherited in AR form. The ARL6 gene corresponds to phenotypes of both BBS1 and BBS3. There are 20 different genes and a corresponding 18 phenotypes in Leber congenital amaurosis. For neuronal ceroid lipofuscinosis, a total of 12 genes corresponds to 14 different subtypes and phenotypes. For Alagille syndrome, three subtypes are classified according to different pathogenic genes with microdeletion in 20p12, JAG1, and NOTCH2. In summary, genotypic and phenotypic heterozygosity exist among these rare diseases.

3.4. Epidemiology of diseases in China's Second List of Rare Diseases

According to data from Orphanet, the epidemiology of the 86 rare diseases is described in Table 3. Data on the newborn incidence, incidence, and prevalence of 71 rare diseases (82.56%) in China's Second List of Rare Diseases are available, including data on the newborn incidence of 7 (8.14%), incidence of 20 rare diseases (23.26%) and the prevalence of 64 (74.42%) rare diseases. As we mentioned above (also see Supplementarry Table S3 (https://www.irdrjournal.com/ action/getSupplementalData.php?ID=222), some rare disorders are groups composed of different disoders with some correlations, hence, only disorders in the group with epidemiological data were collected. Newborn incidence of 0.6/100,000 in the pediatric population and incidence of 1.6-23/100,000 per year in children were reported in systemic juvenile idiopathic arthritis. The birth incidence of familial adenomatous polyposis was as high as 12.05/100,000. In all, an annual incidence of 20 rare diseases available in Orphanet, a relatively broad newborn incidence was observed in malignant hyperthermia of anesthesia, systemic juvenile idiopathic arthritis, primary biliary cholangitis, polycythaemia vera, Lennox-Gastaut syndrome and cutaneous neuroendocrine carcinoma (Merkel cell carcinoma). The annual incidence of betathalassemia major is estimated at 1/100,000 worldwide and 1/10,000 in the European population.

A total of 23 rare diseases or its subtypes showed a prevalence of higher than 1/10,000 including alpha-1-antitrypsin deficiency, ANCA-associated vasculitis, dermatofibrosarcoma protuberans, Fragile X syndrome, neuroendocrine tumor of pancreas, gastrointestinal stromal tumor, giant cell arteritis, Lennox-Gastaut syndrome, Limbal stem cell deficiency, narcolepsy type 1, neuroblastoma, neurotrophic keratitis, pemphigus vulgaris, polycythaemia vera, primary biliary cholangitis, retinopathy of prematurity, gastroschisis, systemic mastocytosis, tenosynovial giant cell tumor (pigmented villonodular synovitis), Hb Bart's hydrops fetalis and thrombotic thrombocytopenic purpura. For thrombotic thrombocytopenic purpura (TTP), the prevalence of iTTP was 14.29/100,000, which is higher than that of the cTTP type. Thirty-five different rare diseases had a prevalence of less than 10/100,000 and greater than or equal to 1/100,000, these included acromegaly, adult-onset Still disease, Bardet-Biedl syndrome, Behçet's disease, CDKL5-deficiency disorder, choroideremia, chronic inflammatory demyelinating polyneuropathy, biliary atresia, cutaneous neuroendocrine carcinoma, cystinosis, eosinophilic gastroenteritis, facioscapulohumeral muscular dystrophy, familial adenomatous polyposis, glioblastoma, Gorlin syndrome, Leber congenital amaurosis, malignant pleural mesothelioma, multiple endocrine neoplasia, and so on. Epithelioid sarcoma, Hutchinson-Gilford progeria syndrome, primary IGF1 deficiency, fibrodysplasia ossificans progressiva, hypoplastic pancreas-intestinal atresia-hypoplastic gallbladder syndrome, cold agglutinin disease, congenital factor VII deficiency and another 13 rare diseases had relatively low prevalence at less than 1/100,000.

4. Discussion

The study nominated the 86 diseases in China's Second List of Rare Diseases using different reference systems. The results showed that most rare diseases have unique identifiers, especially in the Orphanet database. Orphanet nomenclature is a powerful classification tool based on the multidimensional nature of rare diseases, which provides a specific terminology for rare diseases. Each clinical entity is assigned a unique and time-stable ORPHAcode. This includes all disorders, subtypes of disorders, and groups of disorders. Over 6000 rare diseases are coded using ORPHAcodes (11). ORPHAcodes have high sensitivity and accuracy in describing rare diseases. More than half of ORPHAcodes identify diseases with very low prevalence (less than 1 case per million) (12). The International Classification of Diseases is a medical classification list produced by the World Health Organization that is predominantly used in health care systems worldwide. However, less rare diseases are listed in versions older than ICD-10. One ICD code can correspond to different rare entities or to both rare and non-rare entities. This is often not clearly distinguished in health information systems (13,14). ICD-11 was adopted by the World Health Assembly in May 2019 and came into effect in January 2022. This version includes nearly 5,500 rare diseases and each has a unique identifier. Rare diseases in ICD-11 are easily available in health information systems and are continually updated (5, 14). It has a unique identifier for different subtypes of one disease and different conditions

#	Rare diseases	Newborn Incidence / 100,000 persons	Incidence / 100,000 persons	Prevalence / 100,000 persons
1	Achondroplasia	4	-	-
2	Acquired hemophilia A	-	-	-
	Acquired hemophilia B	-	-	-
	hemophilia C	-	-	0.1-0.9
3	Acromegaly	-	0.19-1.1 (annual)	1-9
4	Adult-onset Still disease	-	-	1-9
5	Alagille syndrome	-	-	1.43
6	Alpha-1-antitrypsin deficiency		-	10-50
/	ANCA-associated vascullus	-	-	10-50
	Eosinophilic granulomatosis with polyangilits	-	-	1-9
	Microscopic polyangiitis	-	0.21-1.19	1-9
8	Bardet-Biedl syndrome	_	-	1 (USA)
0	Dahaet's disassa			1.69 (Denmark) 1.52-2.22 (France)
10	Blue rubber bleb payas	-	-	1-9
11	CDKL5-deficiency disorder	-	-	2.36 (UK (Scotland) birth prevalence
12	Choroideremia	-	-	1-9
13	Chronic inflammatory demyelinating polyneuropathy	-	-	1-9
14	Clear cell sarcoma of kidney	-	-	-
15	Cold agglutinin disease	-	-	0.1-0.9
16	biliary atresia		-	-
	Isolated biliary atresia		-	1-9
	Biliary atresia with splenic malformation syndrome	-	-	-
	Hypoplastic pancreas-intestinal atresia-hypoplastic gallbladder syndrome	-	-	< 0.1
17	Congenital factor VII deficiency	-	-	0.1-0.9
18	Cryopyrin associated periodic syndrome- NLRP3-associated	-	-	0.28 (France)
	systemic autoinflammatory disease CINCA syndrome	-	-	0.28 (the whole
	Familial cold urticaria	_	_	spectrum of CAI S)
	Muckle-Wells syndrome	_	_	0.28 (France)
19	Cutaneous neuroendocrine carcinoma (Merkel cell carcinoma)	-	0.2-0.4 (annual, white population)	1-9
20	Cutaneous T-cell lymphomas	-	-	-
	Mycosis fungoides and variants		0.29-0.91	-
	Primary cutaneous CD30+ 1-cell lymphoproliferative disease	-	-	-
21	Adult I-cell leukemia-lymphoma	-	-	1-9
21	Cystinosis		-	1-9
22	Essinophilia astroantaritia	-	0.5	10-30
23	Eosmophine gastroententis	-	-	-
24	Epithenoid salconia Facioscapulohumeral muscular dystrophy	-	-	1_9
26	Familial hemonhagocytic lymphohistiocytosis	_	_	-
27	Familial adenomatous polyposis	12.05	-	1-9
28	Fibrodysplasia ossificans progressiva	-	-	< 0.1
29	Fragile X syndrome	-	-	10-50
30	Gangliosidosis	-	-	-
	GM1 gangliosidosis GM1 gangliosidosis type 1	-	-	0.5-1 (live births) 0.5-1(live births)
	GM1 gangliosidosis type 2	-	-	< 0.1
	GM1 gangliosidosis type 3	-	-	< 0.1
	GM2 gangliosidosis	-	-	1-9
	GM2 gangliosidosis, AB variant	-	-	< 0.1
	Sandhoff disease	-	-	0.1-0.9
	Tay-Sachs disease	-	-	-
31	Gastroenteropancreatic neuroendocrine neoplasm	-	-	-
	Neuroendocrine tumor of stomach	-	-	1-9
	Neuroendocrine carcinoma of pancreas	-	-	-
22	Incurrent contractional atramal tumor	-	-	10-50
.14	VIASI VIIIUSIIIIAI SIIVIIIAI LUIIIVI	-	-	10-20

Table 3. Incidence and prevalence of 86 rare diseases in China's Second List of Rare Diseases recorded in Orphanet database

_

_

33

Generalized pustular psoriasis

0.1-0.9

4 Caratic hypeparadhypoidsan Autoinnear polyrabscripparadhypoidsan - - 0.1.0.9 5 Giant cell artertis - 0.1.0.9 53 Giant cell artertis - 0.1.0.9 54 Giant cell artertis - 0.1.0.9 55 Giant cell artertis - - 76 Giant cell artertis - - 76 Giant cell artertis - - 76 Giant cell artertis - - 77 Giant cell artertis - - - 78 Giant cell artertis - - - 79 Gorin syndrone - - - - 70 Infammats synratic tamor - - - - 70 Infammats synratic tamor - - - - 71 Infammats synratic tamor - - - - 71 Infammats synratic tamor - - - - <	#	Rare diseases	Newborn Incidence / 100,000 persons	Incidence / 100,000 persons	Prevalence / 100,000 persons
Autoimmic polymethy roution - - 0.10 Parallal isolated hypoparathy roution - - 0.10 Securably poparathy roution - - 0.10 Securably poparathy roution - - 0.10 Securably poparathy roution - - - Securation - - - - Securation - - - - - Securation - - - - - - Securation - - - - - - - Securation - - - - - - - Securation - - - - - - - Securation <td>34</td> <td>Genetic hypoparathyroidism</td> <td>-</td> <td>-</td> <td>-</td>	34	Genetic hypoparathyroidism	-	-	-
Familal isolated hypoparathyroidism - - 0.10.9 Sesadiolypoparathyroidism - 0.10.9 Sesadiolypoparathyroidism - 0.58 Giant cell attoritis - 0.50 Giant cell attoritis - - Giant cell tamor of bone - - Gia		Autoimmune polyendocrinopathy type 1	-	-	0.1-0.9
Pseudokyoparathyroidism -		Familial isolated hypoparathyroidism	-	-	< 0.1
55 Giant cell nuror of bone - 5.88.20 (mmank) [0-50 6 Giant cell nuror of bone - - - 7 Glamzman thrombashenia - - - 9 Gorin syndrome - - - - 9 Gorin syndrome - - - - - 11 Hutchinson-Gilford progens syndrome -		Pseudohypoparathyroidism	-	-	0.1-0.9
addite over 50 years 36 Giant cell tumor of bone - - - 37 Glazzmann thrombusthenia - - - 38 Globhastoma 3 1-9 39 Gorfin syndrome - - 1-9 40 Hidrihonson-Gliftod progenis syndrome - - - 41 Hutchinson-Gliftod progenis syndrome - 1-9 42 Infihamatory myoffroblastic tumor - 1-9 43 Leber congenital annauxosis - 1-9 44 Lennox-Gastaut syndrome - 01-028 10-50 45 Limbal stem cell deficiency - - - 46 Malignant plevart mesotheliona - - - 47 Malignant plevart mesotheliona - - - - 48 Melanoma - - - - - 44 Malignant plevart mesotheliona - - - -	35	Giant cell arteritis	-	5.88-20 (annual,	10-50
6 Giant cell tumor of bone - - 71 Gianzanam furombasthenia - - - 73 Gianzanam furombasthenia - - - - 74 Gianzanam furombasthenia - - - - - 74 Hidradenia sepportavia - - - - - 75 Heinanactosia sequencia - - - - - 74 Lenox-Castaut syndrome - 0.1-0.28 10-50 74 Lenox-Castaut syndrome - 0.1-0.28 10-50 74 Maligiant hyperthermia - - - 74 Maligiant plearul mesolelisma - - - 74 Maligiant melanoma of the mucosa - - - 75 Maligiant cleanoma of the mucosa - 1.9 - 76 Maligiant cleanoma of the mucosa - 2.86 (MEN2) 76 Maliginant melanoma - - <td></td> <td></td> <td></td> <td>adults over 50 years</td> <td></td>				adults over 50 years	
10 Guard cell tumor of bone - - - - 30 Gioblastoran - 3 1-9 31 Gioblastoran - 3 1-9 32 Gioblastoran - 3 1-9 34 Hidrahomits supportativa - - - 34 Hidrahomits supportativa - - - 34 Licher consciential annazory myofthroblastic tumor - 1-9 - 34 Licher consciential annazory - 1-9 - 1-9 34 Lindhu stern cell deficiency - - 1-9 - 34 Maligrant hyperthermia of anesthesia - - - - 36 Muliginant plearit mesothelioma - - - - - 36 Muliginant melanoma - - - - - 37 Muliginant melanoma - - - - - - - <td< td=""><td>26</td><td></td><td></td><td>old)</td><td></td></td<>	26			old)	
31 Outzonant nucleosaterina - <td>36</td> <td>Giant cell tumor of bone</td> <td>-</td> <td>-</td> <td>-</td>	36	Giant cell tumor of bone	-	-	-
30 Corlin syndrome - - - 1-9 40 Hidrachanik supurativa - - - - 41 Hutchinson-Gillord progeria syndrome - - - - 42 Inflammatory myoffbroblastic tunor - - - - 43 Leber congenital manaros - 1-9 - - 44 Lemox-Gastaut syndrome - 0.1-0.28 10-50 45 Limbal stem cell deficiency - - - 46 Malignant hyperthermia - - - 47 Malignant pleural mesobalioma - - - - 48 Melanoma - - - - - 49 Masignant melanoma - - - - - 50 Moneopenic non-syndromic obesity-Genetic non-sy	3/ 20	Glanzmann Inrombasinenia	-	-	-
9111119Hiddachins septensiva1Hukrhinson-Gilford progeria syndhome	30	Griobiastollia	-	5	1-9
1 Industrials appointent -	40	Hidradenitis suppurativa	-	-	1-9
1Inflammatory myoffloodiastic tumor113Leber congenital manarosis43Leber congenital manarosis-1.944Lemox-Castaut syndrome-0.10.2845Limbol stem cell deficiency46Malignant hyperthermia of anesthesia-4534247Malignant hyperthermia of anesthesia-4534248Malignant nelanoma49Malignant melanoma of the mucosa40Malenoma of the mucosa40Metachromatic leakodystrophy50Monogenic non-syndromic51Multiple endocrine neoplasia52Narcolepsy type 153Narcolepsy type 254Neurobhorantosis55Neurobhorantosis56Neurobhorantosis57Neurobhorantosis58Neurobhorantosis59Neurobhorantosis50Neurobhorantosis50Neurobhorantosis50Neurobhorantosis50Neurobhorantosis50Neurobhorantosis51Neurobhorantosis52Neurobhorantosis53<	41	Hutchinson-Gilford progeria syndrome		_	< 0.1
43 Leber congenital manurosis - 1-9 44 Lemox-foctatat syndrome - 0.1-0.28 10-50 45 Limbal stem cell deficiency - - - 46 Malignam hyperthermia of anesthesia - - - 47 Malignam tiperul mesothetioma - - - 47 Malignam tiperul mesothetioma - - - Conjunctival malignant melanoma - - - - Uveal melanoma - - - - - 90 Metachromatic teakodystrophy - - - - - 91 Matrix for syndromic obssity-Genetic non-syndromic - - - - 92 Narcolepsy type 1 - - 10-50 Narcolepsy type 2 - - - 93 Neurofibromatosis - 1-3 19 Full NP2-related schwannomatosis - 1-9 94 Hardifformatosis - <td< td=""><td>42</td><td>Inflammatory myofibroblastic tumor</td><td>-</td><td>-</td><td>-</td></td<>	42	Inflammatory myofibroblastic tumor	-	-	-
44 Lemmost.Castant syndrome - 0.1-0.28 10-50 45 Limble strem cell deficiency - - 10-50 46 Malignant hyperthermia of anesthesia - 45.342 - 47 Malignant plearul mesolhesia - - - 48 Melanoma - - - Conjunctival malignant melanoma - - - - 10 Walignant melanoma - - - - 10 Malignant melanoma - - - - 10 Melanomatic encosyndromic obesity-Genetic non-syndromic - - - 20 Marcolepsy type 1 - - - - 21 Matrolepsy type 1 - - - - - 21 Narcolepsy type 1 - - - - - 22 Narcolepsy type 1 - - - - - 23 Narcolepsy type 1	43	Leber congenital amaurosis		-	1-9
45 Limbal stem cell deficiency - 10-50 46 Malignant hyperthermia of anesthesia - - 47 Malignant hyperthermia of anesthesia - - 48 Melanoma - - 49 Melanoma - - Conjunctival malignant melanoma - - - Conjunctival malignant melanoma - - - Vival melanoma - - - - 9 Metaformatic leukodystrophy - - - - 50 Monogenic non-syndromic obesity-Genetic non-syndromic - - 2.86 (MEN2) 51 Multiple endocrine neoplasia - - 2.86 (MEN2) 52 Narcolepsy type 1 - - - 53 Neuroblistoma - 1.43 (amuul, 15 10-50 54 Neuroblistoma - - - - 55 Neuroblistomatosis - - - - 55 Neuroblistomatosis - - - - - <td>44</td> <td>Lennox-Gastaut syndrome</td> <td>-</td> <td>0.1-0.28</td> <td>10-50</td>	44	Lennox-Gastaut syndrome	-	0.1-0.28	10-50
46 Malignant hyperthermia - - Malignant hyperthermia of anesthesia - 45342 - 47 Malignant pleural mesothelioma - - - 48 Melanoma - - - Conjunctival malignant melanoma - - - - Conjunctival malignant melanoma - - - - Veal melanoma - - - - - 9 Metachromatic leukodystrophy - - - - - 90 Monogenic non-syndromic obesity-Genetic non-syndromic - - 3.33-10 (MENI) 51 Matrolepsy type 1 - - - - 52 Narcolepsy type 2 - - - - 53 Neurofhromatosis - 1.43 (annual, 15 10-50 54 Neurofhromatosis type 1 - - - - 55 Neurofhromatosis type 1 - - - - 56 Neurofhromatosis type 1 - - - <td>45</td> <td>Limbal stem cell deficiency</td> <td>-</td> <td>-</td> <td>10-50</td>	45	Limbal stem cell deficiency	-	-	10-50
Malignant hyperthermin of anesthesia-4542-Malignant pleard meschelionaRolanomaConjunctival malignant melanomaMalignant melanomaMultiple and of the mucosa19Metachomatic leukodystrophy20Metachomatic leukodystrophy21Matoperic non-syndromic obesity-Genetic non-syndromic25Marcolepsy26Narcolepsy type 130Neuroblastoma-1.43 (mnuul, 1510-5031Neuroblastoma32Neurobloromatosis33Neurobloromatosis1.9-34Neurobloromatosis1.9-35Neurobloromatosis1.9-36Neurobloromatosis537Neurobloromatosis538Neurobloromatosis539ATP13A2-related jurnine neuronal ceroid lipofuscinosis530Neurotrophic keratikis30Neurotrophic keratikis30	46	Malignant hyperthermia	-	-	-
47 Malignant plearn laceordiciona - - 48 Melanoma - - Conjunctival malignant melanoma - - - Malignant melanoma of the mucosa - - - Uval melanoma - - 0.10.9 Monogenic non-syndromic obesity-Genetic non-syndromic - 0.10.9 Multiple endocrine neoplasia - - - 21 Matrolepsy type 1 - - - Narcolepsy type 2 - - - - Narcolepsy type 1 - - - - Narcolepsy type 2 - - - - Narcolepsy type 1 - - - - Narcolepsy type 2 - - - - Narcolepsy type 1 - - 10-50 Veurofibromatosis - - 10-50 - Full NP2-related schwanomatosis - - - - 55 Neurofibromatosis type 1 - - - -		Malignant hyperthermia of anesthesia	-	45342	-
48 Melanoma - - - Conjunctival malignant melanoma - - - - Mulignant melanoma of the mucosa - - 1-9 Vucat melanoma - - 1-9 49 Metachromatic feukodystrophy - - 0.10.9 50 Monogenic non-syndromic obesity-Genetic non-syndromic - - - 51 Multiple endoerine neoplasia - - 3.33-10 (MEN1) 52 Narcolepsy type 1 - - - - 53 Neuroblastoma - 1.43 (annula, 15 10-50 Narcolepsy type 2 - - - - 54 Neurofibromatosis - - 1-9 7 Full NF2-related schwannomatosis - - 1-9 7 Natrolepsy type 1 - - - 55 Neuronal ceroid ipofuscinosis - - - 7 Full NF2-related schwannomatosis - - - 8 Naurofibromatosis type1 -	47	Malignant pleural mesothelioma	-	-	-
Conjunctival malignant melanoma< 0.1Malignant melanoma of the mucosaUveal melanoma1.49Metachromatic leukodystrophy0.14.0.95Monogenic non-syndromic obesity-Genetic non-syndromicobesity1Multiple endocrine neoplasia3.33-10 (MEN1)22Narcolepsy type 1Narcolepsy type 11.0-50-Narcolepsy type 1Narcolepsy type 11.0-50Narcolepsy type 153NeurofibromatosisFull NF2-related schwannomatosis54Neurofibromatosis type 155Neuronal ceroid lipofuscinosis5 (Finland)56Neuronal ceroid lipofuscinosis5 (Finland)57Neuronal ceroid lipofuscinosis5 (Finland)58Neuronal ceroid lipofuscinosis<	48	Melanoma	-	-	-
Malignant melanoma - - - Uceal medanoma - - 0.1-0.9 Monogenic non-syndromic obesity-Genetic non-syndromic obesity - - 0.1-0.9 Multiple endocrine neoplasia - - - - Narcolepsy - - - 2.86 (MEN2) Narcolepsy type 1 - - - - Narcolepsy type 2 - - - - Starcolepsy type 2 -		Conjunctival malignant melanoma	-	-	< 0.1
Uveal melanoma - - 1-9 Metachomanic leukodystrophy - - 0.1-0.9 Multiple endocrine neoplasia - - - 28 Marcolepsy - - - Narcolepsy type 1 - - - - 30 Neurolastoma - 1.43 (amuul, 15 10-50 Narcolepsy type 1 - - - - 31 Neurolastoma - 1.43 (amuul, 15 10-50 Valuenolastoma - 1.43 (amuul, 15 10-50 - Full NF2-related schwannomatosis - - - - Neurofibromatosis type 1 - 10-50 - - Neurofibromatosis type 1 - 10-50 - - Stand lipofuscinosis - - - - Neurofibromatosis type 1 - - - - Juvenile neuronal ceroid lipofuscinosis 5 (Finland) - - - 1		Malignant melanoma of the mucosa	-	-	-
49 Metachromatic leukodystrophy - - 0.10.9 5 Monogenic non-syndromic obesity-Genetic non-syndromic -		Uveal melanoma	-	-	1-9
50 Monogenic non-syndromic obesity-Genetic non-syndromic - - - 51 Multiple endocrine neoplasia - - 3.33-10 (MEN1) 52 Narcolepsy type 1 - - 0.650 Narcolepsy type 2 - - 0.50 53 Neuroblastoma - 1.43 (annual, 15 10-50 years old) - - - - 54 Neurofibromatosis - - - 7- Full NF2-related schwannomatosis - - - 7- Full NF2-related schwannomatosis - - - 7- Neurofibromatosis type 1 - - - 7- Neurofibromatosis - - 10-50 7- Neurofibromatosis type 1 - - - 7- Neurofibromatosis - - - 7- Neurotopic lipofuscinosis 5 (Finland) - - 7- Juvenile neuronal ceroid lipofuscinosis 2.22 (Sweden) 0.46 (Sweden) 6.99 (Germany) - -<	49	Metachromatic leukodystrophy	-	-	0.1-0.9
51 Multiple endocrine neoplasia - 3.33-10 (MEN1) 52 Narcolepsy type 1 - - 53 Neurolpsy type 2 - - 53 Neuroblastoma - 1.43 (annual, 15 10-50 54 Neurofibromatosis - - - 55 Neurofibromatosis - - - 56 Neurofibromatosis type 1 - - 1.9 57 Neuronfibromatosis type 1 - - 10-50 7 Full schwannomatosis - - 1.9 7 Full schwannomatosis - - 1.9 7 ATP13.2-related juvenile neuronal ceroid lipofuscinosis - - - 1 Jvenile neuronal ceroid lipofuscinosis 5 (Finland) - - 1 Jvenile neuronal ceroid lipofuscinosis - - 42.02 (Europe) 50 Neurotrphic keratitis - - 42.02 (Europe) 51 Infantile neuronal ceroid lipofuscinosis - - - 52 Neurotrphic keratitis	50	Monogenic non-syndromic obesity-Genetic non-syndromic obesity	-	-	-
52 Narcolepsy type 1 - - 10-50 Narcolepsy type 2 - - - 53 Neuroblastoma - 1.43 (annual, 15 10-50 years old) - - - - 54 Neurofibromatosis - - - - 54 Neurofibromatosis - - - - - 54 Neurofibromatosis type 1 - - - - - - 55 Neurofibromatosis type 1 - - 10-50 -	51	Multiple endocrine neoplasia	-	-	3.33-10 (MEN1) 2.86 (MEN2)
Narcolepsy type 1 - - 10-50 Narcolepsy type 2 - - - 53 Neurofibromatosis - 1.43 (annual, 15 10-50 years old) - - - - Full NF2-related schwannomatosis - - - - Full Schwannomatosis - - - - - Neurofibromatosis type 1 - - 10-50 - </td <td>52</td> <td>Narcolepsy</td> <td>-</td> <td>-</td> <td>-</td>	52	Narcolepsy	-	-	-
Narcolepsy type 253Neuroblastoma-1.43 (annual, 1510-50 $years old)$ years old)54NeurofibromatosisFull NF2-related schwannomatosisNeurofibromatosis type 110-5055Neuronal ceroid ipofuscinosisATP13A2-related juvenile neuronal ceroid lipofuscinosis1nfantli enuronal ceroid lipofuscinosis5 (Finland)Juvenile neuronal ceroid lipofuscinosis2.22 (Sweden)0.46 (Sweden)Juvenile neuronal ceroid lipofuscinosis-0.3 (annual)1-956Neurotrophic keratitis42.02 (Europe)57Osteosarcoma-0.3 (annual)1-958Pemphigus foliaceusPemphigus foliaceusPemphigus foliaceusPemphigus foliaceusPemphigus foliaceusPemphigus foliaceus10PHSCA related overgrowth syndrome10PLSCA related overgrowth syndrome11CLOVES syndrome<		Narcolepsy type 1	-	-	10-50
53 Neuroblastoma - 1.43 (annual, 15 10-50 54 Neurofibromatosis - - - Full NF2-related schwannomatosis - - 1-9 Full schwannomatosis - - 1-9 Neurofibromatosis type 1 - 10-50 55 Neuronal ceroid lipofuscinosis - - ATP13A2-related juvenile neuronal ceroid lipofuscinosis - - - Juvenile neuronal ceroid lipofuscinosis 5 (Finland) - - - Juvenile neuronal ceroid lipofuscinosis 5.222 (Sweden) 0.46 (Sweden) 6.99 (Germany) Late infantile neuronal ceroid lipofuscinosis - - 42.02 (Europe) 56 Neurotrophic keratitis - - 42.02 (Europe) 57 Ostcosarcoma - 0.3 (annual) 1.9 58 Pemphigus - - - 59 Persistent pulmonary hypertension of the newborn - - - 61 PIK3CA related overgrowth syndrome - - - - 62 Penophigus		Narcolepsy type 2	-	-	-
54 Neurofibromatosis - - - Full N2-related schwannomatosis - - 10-9 Full Schwannomatosis type 1 - - 10-50 55 Neurofibromatosis type 1 - 1-9 ATP13A2-related juvenile neuronal ceroid lipofuscinosis - - - Infantile neuronal ceroid lipofuscinosis - - - Juvenile neuronal ceroid lipofuscinosis 5 (Finland) - - Late infantile neuronal ceroid lipofuscinosis 2.22 (Sweden) 0.46 (Sweden) 6.99 (Germany) - - 4.202 (Europe) 57 Osteosarcoma - 0.3 (annual) 1-9 58 Penphigus - - - 59 Persistent pulmonary hypertension of the newborn - - - 61 PHK3CA related overgrowth syndrome - - - - 62 Penophigus foliaceus - - - - - 7 Pernsitent pulmonary hypertension of the newborn - - - - - - -	53	Neuroblastoma	-	1.43 (annual, 15 years old)	10-50
Full NE2-related schwannomatosis - - 1-9 Full schwannomatosis - - 10-50 Stemporal cervid lipofuscinosis - - 1-9 ATP13A2-related juvenile neuronal cervid lipofuscinosis - - - Infantile neuronal cervid lipofuscinosis - - - - Juvenile neuronal cervid lipofuscinosis 5 (Finland) - - - Juvenile neuronal cervid lipofuscinosis 2.22 (Sweden) 0.46 (Sweden) - 6.99 (Germany) - - 42.02 (Europe) 56 Neurotrophic keratitis - - 42.02 (Europe) 57 Osteosarcoma - 0.3 (annual) 1-9 58 Pemphigus - - - 59 Persistent pulmonary hypertension of the newborn - - - 59 Persistent pulmonary hypertension of the newborn - - - 61 PIK3CA related overgrowth syndrome - - - - 61 PIK3CA related overgrowth syndrome - <0.1	54	Neurofibromatosis	-	-	-
Full schwannomatosis - - - Neurofibromatosis type 1 - 10-50 55 Neuronal ceroid lipofuscinosis - 1-9 ATP13A2-related juvenile neuronal ceroid lipofuscinosis - - - Infantile neuronal ceroid lipofuscinosis 5 Finland) - - Juvenile neuronal ceroid lipofuscinosis 5.222 (Sweden) 0.46 (Sweden) - Late infantile neuronal ceroid lipofuscinosis 2.22 (Sweden) 0.46 (Sweden) - 6.99 (Germany) - - - - 57 Osteosarcoma - 0.3 (annual) 1-9 58 Pemphigus - - - 59 Petrosphic keratitis - - - 59 Petrosphigus foliaceus - - - 9 Petrosphigus vulgaris - 0.07-0.7 (annual) 10-50 59 Petrostent pulmonary hypertension of the newborn - - - 61 PlK3CA related overgrowth syndrome - - - CLAPO syndrome - -		Full NF2-related schwannomatosis	-	-	1-9
Neuroinbromatosis type 1 - 10-50 55 Neuronal ceroid lipofuscinosis - 1-9 ATP13A2-related juvenile neuronal ceroid lipofuscinosis - - 0.1 Congenital neuronal ceroid lipofuscinosis 5 (Finland) - - Infantile neuronal ceroid lipofuscinosis 5.222 (Sweden) 0.46 (Sweden) - 56 Neurotophic keratitis - 0.3 (Sweden) - 57 Osteosarcoma - 0.3 (annual) 1-9 58 Pemphigus - - - 7 Osteosarcoma - 0.3 (annual) 1-9 58 Pemphigus - - - 7 Osteosarcoma - 0.3 (annual) 1-9 59 Persitent pulmonary hypertension of the newborn - - - 60 Pheochromocytoma - - - - 61 PIK3CA related overgrowth syndrome - - - - 61 PIK3CA related overgrowth syndrome - - - - 61		Full schwannomatosis	-	-	-
55 Neuronal ceroid lipofuscinosis - - 1-9 ATP13A2-related juvenile neuronal ceroid lipofuscinosis - - <0.1	~ ~	Neurofibromatosis type 1		-	10-50
Al P13A2-related juvenile neuronal ceroid lipofuscinosis - - < < 0.1	55	ATD12A2	-	-	1-9
Congenital neuronal ceroid inpoluscinosisInfantile neuronal ceroid lipofuscinosis5 (Finland)Juvenile neuronal ceroid lipofuscinosis2.22 (Sweden)0.46 (Sweden)6.99 (Germany)6.99 (Germany)-42.02 (Europe)56Neurotrophic keratitis-0.3 (annual)1-957Osteosarcoma-0.3 (annual)1-958Pemphigus/Endemic pemphigus foliaceusPemphigus foliaceusPemphigus foliaceusPemphigus foliaceusPemphigus foliaceusPemphigus rulgaris0.07-0.7 (annual)10-5059Persistent pulmonary hypertension of the newborn60Pheochromocytoma61PIK3CA related overgrowth syndromeCLAPO syndrome<0.1		AIPI3A2-related juvenile neuronal ceroid lipotuscinosis	-	-	< 0.1
Infantic functional cervial iportactions is 2.12 (Sweden) 0.46 (Sweden) Juvenile neuronal cervial lipofuscinosis 2.22 (Sweden) 0.46 (Sweden) Late infantile neuronal cervial lipofuscinosis - 0.3 (Sweden) 56 Neurotrophic keratitis - - 42.02 (Europe) 57 Osteosarcoma - 0.3 (annual) 1-9 58 Pemphigus - - - Pemphigus foliaccus - - - Pemphigus toliaccus - - - Pemphigus vulgaris - 0.07-0.7 (annual) 10-50 59 Persistent pulmonary hypertension of the newborn - - - 60 Pheochromocytoma - - - 61 PIK3CA related overgrowth syndrome - - - CLAPO syndrome - - - - CLAPO syndrome - - <0.1		Lufantile neuronal ceroid linofuscinosis	- 5 (Finland)	-	-
Late infantile neuronal ceroid lipofuscinosis - 0.3 (Sweden) 56 Neurotrophic keratitis - 42.02 (Europe) 57 Osteosarcoma - 0.3 (annual) 1-9 58 Pemphigus - - / Endemic pemphigus foliaceus - - - Pemphigus vulgaris - 0.07-0.7 (annual) 10-50 59 Persistent pulmonary hypertension of the newborn - - - 60 Pheochromocytoma - - - - - 61 PIK3CA related overgrowth syndrome - <		Juvenile neuronal ceroid lipofuscinosis	2.22 (Sweden)	-	0.46 (Sweden)
1 1 1 1 1 56 Neurotrophic keratitis - 42.02 (Europ) 57 Osteosarcoma - 0.3 (annual) 1-9 58 Pemphigus - - / 59 Pemphigus foliaceus - - - 9 Pemphigus vulgaris - 0.07-0.7 (annual) 10-50 59 Persistent pulmonary hypertension of the newborn - - - 60 Pheochromocytoma - - - - 61 PIK3CA related overgrowth syndrome - - - - 61 PIK3CA related overgrowth syndrome - - - - 61 PIK3CA related overgrowth syndrome - - - - 61 PIK3CA related overgrowth syndrome - - - - - 61 PIK3CA related overgrowth syndrome - - <0.1		Late infantile neuronal ceroid linofuscinosis	0.99 (Germany)		0.3 (Sweden)
50 Network in this 12.02 (Eulope) 57 Osteosarcoma 0.3 (annual) 1-9 58 Pemphigus - - 59 Persistent pulmonary hypertension of the newborn - - 59 Persistent pulmonary hypertension of the newborn - - 60 Pheochromocytoma - - 61 PIK3CA related overgrowth syndrome - - 61 PIK3CA related overgrowth syndrome - - 61 CLOVES syndrome - - 62 Polycythaemia regressive overgrowth syndrome with - - <0.1	56	Neurotrophic keratitis		_	42.02 (Europe)
57 Pemphigus - - / 58 Pemphigus foliaceus - - - Pemphigus foliaceus - - - - Pemphigus vulgaris - 0.07-0.7 (annual) 10-50 59 Persistent pulmonary hypertension of the newborn - - - 60 Pheochromocytoma - - - 61 PIK3CA related overgrowth syndrome - - - - 61 PIK3CA related overgrowth syndrome - - - - 61 PIK3CA related overgrowth syndrome - - <0.1	57	Osteosarcoma	_	0.3 (annual)	1-9
Endemic pemphigus foliaceusPemphigus foliaceus-0.07-0.7 (annual)10-509Persistent pulmonary hypertension of the newborn60Pheochromocytoma61PIK3CA related overgrowth syndrome61PIK3CA related overgrowth syndrome61PIK3CA related overgrowth syndrome61PIK3CA related overgrowth syndrome61CLAPO syndrome<0.1	58	Pemphigus	-	-	/
Pemphigus foliaceusPemphigus vulgaris-0.07-0.7 (annual)10-5059Persistent pulmonary hypertension of the newborn60Pheochromocytoma61PIK3CA related overgrowth syndrome61PIK3CA related overgrowth syndrome61CLAPO syndromeCLOVES syndrome<0.1		Endemic pemphigus foliaceus	-	-	-
Pemphigus vulgaris-0.07-0.7 (annual)10-5059Persistent pulmonary hypertension of the newborn60Pheochromocytoma61PIK3CA related overgrowth syndrome61PIK3CA related overgrowth syndromeCLAPO syndromeCLOVES syndrome<0.1		Pemphigus foliaceus	-	-	-
59 Persistent pulmonary hypertension of the newborn - - 60 Pheochromocytoma - - 61 PIK3CA related overgrowth syndrome - - 61 CLAPO syndrome - - 61 CLOVES syndrome - - 62 Congenital infiltrating lipomatosis syndrome with fibroadipose hyperplasia - - <0.1		Pemphigus vulgaris	-	0.07-0.7 (annual)	10-50
60Pheochromocytoma61PIK3CA related overgrowth syndromeCLAPO syndrome<0.1	59	Persistent pulmonary hypertension of the newborn	-	-	-
61 PIK3CA related overgrowth syndrome - - - CLAPO syndrome - - <0.1	60	Pheochromocytoma	-	-	-
CLAPO syndrome< 0.1CLOVES syndrome< 0.1	61	PIK3CA related overgrowth syndrome	-	-	-
CLOVES syndrome< 0.1Congenital infiltrating lipomatosis of the face< 0.1		CLAPO syndrome	-	-	< 0.1
Congenital infiltrating lipomatosis of the face< 0.1Hemihyperplasia-multiple lipomatosis syndrome< 0.1		CLOVES syndrome	-	-	< 0.1
Hemihyperplasia-multiple lipomatosis syndrome - - < 0.1		Congenital infiltrating lipomatosis of the face	-	-	< 0.1
Megalencephaly-capillary malformation-polymicrogyria - - < 0.1		Hemihyperplasia-multiple lipomatosis syndrome	-	-	< 0.1
syntrome Segmental progressive overgrowth syndrome with fibroadipose hyperplasia< 0.162Polycythaemia vera-1-2.7810-5063Primary biliary cholangitis-0.33-5.8(annual)10-5064Primary ciliary dyskinesia3.33-6.67		Megalencephaly-capillary malformation-polymicrogyria	-	-	< 0.1
Segmental progressive overgrowth syndrome with fibroadipose hyperplasia-<		syndrome			< 0.1
62Polycythaemia vera-1-2.7810-5063Primary biliary cholangitis-0.33-5.8(annual)10-5064Primary ciliary dyskinesia3.33-6.67		fibroadinose hyperplasia	-	-	∨ 0.1
62Primary biliary cholangitis-0.33-5.8(annual)10-5064Primary ciliary dyskinesia3.33-6.67	62	Polycythaemia yera	-	1-2 78	10-50
64 Primary ciliary dyskinesia 3.33-6.67	63	Primary biliary cholangitis	-	0.33-5.8(annual)	10-50
	64	Primary ciliary dyskinesia	3.33-6.67	-	

Table 3. Incidence and prevalence of 86 rare diseases in *China's Second List of Rare Diseases* recorded in Orphanet database (continued)

#	Rare diseases	Newborn Incidence / 100,000 persons	Incidence / 100,000 persons	Prevalence / 100,000 persons
65	Primary IGF1 deficiency	_	-	< 0.1
66	Primary immunodeficiency	-	-	1-9
67	Primary myelofibrosis	-	1 (annual)	1-9
68	Primary sclerosing cholangitis	-	-	1-9
69	Interstitial lung disease	-	-	-
70	Recurrent pericarditis	-	-	-
71	Retinopathy of prematurity	-	-	10-50
72	Rett syndrome	-	-	1-9
73	Short bowel syndrome	-	-	1-9
	Gastroschisis		-	10-50
	Small bowel atresia		-	4-14.29 (live births,
				Europe)
74	Systemic juvenile idiopathic arthritis	0.6 (prediatric population)	1.6-23 (annual)	1-9
75	Systemic mastocytosis	-	-	10-50
	Aggressive systemic mastocytosis	-	-	0.1-0.9
	Indolent systemic mastocytosis	-	-	10-50
	Systemic mastocytosis with associated hematologic neoplasm	-	-	1-9
	Mast cell leukemia	-	-	< 0.1
	Acute mast cell leukemia	-	-	-
76	Takayasu arteritis	-	-	1-9
77	Tenosynovial giant cell tumor-Pigmented villonodular synovitis	-	-	10-50
78	Thalassemia major	-	-	-
	Beta-thalassemia major	-	1 (worldwide) 10 (EU)	-
	Hb Bart's hydrops fetalis		-	50-500 (live births, Southeast Asia)
79	Thrombotic thrombocytopenic purpura	0.1-0.61(iTTP)	-	1.29 (iTTP, France) 0.04-1.67 (cTTP)
80	Transthvretin amyloidosis	-	-	0.1-0.9
	ATTRV30M amyloidosis	-	0.87 (annual, Portugal)	22.94 (adults)
81	Tumor necrosis factor receptor associated periodic syndrome	-	0.57 (annual, children under 16, Germany)	
82	Tumor-induced osteomalacia	-	-	-
83	Von Hippel-Lindau syndrome	2.78	-	1-9
84	Von Willebrand disease type3	-	-	0.1-0.9
85	Waldenström macroglobulinemia- Lymphoplasmacytic	-	0.38 (annual, USA)	0.99 (Europe)

Table 3. Incidence and prevalence of 86 rare diseases in *China's Second List of Rare Diseases* recorded in Orphanet database (continued)

in a group. ICD-11, Orphanet, OMIM, MalaCards and other databases all cross-reference each other.

West syndrome-Infantile spasms syndrome

86

According to global epidemiologic data and the 2021 definition of rare diseases, conditions with a relatively high newborn incidence and/or prevalence (1/10,000) are recorded in *China's Second List of Rare Diseases*. Data on these registered rare diseases are readily available to advance research and development of orphan drugs and treatments for rare diseases.

In conclusion, in this study, we reviewed the classification, nomenclature, and epidemiology of 86 rare diseases in *China's Second List of Rare Diseases*. Including the 121 rare diseases in the first list, a total of 207 rare diseases have been described by the Chinese government. Administrative policies regarding rare diseases have been enacted, which refer to research, medical insurance, orphan drugs, and standards for diagnosis and treatment. These policies make important

contributions to progress in the area of rare diseases in China. The diseases on China's second list are important research topics and focusing on these will help China become a healthcare model with respect to rare diseases. The inclusion of conditions with relatively higher prevalence than those included in the current definitions will benefit more patients with rare diseases. With further development of national registries, rare diseases with very low prevalence will likely emerge.

1-9

Funding: This work was supported by a grant from the Natural Science Foundation of Shandong Province (General program ZR2023MH276) and Academic Promotion Program of Shandong First Medical University (LJ001).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

- Shourick J, Wack M, Jannot AS. Assessing rare diseases prevalence using literature quantification. Orphanet J Rare Dis. 2021; 16:139.
- Zhi W, Liu M, Yang D, Zhang S, Lu Y, Han J. Analysis of marketed orphan drugs in China. Intractable Rare Dis Res. 2023; 12:132-140.
- Li X, Wu L, Yu L, He Y, Wang M, Mu Y. Policy analysis in the field of rare diseases in China: A combined study of content analysis and Bibliometrics analysis. Front Med (Lausanne). 2023; 10:1180550.
- He J, Kang Q, Hu J, Song P, Jin C. China has officially released its first national list of rare diseases. Intractable Rare Dis Res. 2018; 7:145-147.
- World Health Organization. Rare diseases. https://www. who.int/standards/classifications/frequently-askedquestions/rare-diseases (accessed October 2, 2024).
- Lu Y, Han J. The definition of rare disease in China and its prospects. Intractable Rare Dis Res. 2022; 11:29-30.
- World Health Organization. ICD-10 Version:2019. https://icd.who.int/browse10/2019/en (accessed October 4, 2024).
- World Health Organization. International Statistical Classification of Diseases and Related Health Problems (ICD). https://www.who.int/standards/classifications/ classification-of-diseases (accessed October 4, 2024).
- Bodenreider O. The Unified Medical Language System (UMLS): Integrating biomedical terminology. Nucleic Acids Res. 2004; 32:D267-D270.
- Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999; 20:109-117.
- 11. Nguengang Wakap S, Lambert DM, Olry A, Rodwell C,

Gueydan C, Lanneau V, Murphy D, Le Cam Y, Rath A. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020; 28:165-173.

- Mazzucato M, Pozza LVD, Facchin P, *et al.* ORPHAcodes use for the coding of rare diseases: Comparison of the accuracy and cross country comparability. Orphanet J Rare Dis. 2023; 18:267.
- Rath A, Aymé S, Bellet B. Classification of rare diseases: A worldwide effort to contribute to the International Classification of Diseases. Orphanet J Rare Dis. 2010; 5:021.
- Aymé S, Bellet B, Rath A. Rare diseases in ICD11: Making rare diseases visible in health information systems through appropriate coding. Orphanet J Rare Dis. 2015; 10:35.
- Jia J, An Z, Ming Y, Guo Y, Li W, Liang Y, Guo D, Li X, Tai J, Chen G, Jin Y, Liu Z, Ni X, Shi T. eRAM: Encyclopedia of rare disease annotations for precision medicine. Nucleic Acids Res. 2018; 46:D937-D943.

Received November 2, 2024; Revised November 21, 2024; Accepted November 25, 2024.

[§]These authors contributed equally to this work.

*Address correspondence to:

Yanqin Lu, The First Affiliated Hospital of Shandong First Medical University & Shandong Provincial Qianfoshan Hospital, No. 16766 Jingshi Road, Ji'nan, Shandong 250013, China.

E-mail: yqlu@sdfmu.edu.cn

Released online in J-STAGE as advance publication November 29, 2024.