

The Clinical phenotypes and Follow-up of 51 Chinese patients with 22q11.2 Deletion Syndrome

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Abstract

Objectives

22q11.2 Deletion Syndrome (22q11.2 DS) is an immunodeficiency disorder characterized by a broad spectrum of clinical phenotypes, including facial dysmorphism, congenital heart and palate malformations, immune deficiencies, endocrine abnormalities, hypocalcemia as well as neurodevelopmental disorders. We aim to describe the clinical phenotypes and follow-up of a Chinese pediatric cohort with 22q11.2 DS.

Methods

A retrospective study was conducted on patients diagnosed with 22q11.2 DS from August 2008 to October 2025. The clinical, immunological, neurological and follow-up data were collected from electronic medical records. Diagnosis was confirmed using fluorescence in situ hybridization (FISH), multilink probe amplification technique (MLPA), array comparative genomic hybridization (aCGH) or whole-exome sequencing (WES).

Results

The general clinical manifestations of 51 patients included: (1) Facial dysmorphism (31.4%, 16/51); Palatopharyngeal malformations (21.6%, 11/51); Congenital heart disease (76.5%, 39/51); Endocrine abnormalities (45.1%, 23/51). (2) Immune characteristics: The incidence of recurrent infections was 31.4% (16/51); Immunomodulatory therapy (thymopentin or IVIG) was administered to 39.2% (20/51) of patients. T-cell deficiency (30/51), associated with thymic hypoplasia or aplasia (23.5%, 12/51). (3) Central nervous system characteristics: Neurological abnormalities (58.8%, 30/51), cognitive and developmental delay, epilepsy, and hypocalcemic seizures were the most common. Intelligence testing (25.5%, 13/51) revealed subnormal scores in all cases. Neuroimaging (89.7%, 35/39) commonly showed subdural hemorrhage and cerebral dysgenesis. (4) Follow-up data: As for 45 patients, T-cell immunodeficiency was in 26.7% (12/45) and ongoing immunomodulatory therapy was in 15.6% (7/45). The rate of neurodevelopmental abnormalities increased to 71.1% (32/45), learning difficulties being most common.

Conclusion

We found congenital heart disease combined with facial deformity should be vigilantly of 22q11.2 DS and carried out genetic testing. Systematic follow-up and monitoring of immune function and neurodevelopmental abnormalities are beneficial for improving the prognosis of the children.

Introduction

22q11.2 deletion syndrome (22q11DS), also referred to as DiGeorge or velocardiofacial syndrome, is a microdeletion disorder with an estimated incidence of 1 in 2000–4000 live births^[1]. The deletion typically involves approximately 50 protein-coding genes within the q11.2 region of chromosome 22, leading to highly variable phenotypic expression, including facial dysmorphism, congenital cardiac and palatal malformations, immune deficiencies, endocrine dysfunction, hypocalcemia, and neurodevelopmental impairments^[2]. Additional associated features encompass renal anomalies, hearing loss, growth retardation, psychiatric disorders, and feeding difficulties^[3]. Comprehensive management of pediatric patients with 22q11.2 DS is crucial for early identification, assessment, monitoring, and treatment of associated conditions to enhance survival and quality of life into adulthood.

22q11.2 DS can be categorized into several subtypes: 22q11.2 deletion without T-cell lymphopenia, with mild or significant T-cell lymphopenia, with congenital athymia, and with congenital athymia and autoimmune dysregulation (Omenn-like syndrome)^[4]. Studies indicate that 75–80% of patients exhibit immune system abnormalities, including increased susceptibility to infections, autoimmune diseases and atopic reactions^[5]. T-cell counts, which correlate with thymic size in early childhood, are often reduced. The gene deletion effects on secondary lymphoid organs or cell-intrinsic effects on lymphocytes could play a role in clinical immune concerns during adulthood in 22qDS^[6]. Neurological manifestations frequently include learning disabilities, autism spectrum disorder (ASD), cognitive deficits and speech delays, visuospatial and arithmetic impairments, attention deficit hyperactivity disorder (ADHD), and coordination deficits. Approximately 30% of patients develop schizophrenia, representing a 12- to 80-fold increased risk compared to the general population^[7]. These features are strongly associated with long-term prognosis and adult outcomes.

Until now, The largest cohort in China was studying fetal phenotypic and genotypic characteristics of 64 22qDS fetus^[8]. However, Zhao Yingjie et al. evaluated IQ scores in 1,478 subjects with 22q11.2DS and results indicate that haploinsufficiency of genes in the LCR22B-D region (BD) exert an additional negative impact on IQ^[9]. But they all don't systematic description of clinical phenotypes and immunodeficiency characteristics. Ella Nissan, et al reported general information, laboratory results, and clinical features with 98 patients of DiGeorge syndrome^[10]. So, there is a scarcity of systematic analyses focusing on the phenotypic spectrum of 22q11.2 DS in Chinese pediatric populations. Therefore, we conducted a retrospective review of clinical, immunological, and neurological manifestations among patients diagnosed at our institution. This study aims to enhance the understanding of 22q11.2 DS and improve clinical management and quality of life for affected children in China.

Methods

Patients

We retrospectively collected data from 51 pediatric patients with a confirmed genetic diagnosis of 22q11.2 deletion syndrome treated in the Department of Pediatric Immunology at Fudan University in the period from August 2008 to October 2024. Data included genetic, clinical, immunological, neurological and imaging findings retrieved from electronic medical records. A subset of patients underwent intellectual assessment. Written informed consent was obtained from the parents of all participating patients, and the study was approved by the Ethics Committee of the Children's Hospital of Fudan University.

Genetic diagnostic methods

Diagnosis was confirmed using FISH with a dual-color DNA probe (Vysis LSI TUPLE1, Abbott), MLPA (SALSA MLPA P250 kit, MRC Holland), aCGH (Agilent Custom Human Genome CGH Microarray 4×180K), or WES. For WES, genomic DNA was extracted from patient and parental blood samples. Genomic DNA fragments were enriched for the target region of the consensus coding sequence exons and subsequently sequenced on the HiSeq 2000 sequencer(Illumina, San Diego, CA). The raw data were mapped to the human genome reference sequence (hg19). Nucleotide changes observed in more than 5% of the aligned reads were called and reviewed with NextGENe software (SoftGenetics, State College, PA).

Serum immunoglobulin and lymphocyte subset detection

As previously reported^[11], serum IgG, IgA and IgM were determined by an automated clinical chemistry analyzer (Erba Diagnostics, Mannheim, Germany). IgE was assessed with UniCAP (Pharmacia, Uppsala, Sweden). Flow cytometry was performed according to our previously published protocol^[12]. Lymphocyte subsets were analyzed by flow cytometry (FACSCalibur, BD Biosciences) using BD Multitest IMK kits and additional markers for T-cell and B-cell subpopulations. T cell subsets were defined by antihuman CD3 (PerCP-Cy5.5), anti-CD8(BV510),anti-CD4,(FITC; fluorescein isothiocyanate), anti-CD27 (APC;allophycocyanin), anti-CD45RA (PE-Cy7), anti-TCRαβ(PE; phycoerythrin) and anti-TCRγδ (BV421). The following B cell subsets were detected: anti-CD19 (APC),anti-human CD24 (PE), anti-CD27 (BV450), anti-CD38(PerCP-Cy5.5) and anti-IgD (BV510) (BD Biosciences).

Diagnosis of Neurological abnormalities

Neurological abnormalities were evaluated based on clinical manifestations, intelligence assessment, brain magnetic resonance imaging (MRI), brain computed tomography plain scan (CT) and electroencephalogram (EEG). Diagnostic criteria referred to " Nelson Textbook of Pediatrics^[13] ". Classification mainly included cognitive and developmental delay, epilepsy, ataxia, and microcephaly, etc. Intelligence assessment was performed according to age-appropriate standards. Thymus size was assessed via chest imaging (chest X rays and CT). Brain MRI and CT abnormalities were interpreted with reference to "CAFHEY’S Pediatric Diagnostic Imaging^[14] ", including brain dysplasia (widened subarachnoid space, widened sulci and fissures, enlarged ventricles), brain atrophy (reduced brain volume, widened sulci and fissures), cerebellar dysplasia (reduced cerebellar volume, widened cerebellar sulci)%corpus callosum dysplasia (partial absence) and intracerebral injury foci (cortical signal abnormalities, white matter reduction).

Statistical Analysis

Normally distributed measurement data are expressed as mean ± standard deviation, while non-normally distributed data are expressed as median and the interquartile range (Q1-Q3). Categorical data are expressed as frequency and percentage. Descriptive analysis was conducted on clinical phenotype data.

Results

1. Demographic Features

Fifty-one patients were diagnosed with 22q11.2 DS, with a female-to-male ratio of 21:30 and a median age at diagnosis of 4 months (range: 0–99 months). All patients were from nonconsanguineous families. General clinical features are detailed in Table 1.

2. Clinical manifestations

2.1 Facial dysmorphism

Facial dysmorphism occurred in 31.4% (16/51) of patients. Three cases exhibited a small mouth and nose with asymmetric crying facies; four had micrognathia; one had microcephaly. Other features included a spherical nasal tip, ocular hypertelorism, fish-like lips, narrow palpebral fissures, low-set ears, and a high palatal arch.

2.2 Palatopharyngeal malformations

Eleven patients (21.6%) exhibited palatopharyngeal malformations, including throat puffing (2 patients), congenital laryngeal stridor (2 patients), congenital laryngeal chondrodysplasia (5 patients), and cleft palate (2 patients).

2.3 Congenital heart disease

Congenital heart disease was identified in 39 patients (76.5%). Specific defects included patent ductus arteriosus (12 patients), ventricular septal defect (15 patients), atrial septal defect (16 patients), tetralogy of Fallot (7 patients), patent foramen ovale (14 patients), pulmonary stenosis (3 patients), and anomalous pulmonary venous drainage (2 patients). Cardiac surgery was performed in 22 patients, and two patients died after surgery.

2.4 Endocrine abnormalities

Endocrine abnormalities were documented in 23 patients (45.1%), including hypocalcemia (13 patients), hypoparathyroidism (10 patients), hypothyroidism (5 patients), and dwarfism (2 patients).

2.5 Infection manifestations

All patients experienced infections of varying severity or immoderate inflammation reaction (Figure 1). The most common manifestation included recurrent respiratory infections (9 patients, 17.6%), recurrent pneumonia (7 patients, 13.7%) and septicemia (4 patients, 7.8%). Less common infections involved maxillofacial infection, enteritis, and otitis media. Immoderate inflammation included Kawasaki disease, hemophagocytic syndrome. One patient P11 died of severe pneumonia and respiratory failure.

Infectious pathogens were detected in 43.1% (22/51) patients (Figure 2). Bacterial infection included Streptococcus viridans(5 patients) and Pseudomonas aeruginosa (6 patients), Staphylococcus aureus (5 patients), Escherichia coli (2 patients), Neisseria species(5 patients), and MRSA (1 patient). Viral pathogens included rhinovirus (2 patients), CMV (1 patient), and respiratory syncytial virus (2 patients). mNGS identified CMV, EBV and circovirus infection in P26 patient; another patient P22 had Candida albicans, Staphylococcus aureus and EBV infection.

2.6 Neurological manifestations and neuroimaging results

Neurological abnormalities (Table 2) were observed in 30 patients (58.8%), with a median onset age of 3 months and median diagnosis age of 6.16 months. Epilepsy (9 patients) and hypocalcemic seizures (8 patients) were the most common neurological diagnoses. Other manifestations included dystonia (2 patients), ataxia (1 patient), viral encephalitis (1 patient), learning difficulties (3 patients), hearing impairment (1 patient), stereotyped movements (1 patient), tic disorder (1 patient), language development delay (2 patients), and emotional abnormalities (1 patient).

Neuroimaging was performed in 39 patients (76.5%), with abnormal findings in 35 (89.7%). Common observations included cerebral dysgenesis (7 patients), subdural bleeding (3 patients), scalp hematoma (1 patient), brain atrophy (1 patient), corpus callosum dysplasia (1 patient), intracerebral injury foci (1 patient), delayed myelination (1 patient), and cystic lesions (1 patient). Electroencephalogram abnormalities were identified in 10 patients (19.6%), including epileptiform discharges in 3 patients. Intelligence assessments, performed in 13 patients (25.5%), revealed subnormal scores in all cases.

2.7 Other system manifestations

Additional manifestations involved multiple organ systems, including dermatological (dermatitis, 4 patients), abdominal (umbilical hernia, 4 patients; abdominal hernia, congenital diaphragmatic distension, each 2 patients), musculoskeletal (butterfly-shaped thoracic vertebrae, 2 patients; distal rib enlargement, scoliosis, left equinovarus, each 1 patient), genitourinary (cryptorchidism, hypospadias, left hydronephrosis, each 1 patient), and other anomalies (triphalangeal thumb, left blepharoptosis, congenital bronchial malformation, esophageal stenosis, pharyngeal cyst, bronchostenosis, each 1 patient). Also noted were hematological abnormalities (thrombocytopenia and idiopathic thrombocytopenic purpura, each 1 patient), hearing loss (1 patient), and enuresis (1 patient).

Table 1 Demography and clinical general manifestations of 22q11.2 DS

Patient	Diagnosis age (month)/Sex	Gene Microdeletion	Facial Features	Congenital Heart Defects
P1	0.2/M	-	small mouth and nose ,crooked mouth to the left when crying	PDA,PFO
P2	19.9/M	-	N	VSD
P3	0.5/M	-	N	PDA
P4	1.9/M	-	N	VSD,PFO
P5	5.4/M	-	N	PA,VSD,ASD
P6	8.1/F	-	N	PA,VSD,ASD
P7	3.9/F	-	N	ASD,VSD,PDA
P8	1.1/M	-	small jaw	ASD,PFO
P9	4.3/M	-	N	PFO
P10	4/M	-	N	PS,VSD
P11	4.2/M	-	N	PA,VSD
P12	10/F	-	N	TOF,PDA,PFO
P13	1.1/M	-	N	PFO
P14	6.9/F	-	N	TOF,ASD,PFO
P15	5.5/M	-	N	TOF
P16	1.9/F	-	N	VSD,ASD,PDA
P17	3.5/M	-	N	TOF,PDA,PFO
P18	2.6/M	-	N	ASD,VSD,PDA
P19	1.8/F	-	small jaw	PDA,PFO
P20	2/F	2.56MB	spherical nose tipocular hypertelorism	ASD
P21	0.1/M	-	N	PDA
P22	12/F	TBX1	small mouth and nose ,crooked mouth to the left when crying	N
P23	0/F	3.2MB	ocular hypertelorism, fish lip,small palpebral fissure	VSD,ASD
P24	17/M	2.5 MB	N	N
P25	0.03/M	2.18MB	N	ASD
P26	2/F	TBX1	N	ASD
P27	0/M	-	small jaw, ocular hypertelorism, low-set ears	N
P28	3/M	-	N	ASD,PFO

P29	9/M	-	unusual facies	VSD,APVD,PFO
P30	36/M	-	N	N
P31	36/F	-	low-set ears, fish lip, spherical nose tip	N
P32	18/F	7.085MB	microcephaly	PFO
P33	23/F	2.5MB	N	N
P34	4/F	2.6MB	N	N
P35	0.07/M	2.5MB	ocular hypertelorism, collapsed nose	ASD,PDA
P36	1/F	3.15MB	small jaw, fish lip	PFO
P37	0/M	-	N	VSD
P38	56/F	-	ocular hypertelorism, low-set ears, high palatal arch	PDA
P39	0.4/M	-	N	N
P40	1.3/F	-	small mouth and nose ,crooked mouth to the left when crying	N
P41	4/F	-	N	ASD
P42	59/M	-	N	N
P43	3/M	-	fish lip, ocular hypertelorism, high palatal arch	VSD,ASD,PDA
P44	4/M	-	N	TOF,PFO
P45	7/M	-	N	TOF
P46	89/F	-	N	N
P47	16/M	-	N	ASD,APVD
P48	12/M	-	N	TOF
P49	99/M	-	N	VSD
P50	21/M	-	high palatal arch	N
P51	21/F	-	N	VSD, ASD

Note:F-Female; M-Male; N-Normal; PDA-Patent Ductus Arteriosus; VSD-Ventricular Septal Defect; ASD-Atrial Septal Defect; TOF-Tetralogy of Fallot; PFO-Patent Foramen Ovale; PS-Pulmonary Stenosis; PA-Pulmonary Atresia; APVD-Anomalous Pulmonary Venous Drainage; ITP-idiopathic thrombocytopenic purpura; N-Normal; - Unavailable data

Table 2 Neurological manifestations and neuroimaging results of 22q11.2DS

Patient	Neuro-onset Age (month)	Diagnosis Age (month)	Delayed Development	Intellectual Disability	Neurological Manifestation
P1	6	6.16	+	+	subdural bleeding, scalp hematoma
P2	0	6	+	+	epilepsy, dystonia
P7	12	15	+	+	subdural bleeding
P8	4.4	4.4	+	+	epilepsy;subdural bleeding
P9	8	18	+	+	dystonia
P11	unknown	unknown	+	+	low calcium convulsions
P12	9	17	+	+	low calcium convulsions&epilepsy
P13	1.4	1.4	+	+	low calcium convulsions, epilepsy
P20	18	18	+	+	viral encephalitis
P21	0.1	10	+	+	low calcium convulsions, ataxia
P22	9	17	+	+	epilepsy
P23	8	8	+	+	-
P24	17	17	+	+	-
P25	8	8	+	+	-
P26	17	17	+	+	epilepsy
P28	0	3	+	+	hearing impairment
P32	21	24	+	+	-
P33	10	23	+	+	-
P35	0	3	+	+	monotonous whole body movement
P38	12	15	+	+	epilepsy
P39	10	15	+	+	low calcium convulsions
P41	0.2	1.6	+	+	low calcium convulsions
P42	6	139	+	+	low calcium convulsions
P43	7	7	+	+	learning difficulty
P45	0.2	7	+	+	epilepsy
P46	84	89	+	+	learning difficulty
P47	6	108	+	+	epilepsy, tic disorder
P48	19	19	+	+	language development delay
P49	24	111	+	+	language development delay,learning difficulty,ε
P50	0	21	+	+	low calcium convulsions

Note: MRI: Brain magnetic resonance imaging; CT: brain computed tomography plain scan ; + Positive; - Unavailable data

3. Immune function characteristics

The serum immunoglobulin level were available for 70.6% (36/51) patients (Table 3). Approximately two-third of the patients showed abnormal level. Elevated IgE levels (range: 172.41–6980 KU/L; reference <100 KU/L) were observed in 6 patients. Immunoglobulin abnormalities included elevated IgG and IgM (11 and 7 patients, respectively), decreased IgM and IgG (7 and 3 patients, respectively), and elevated or decreased IgA (8 and 3 patients, respectively).

Lymphocyte subset analysis were available for 78.1% (40/51) patients (Table 4), which all had varying degrees of abnormalities. All the 40 patients were partial DiGeorge. The results revealed normal total T-cell counts in 10 patients and reduced total T-cell counts in 30 patients. The others included decreased CD8⁺ and CD4⁺ lymphocytes cell counts in 27 and 28 patients, respectively. Total B-cell and NK-cell counts were decreased in 9 and 11 patients, respectively. Subset analysis in four patients showed increased CD4⁺ terminal T cells in three patients. Patient 34 (P34) exhibited elevated double-negative T cells with reduced memory B cells and naïve T cells. Two patients had markedly reduced γδ T-cell counts.

Abnormal thymic volume was observed in 12 patients (23.5%), including one case of thymic aplasia. All patients received symptomatic anti-infective therapy, and immunomodulatory agents (thymopentin or IVIG) were administered to 20 patients (39.2%). After treatment with thymopentin or IVIG, the levels of reduced total T cells all had recovered to varying degrees.

Table 3 Serum immunoglobulin level and lymphocyte subset detection

Patient	Immunophenotypic Age(month)	CD3+ (cell/ul)	CD3+ (%)	CD3+CD4+ (cell/ul)	CD3+CD4+ (%)	CD3+CD8+ (cell/ul)	CD3+CD8+ (%)	CD19+ (cell/ul)	CD19+ (%)	CI
P1	-	-	-	-	-	-	-	-	-	-
P2	-	-	-	-	-	-	-	-	-	-
P3	-	-	-	-	-	-	-	-	-	-
P4	3	2241	41.80%	1513	28.1%↓	699	13%↓	2833↑	52.6%↑	27
P5	5	2635	56.20%	2087	44.50%	492	10.5%↓	1494	31.80%	51
P6	8	684↓	22.8%↓	510↓	17%↓	129↓	4.3%↓	1440	48%↑	82
P7	6	1866↓	65.40%	907↓	31.83%↓	906	31.80%	356↓	12.4%↓	58
P8	8	327↓	32.7%↓	253↓	25.3%↓	71↓	7.1%↓	591↓	59.1%↑	63
P9	4	780↓	26%↓	237↓	8%↓	233↓	8%↓	839	28%	14
P10	3	592↓	50%↓	398↓	33%↓	170↓	14%↓	260↓	22%	28
P11	4	2145↓	45.3%↓	1318↓	27.8%↓	787	16.60%	2275↑	48.1%↑	27
P12	9	803↓	43%↓	572↓	31%↓	173↓	9%↓	841	45%↑	18
P13	1	529↓	24%↓	400↓	18%↓	117↓	5%↓	1050	47%↑	54
P14	7	2209↓	46.1%↓	1149↓	24%↓	1041	21.70%	1346	28.1%↑	11
P15	-	-	-	-	-	-	-	-	-	-
P16	-	-	-	-	-	-	-	-	-	-
P17	-	-	-	-	-	-	-	-	-	-
P18	-	-	-	-	-	-	-	-	-	-
P19	-	-	-	-	-	-	-	-	-	-
P20	2	913.8↓	35.91%↓	716.31↓	28.15%↓	177.85↓	6.99%↓	689.85	27.11%	92
P21	77	735.3↓	58.18%↓	295.93↓	23.42%↓	372.94↓	29.51%	283.85	22.46%↑	19
P22	72	1691.1	45.46%↓	795.13	21.38%↓	664.35	17.86%↓	798.61↑	21.47%	12
P23	7	1465↓	38.94%↓	1013.38↓	26.94%↓	391.02↓	10.39%↓	1644	43.7%↑	60
P24	18	1371.15↓	59.58%	815.17↓	35.41%	363.81↓	15.8%↓	663.99	28.84%↑	24
P25	8	4445.4	46.48%↓	2035.01	21.28%↓	2281↑	23.85%	2665.96↑	27.88%	23
P26	24	1987.2	34.9%↓	983.04	17.26%↓	788.16	13.84%↓	1338.24	23.50%	22
P27	23	857↓	45.6%↓	374.63↓	19.93%↓	392.35↓	20.88%	463.73	24.67%	52
P28	9	971.2↓	29.51%↓	725.28↓	22.07%↓	226.44↓	6.88%↓	1700.79	51.68%↑	56
P29	9	1803.2↓	47.95%↓	949.42↓	25.24%↓	786.04	20.90%	1257.07	33.42%↑	66
P30	72	1199.7↓	37.17%↓	713.31	22.1%↓	334.65↓	10.37%↓	770.98↑	23.88%↑	12
P31	36	816.4↓	43.1%↓	482.76↓	25.49%↓	262.79↓	13.87%↓	724.88	38.27%↑	32
P32	20	3854.4	63.69%	2315.53	38.26%	1315.9	21.74%	1475.59↑	24.38%	68
P33	21	1335.8↓	42.36%↓	1204.05	38.18%	96.72↓	3.07%↓	462.56↓	14.67%	13
P34	20	1320.8↓	44.18%↓	914.98↓	30.60%	355.42↓	11.89%↓	1406.09	47.03%↑	23
P35	5	453.1↓	31.62%↓	316.27↓	22.07%↓	124.81↓	8.71%↓	382.93↓	26.72%	56
P36	9	1018.8↓	58.66%↓	765.64↓	44.08%↓	187.74↓	10.81%↓	448.2↓	25.81%	24
P37	0.2	677.4↓	53.99%↓	414.89↓	33.07%↓	258.34↓	20.59%	293.19↓	23.37%	24
P38	65	1558.5	54.89%↓	944.96	33.28%	525.12↓	18.49%↓	548.52	19.32%	70
P39	0.5	1958.9	66.93%	1300.5↓	44.44%	652.19↓	22.28%	295.39↓	10.09%	63
P40	1.5	880.26↓	38.21%↓	641.91↓	27.86%↓	227.10↓	9.86%↓	831.04	36.07%↑	54
P41	9	971.3↓	30.93%↓	438.65↓	13.97%↓	511.12↓	16.27%	997.89	31.77%↑	11
P42	-	-	-	-	-	-	-	-	-	-

P43	50	1348↓	47.87%↓	712.59	25.31%↓	587.81	20.87%	771.7↑	27.41%↑	66
P44	36	2866.38	58.44%	1580.37	32.22%	1106.47	22.56%	1453.02	29.62%↑	50
P45	-	-	-	-	-	-	-	-	-	-
P46	84	1859.09	59.02%↓	1111.6	35.29%	615.48	19.54%↓	289.86↓	9.2%↓	97
P47	48	1367.9↓	53.35%↓	827.58↓	32.28%	434.48↓	16.95%↓	935.17	36.48%↑	22
P48	12	1528.9↓	54.67%	795.12↓	28.43%	642.05	22.96%	815.57	29.16%↑	41
P49	92	1230.8↓	60.71%	604.56↓	29.82%	475.97↓	23.48%	532.75	26.28%↑	22
P50	30	1091.9↓	48.77%↓	602.55↓	26.92%	319.8↓	14.29%↓	811.18	36.24%↑	29
P51	-	-	-	-	-	-	-	-	-	-

Note: The above immunology manifestations are the patients' first check to the number of peripheral blood lymphocytes. Lymphocyte abnormal value among different age according to Reference Values for Peripheral Blood Lymphocyte Subsets of Healthy Children in China^[9]. The reference value of IgG, IgA, IgM and IgE list according to age respectively. 1-3m 2.75–7.50 g/L, 0.05–0.60 g/L, 0.10-0.70 g/L and < 100 KU/L; 4-6m 3.7–8.3g/L, 0.14–0.5 g/L, 0.33-1.25 g/L and < 100KU/L;7-11m 3.5–8.9 g/L, 0.06-0.54 g/L, 0.36-1.2g/L and < 100 KU/L;12-36m 5.52–11.46 g/L, 0.06-0.74 g/L, 0.6-2.12 g/L and < 100 KU/L.- Unavailable data

Table 4 Immunology manifestations of precise classification of T and B lymphocytes

P25%	P26%	P34%	P35%	
Total T cells	51.09	37.03↓	56.33	30.99↓
CD4+ cells	21.18↓	13.97↓	38.59	21.14↓
CD8+ cells	29.16	18.59	17.7	8.34↓
Double-negative T cells	2.02	13.06↑	6.89↑	4.91
TCRaβ+ double-negative T cells	0.51	0.71	0.04↓	0.69
TCRγδ+T cells	1.77↓	6.37	7.86	1.01↓
CD4+ naive T cells	79.94	62.71	20.81↓	60.13
CD4+ Central memory T cells	13.35	30.2	26.19	29.32
CD4+ effector memory T cells	2.05	4.98↑	51.25↑	9.24↑
CD4+ terminal T cells	4.66↑	2.11↑	1.74↑	1.31
CD8+ naiveT cells	41.86↓	53.25	12.98↓	84.52
CD8+ Central memory T cells	3.51↓	19.95	19.38	11.11
CD8+ effector memory T cells	3.75	2.99	60.21↑	3.6
CD8+ end-stage T cells	50.88↑	23.81	7.44	0.77
CD19+B cells	27.84	27.59	27.54	31.7↑
Initial B cells	88.64	85.5	92.95↑	96.56
B cells in the marginal zone	2.59↓	6.42	1.51↓	2.14↓
Memory B cells	5.28	4.46	1.75↓	0.24↓
Transitional B cells	15.94	9.38	1.95↓	24.18
Plasmacytocyte	3.69	0.74	0.04↓	0.06↓

Note: The above immunology manifestations are the patients'first check to the number of peripheral blood lymphocytes. Lymphocyte abnormal value among different age according to Reference Values for Peripheral Blood Lymphocyte Subsets of Healthy Children in China^[9].

3. Follow-up and outcomes

Follow-up data (Table 5) were available for 45 patients (median age: 13.5 years; range: 1.7–17 years). Three patients were lost in follow-up. Persistent occurrence of clinical symptoms were found in 12 patients (26.7%). The most common was recurrent respiratory tract infections (9 patients). Other ongoing issues included recurrent allergies, eczema, recurrent rhinitis, and thrombocytopenia (each 1 patient). Immunomodulatory therapy was continued in 7 patients (15.6%). Endocrine abnormalities persisted in 11 patients, including hypocalcemia (3 patients) and hypothyroidism (1 patient),short stature(8 patients).

Neurological impairments were identified in 32 patients (71.1%), with learning difficulties being the most common (20 patients). Other prevalent issues included language development delay (10 patients) and cognitive and developmental delay (3 patients). Additional manifestations included hearing impairment (1 patient), cerebral palsy (1 patient), quadriplegia (1 patient), emotional abnormalities (2 patient), seizures (1 patient), and attention deficit hyperactivity disorder (2 patients).

Table 5 Follow-up of results of 22q11.2DS

Patient	Current age(year)	Immunodeficiency manifestations	Neurological manifestations	Endocrine manifestati
P1	15	N	learning difficulty	-
P2	17	N	N	-
P3	15	N	N	-
P4	12	N	learning difficulty	N
P5	12	N	N	-
P6	13	N	N	-
P7	12	N	learning difficulty	hypocalcemia, short s
P8	14	N	N	-
P9	lost	-	-	-
P12	14	N	cognitive and development delay	-
P13	14	N	language development delay, learning difficulty	hypocalcemia
P14	13	N	learning difficulty	N
P15	12	N	learning difficulty	N
P16	12	N	N	-
P18	12	N	language development delay, learning difficulty	N
P19	13	N	N	-
P20	2.5	recurrent respiratory tract infection	language development delay	short stature
P21	13	N	learning difficulty, seizures	hypocalcemia
P22	6	recurrent respiratory tract infection	language development delay	hypothyroidism
P23	5	N	language development delay	-
P24	6	repeated allergies, eczema	language development delay, ADHD	-
P25	1.7	N	language development delay	short stature
P26	lost	-	-	-
P27	6	recurrent respiratory tract infection	language development delay	short stature
P28	9	recurrent respiratory tract infection	ADHD	-
P29	7	recurrent respiratory tract infection	-	short stature
P30	8	recurrent respiratory tract infection	N	N
P31	10	recurrent rhinitis	learning difficulty, emotional abnormalities	N
P32	7	N	learning difficulty	N
P33	9	N	N	-
P34	3.5	recurrent respiratory tract infection	short stature	thymopentin
P35	lost	-	-	-
P36	4	N	cognitive and developmental delay	N
P37	6	N	N	N
P38	11	recurrent respiratory tract infection	learning difficulty	-
P39	9	N	learning difficulty, cognitive and developmental delay	N
P40	6	N	N	N
P41	11	thrombocytopenia	learning difficulty	short stature
P42	12	N	learning difficulty, emotional abnormalities	-
P43	10.7	N	learning difficulty,	short stature
P44	13	N	learning difficulty	N
P45	13	N	cerebral palsy, quadriplegia	-
P46	17	N	learning difficulty	-

P47	11	N	language development delay, learning difficulty	N
P48	9	N	N	-
P49	14	N	N	-
P50	8	recurrent respiratory tract infection	learning difficulty	N
P51	12	N	learning difficulty, language development delay, poor hearing	N

Note: ADHD- Attention deficit hyperactivity disorder; N-Normal; - Unavailable data

Discussion

22q11.2 deletion syndrome is a multisystem disorder caused by a heterozygous 3 Mb microdeletion within the 22q11.2 chromosomal region^[15]. However, hemizygosity of the affected genes does not fully account for the considerable phenotypic variability observed among patients, additional mutations in genes located outside the deleted region, leading to “dual diagnosis”, have been described in 1% of patients. Besides, the genetic and epigenetic mechanisms implicated in the pathogenesis of the clinical manifestations of 22q11.2 DS^[16].

One Chinese cohort found that all 43 of their study participants with 22q11.2 DS had typical facial findings consisting of a vertically long face, narrow palpebral fissures, flesh nose with a broad nasal root, flattened malar region, retrognathia, and overfolded helix^[17]. In our cohort, facial dysmorphism was observed in 31.4% of patients, the most prevalent features in our study included asymmetric crying facies and small jaw. We speculated that this might be due to in our cohort aged 0 to 99 months resulting the inconsistent facial features. Palatopharyngeal anomalies were identified in 21.6% of patients, which is notably lower than the 67% reported in the literature^[18]. Another Literature indicate that palatopharyngeal abnormalities are present in 49%-69% of 22q11.2 patients^[19]. This discrepancy may reflect ethnic differences, variability in diagnostic scrutiny, or the influence of local genetic backgrounds. Patients with velopharyngeal insufficiency, which may cause serious disorders in functional speech, with poor intelligibility, a glottal stop with hypernasality and a pharyngeal fricative, and dropping and weakening of consonants^[20]. Therefore, specialized therapy and long-term clinical follow-up are necessary to velopharyngeal disfunction with 22q11.2DS.

The most frequent endocrine disorders associated with DGS/VCFS are short stature, hypocalcemia, thymic related immunodeficiency, and, less frequently, autoimmune and thyroid disorders^[21]. Another literature reported that Deletions of 22q11.2 are associated with a number of endocrine disorders, most commonly hypoparathyroidism, hypothyroidism and growth hormone deficiency^[22]. In our cohort, hypoparathyroidism ,hypocalcemia hypothyroidism and short stature were the most common, which were consistent with literature. As for treatment, five patients exhibited hypothyroidism requiring lifelong thyroxine replacement, and two presented with short stature associated with growth hormone deficiency, treating with growth hormone regularly. These findings reinforce the need for systematic monitoring of calcium-parathyroid axis, thyroid function, and growth parameters in this population to enable early intervention and prevent complications.

Approximately 60–80% of patients have a cardiac malformation most commonly including a subset of conotruncal defects (tetralogy of Fallot, truncus arteriosus, interrupted aortic arch type B), conoventricular and/or atrial septal defects, and aortic arch anomalies^[23]. Congenital heart disease was present in 76.5% of our patients, aligning closely with the above reported rates. Ventricular and atrial septal defects were the most common cardiac anomalies in our study, consistent with established literature. It is noteworthy that children with 22q11.2 DS face elevated risks of postoperative complications following cardiac surgery, including infections and renal impairment^[24]. These findings underscore the necessity of early genetic diagnosis to inform surgical planning and perioperative management.

Complete absence of thymus, though very rare and affecting less than 1% of patients with 22q11.2DS, is associated with a form of severe combined immunodeficiency (SCID). The degree of immunodeficiency can present differently depending on the extent of thymic hypoplasia^[25]. The immune deficiency also affects the humoral function of the immune system. This is thought to be the result of aberrant T cell help rather than B cell exhaustion evidenced by normal bone marrow B cell output as measured by kappa-deleting recombination excision circles (KRECs)^[26]. Besides, In terms of the humoral immune deficiency, there may be low gamma globulinemia, poor specific antibody response, and changes in B cell maturation. The fundamental cause of abnormal B cell maturation is likely to be impaired T cell assistance, rather than abnormal B cell proliferation or exhaustion^[27]. Previous reports found that > 30% of patients had an antibody defect, which could contribute to an increased risk of recurrent infections and up to 6% of 22q11.2DS have low IgG levels (defined as < 500 mg/dL) after 3 years of age^[28]. Selective IgA deficiency is present in up to 13% of 22q11.2DS^[29]. Selective IgM deficiency is less common but has also been reported in association with 22q11.2DS^[30, 31]. The immunological profile of our cohort was characterized by T-cell deficiency and B- cell deficiency in a substantial number of patients, correlating with the high prevalence of thymic hypoplasia/aplasia (23.5%). Besides, 40 patients were all Partial Digeorge by immunophenotyping characteristics. The possible reason was that the incidence rate of complete Digeorge was low and our sample size was small. The proportion of patients with decreased IgG level or decreased IgM level or decreased IgA level was 8.3%, 19.4%, 8.3% respectively. In a cohort, 63 of the 74 patients (85%) had a history of recurrent infections. Recurrent respiratory tract infections were reported in 58 patients (78%), more than ear infections in 31 (42%) and pneumonias in 16 patients (22%), respectively^[32]. Notably, patients in our cohort occurred with recurrent respiratory infections (17.6%), recurrent pneumonia (13.7%) and septicemia (7.8%), which was lower than that reported. We speculated that the widespread use of immunomodulatory therapies (thymopentin or IVIG) in our cohort (39.2%) may have contributed to this reduced infection rate. McDonald-McGinn,etal reported that the majority of patients with the deletion are modestly immunocompromised and do not develop opportunistic infections. Viral infections can be prolonged, and abnormal palatal anatomy may lead to compromised drainage and an increased susceptibility to upper airway bacterial infections. Approximately one-quarter to one-third of the patients had either recurrent sinusitis or otitis media, and 4%-7% had recurrent lower airway infections^[33]. In terms of our cohort, the spectrum of

opportunistic pathogenic highlighted a predominance of *Streptococcus viridans*, *Pseudomonas aeruginosa*, and *Neisseria* species. As for virus, CMV and respiratory syncytial virus were the most common, emphasizing the need for vigilant microbiological surveillance in these immunocompromised patients.

Neurological and neurodevelopmental abnormalities represented a major clinical concern with affecting 58.8% of patients at initial assessment and increasing to 71.1% during follow-up in our study. Patients with 22q11.2 DS are at elevated risk for a spectrum of neurological manifestations, including epilepsy, neuropsychiatric disorders, and structural brain abnormalities^[34]. One study showed that acute symptomatic seizures such as hypoglycemia and epilepsy are more common in children with 22q11.2DS relative to the general pediatric population^[35, 36]. In regard to unprovoked seizures, the percentage of patients meeting the criteria of epilepsy varies from 4%^[37] to 15.2%^[36], depending on the study. In our study, 30% of patients were diagnosed with epilepsy, while hypocalcemic seizures occurred in 26.7%. The relatively high prevalence of epilepsy and hypocalcemic seizures in our cohort may reflect earlier detection and diagnosis in pediatric settings. These findings underscored the necessity of longitudinal neurological and developmental follow-up to monitor disease progression and implement timely interventions. The reported patterns of neuroimaging abnormalities in 22q11.2DS included reduced surface area, cortical thickening with regional thinning, and subcortical changes^[38]. Mouse models indicate decreased neural progenitors in layers 2/3 may underlie aberrant connectivity^[39]. Our results found that cerebral dysgenesis and subdural hemorrhage were the most common, further supporting structure-function correlations, which was basically consistent with literature.

22q11.2DS is a multisystem genetic disorder necessitating lifelong multidisciplinary care, particularly during the transition from pediatric to adult services^[4]. Longitudinal follow-up is crucial for early detection of comorbidities and quality-of-life improvement. Our cohort exhibited recurrent respiratory infections in 9 patients and ongoing immunomodulatory therapy in 7 patients, which was inconsistent with one literature reported that only 40% of patients aged > 9 years with the deletion were thought to be as healthy as others their age^[33]. Furthermore, we found that neurodevelopmental and psychiatric manifestations progressed over time, affecting 71.1% of patients during follow-up, predominantly learning difficulties, language development delay and cognitive development delay. These observations align with established evidence of cognitive inflexibility and social cognition deficits in adulthood^{[40][41]}. Consequently, long-term care strategies should emphasize regular monitoring and early intervention for both immunological and neuropsychiatric sequelae.

This study has several limitations, including its retrospective design and modest sample size, which may limit the generalizability of the findings. In addition, the single-center nature of the study may introduce selection bias. Nevertheless, our findings first provided valuable insights into the phenotypic expression of 22q11.2 DS in a Chinese pediatric cohort.

In conclusion, our results affirm that T-cell immunodeficiency and neurodevelopmental abnormalities are core features of 22q11.2 DS critically influencing long-term outcomes. Early genetic testing should be considered in children presenting with congenital heart disease, unexplained hypocalcemia, seizures, or recurrent infections. Comprehensive and prolonged follow-up, involving immunology, neurology, endocrinology, and mental health services, is essential to optimize quality of life and functional outcomes in these patients.

Declarations

Publishing Units: Department of Pediatric Immunology at Fudan Children's hospital

Ethics: Fudan University Pediatric Ethics Review [2025] 198, Study on the Association between 22q11.2DS Immunodeficiency and Neurodevelopmental Abnormalities, which is in accordance with the "Declaration of Helsinki"; Ethics Committee of Children's Hospital of Fudan University.

Human Ethics and Consent to Participate declarations: not applicable.

Clinical trial number: not applicable

Author contribution: Wei Dong is the one responsible for collecting the data and writing the paper. Haili Yao is the director in charge of managing these 22q11.2DS patients. Professor Xiaochuan Wang is my supervisor, the person responsible for the article's conception and overall management of the patients, and Bijun Sun is the one responsible for providing 30% of the case data. Wenjie, Wang is in charge of managing these 22q11.2DS patients. Jinqiao, Sun is in charge of managing these 22q11.2DS patients.; Qinhua, Zhou is in charge of managing these 22q11.2DS patients.; Jia, Hou is in charge of managing these 22q11.2DS patients.; Wenjing, Ying is in charge of managing these 22q11.2DS patients.; Chenghao, Wang is in charge of managing these 22q11.2DS patients.; Luyao, Liu is in charge of managing these 22q11.2DS patients.; Lipin, Liu is in charge of managing these 22q11.2DS patients.

Data availability: All the data of the patients can be obtained completely. All the data are original data. All authors have no conflicts of interest. All authors work in Department of Pediatric Immunology at Fudan Children's hospital

Conflict of interest declaration: All the data are original data. All authors have no conflicts of interest. The article was not submitted to other publications. After being accepted by the magazine, the copyright of the article belongs to the magazine.

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Figures

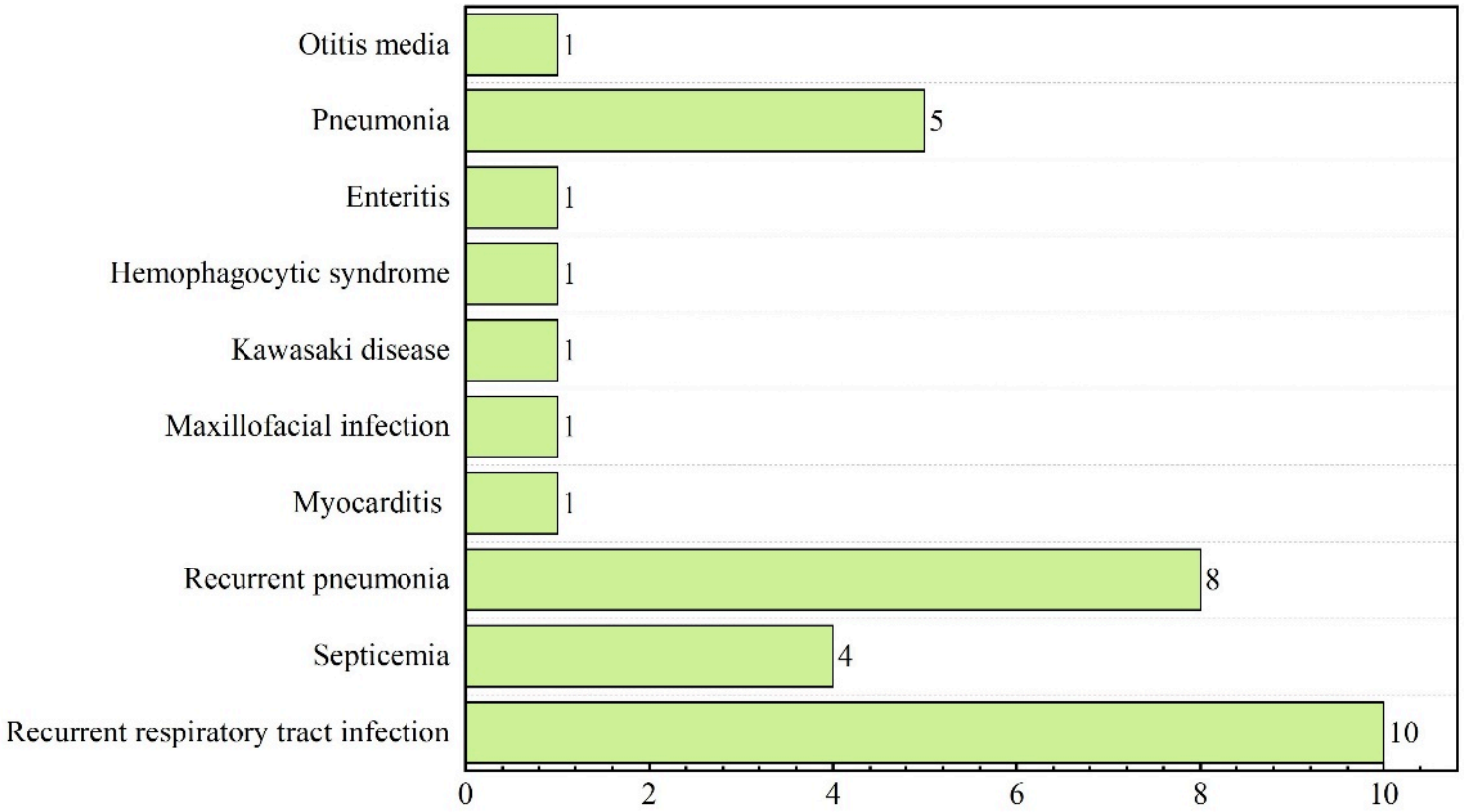


Figure 1
Infection classification of 22q11.2 DS

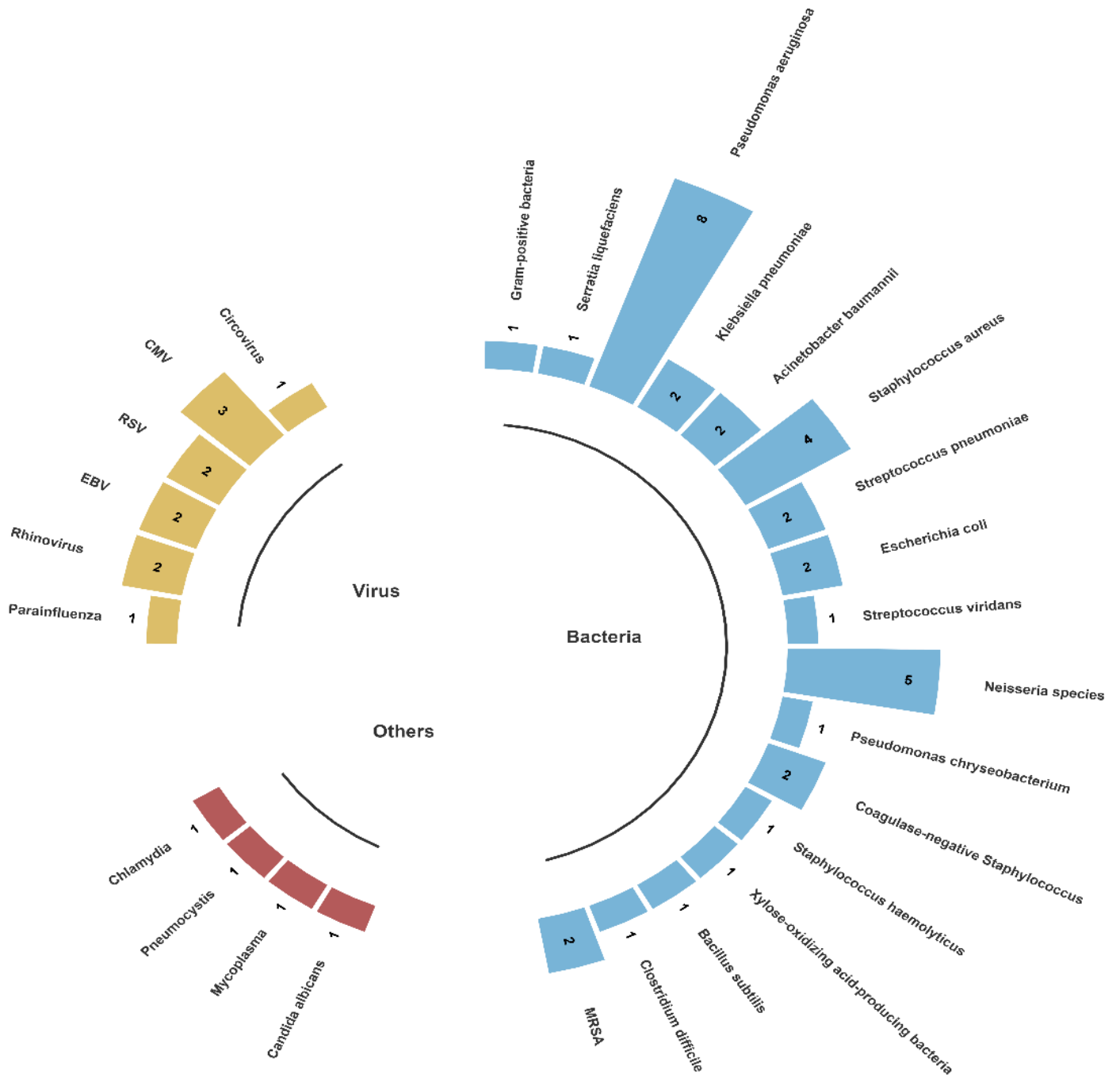


Figure 2

Pathogen classification of 22q11.2 DS