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Case Report

When Should We Raise Clinical Suspicion of DiGeorge Syndrome: Two Case Reports from a Tertiary Hospital in Indonesia

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Abstract

DiGeorge syndrome (DGS) or 22q11.2 deletion syndrome (22q11.2DS) is the most common genetic microdeletion in humans, with an incidence rate of 1:3000 to 6000 live births. Early detection and diagnosis of DiGeorge syndrome are challenging to clinicians due to its phenotype variability. We report two cases of DiGeorge syndrome, each demonstrating a different combination of clinical phenotypes. Two girls (2 years-3 months old and 2 years-2 months old) were diagnosed with 22q11.2DS following chromosomal microarray analysis (CMA) results. The patients in both cases showed some similar clinical phenotypes, including developmental delay, seizure, recurrent infections, hypothyroidism, and dysmorphic features (down-slanting palpebral fissure, bulbous nose, low-set ears, and small down-turned mouth).

However, the patient in case 2 exhibits more typical phenotypes, including congenital heart defect and hypocalcemia. Besides congenital heart anomalies, clinicians should raise clinical suspicion of DiGeorge syndrome in the presence of developmental delay, seizure, signs of immunodeficiency (recurrent infections), and dysmorphic features in children. Phenotype variability of DiGeorge syndrome is primarily attributed to the specific gene involved in the deletion, incomplete penetrance, and variable expressivity.

Keywords
22q11.2 deletion; development delay; immunodeficiency; hypocalcemia

1. Introduction

DiGeorge syndrome (DGS), also called the 22q11.2 deletion syndrome (22q11.2DS), is one of humans' most common genetic microdeletion syndromes [1]. The incidence of DGS in live births is 1 in 3000-6000, with no gender predilection [2, 3]. Most cases arise de novo [4]. In some cases (8-28%), DGS is inherited autosomal dominantly [5]. DiGeorge syndrome can manifest in a broad phenotypic presentation. In approximately 90% of cases, the underlying cause is a microdeletion in chromosome 22, specifically on the long arm (q) at the 11.2 locus (22q11.2) [6]. Over 90 genes are located at the 22q11.2 locus. The most extensively studied gene is T-box transcription factor 1 (*TBX1*), associated with the most prominent phenotypes characteristic of DGS [6]. Additionally, *TBX1* correlates with neuromicrovascular anomalies, which may be responsible for the behavioral and development delay observed in DiGeorge syndrome [7, 8].

It should be noted that less than 1% of DGS patients present with complete DGS, which represents the most severe subtype of DGS with an unfavorable prognosis [6]. In such cases, mortality typically occurs before 12 months in the absence of thymic or hematopoietic cell transplantation [6]. In contrast, the less severe form of DGS (partial DGS) lacks a clearly defined prognosis, as this is contingent upon the clinical severity of the disorder [6].

Infants with DiGeorge syndrome typically present with main clinical features, including immunodeficiency (~75% of patients), congenital cardiac anomalies (~75%), hypocalcemia due to hypoparathyroidism (~50%), developmental delay (~90%), and palatal abnormalities (~75%) [1, 9]. Psychiatric disorders affect 60% of adults with DGS [1]. Additionally, other clinical symptoms may manifest in DGS patients during childhood, including hypothyroidism (~20-30%) [10-12], hearing loss [5], otitis media, and feeding problems [13]. Furthermore, DGS has also been linked to an increased risk of acute symptomatic seizures as the manifestation of hypocalcemia. It has been reported that 1-14.5% of DGS patients experience hypocalcemia-induced seizures [14-16].

Definitive diagnosis of DGS is made by identifying microdeletion of chromosome 22 at the 22q11.2 locus by various techniques, including fluorescence in situ hybridization (FISH) and multiplex ligation-dependent probe amplification (MLPA) [17]. The high variability of the clinical phenotype made the diagnosis of DGS challenging, especially for clinicians who were not familiar with this syndrome. Early and prompt management can enhance patients' quality of life and neurodevelopment outcomes. Thus, early diagnosis of DGS is crucial [1]. This report describes two cases of DiGeorge syndrome diagnosed at a tertiary hospital in Indonesia, highlighting clinical

phenotypes that should alert clinicians to the possibility of DGS, particularly for the Indonesian pediatric population. To our knowledge, this is the first article reporting cases of DiGeorge syndrome in Indonesia.

2. Case Presentation

2.1 Case 1

A seven-month-old girl was referred to the pediatric neurology clinic at our center due to frequent episodes of seizures without fever, which began at six months of age. The characteristics of the first episode of seizure were generalized tonic seizures with upward gazing that lasted for 2 minutes. She experienced ten episodes of seizures with the same characteristics within a month before visiting our clinic. Neurological assessment revealed normal reflexes with no signs of focalization. An Electroencephalogram performed when she was seven months old revealed no epileptogenic wave and no sign of a slow wave. Based on the clinical findings and EEG results, she was diagnosed with generalized epilepsy and was prescribed antiepileptic medications (valproic acid and vitamin B6). She responded well to the antiepileptic treatment with no recurrent seizures. Calcium level was not checked at that time.

Her perinatal history was unremarkable. She was born to a 25-year-old mother (G1P1A0) via normal vaginal delivery, with a birth weight of 2800 grams. There were no complications or health issues during the neonatal period. She had a history of frequent upper respiratory tract infections (common cold). At 1 year and 7 months, anthropometric evaluation revealed normal growth with a body weight of 8.5 kg and body length of 76 cm. The Z-scores were as follows: WAZ -0.67 SD, HAZ -1.23 SD, and WHZ -0.09 SD. However, the developmental evaluation performed when she was 1 year and 9 months old showed global developmental delay (speech delay and gross motoric delay). Her motoric developmental milestones were walking with assistance, as she had not yet been able to walk independently without support. She could also not sit up straight from a squatting position, jump, walk upstairs without support, or kick an object. Her speech and language development were limited to five words: “mama,” “maem” (eat), “gak” (no), “emoh” (no), “sana” (there), and “sini” (here). She had received all required immunizations as per the national immunization program up to 2 years of age, with no significant adverse reactions to the vaccinations.

At 1 year and 9 months old, she was referred to the pediatric endocrinology clinic for evaluation and management of hypothyroidism. Thyroid function tests indicated subclinical hypothyroidism, with elevated TSH levels at 11.09 mIU/L (reference range: 0.51-4.94) and normal FT4 level of 16.11 pmol/L (reference range: 10.6-19.4 pmol/L). At the age of 2 years and 1 month, the pediatric endocrinologist noted dysmorphic features in the patient upon examination, including down-slanting palpebral fissure, small-down-turned mouth, low-set ears, bulbous nose, and tapering fingers (refer to Figure 1). Based on these clinical findings (developmental delay, dysmorphic features, and recurrent upper respiratory infection), the pediatric endocrinologist began to suspect DiGeorge syndrome.

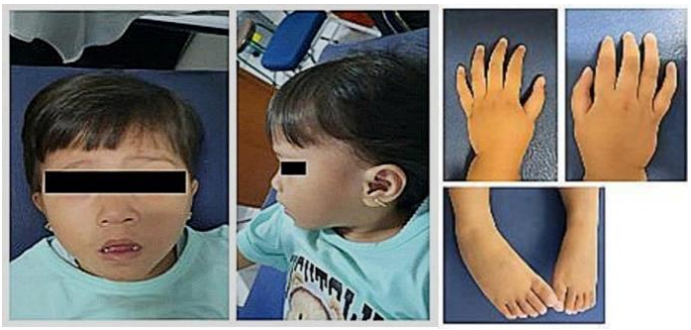

Figure 1 The image on the left shows a down-slanting palpebral fissure (blurred for confidentiality), a bulbous nose, a small downturned mouth, and low-set ears—the image on the right shows tapering fingers**.**

The patient was subsequently referred for audiological assessment and echocardiography to exclude hearing impairment and congenital heart anomalies commonly associated with DiGeorge syndrome. The results of both evaluations were unremarkable. The total calcium level was also measured, with a result of 2.4 mmol/L (reference range: 2.12-2.52 mmol/L), indicating normocalcemia. Laboratory tests and other imaging modalities to assess parathyroid hormone levels, as well as the size and structure of the parathyroid and thymus glands, had not been conducted when this case report was written. Additionally, immunological parameters (T-cell immunity parameters, immunoglobulin levels, and flow cytometry for thymic functions) were not performed due to the unavailability of the necessary laboratory resources at our center.

Chromosomal microarray analysis (CMA) to confirm DGS was done when she was 2 years 3 months old. The CMA revealed a pathogenetic 2.1 Mb microdeletion at the 22q11.2 locus, thereby confirming the diagnosis of 22q11.2 deletion syndrome (refer to Figure 2 and Figure 3 for further details). A three-generation pedigree was constructed to examine the inheritance pattern of DGS. There was no other history of DGS in the immediate family. No instances of consanguinity were identified within the family (refer to Figure 4 for further details).

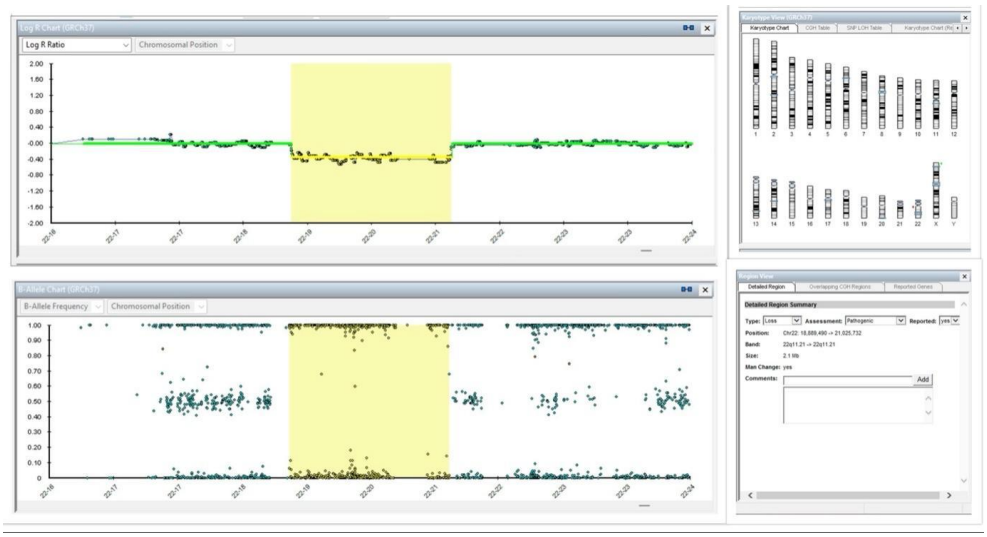

Figure 2 Chromosomal microarray analysis using the Human CytoSNP-850K Bead-Chip kit chromosomal microarray demonstrating 2.1 Mb pathogenic microdeletion of Chr22: 18,889,490-21,025,732.

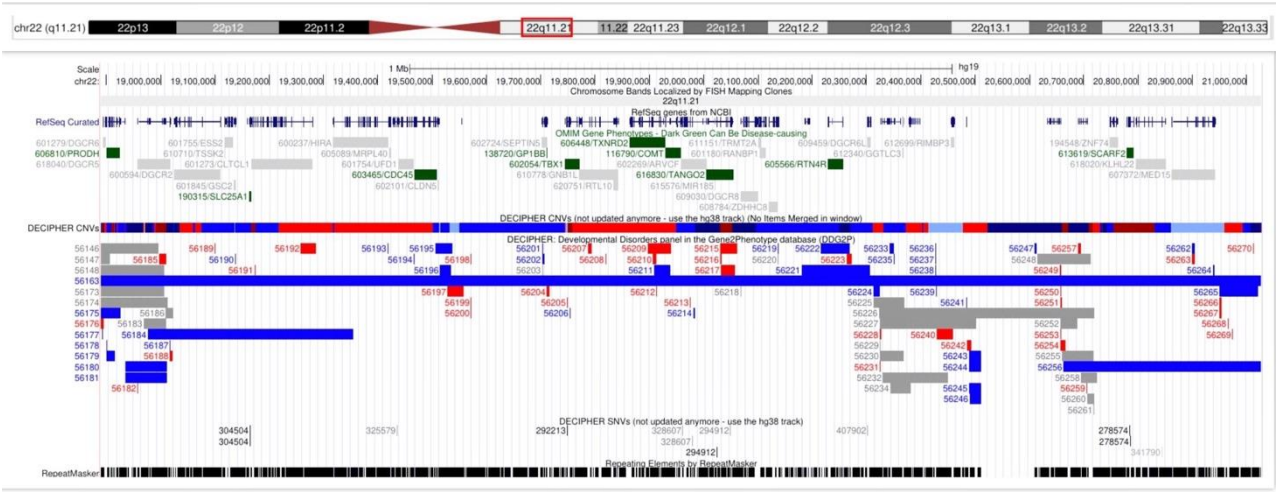

Figure 3 Genes associated with the 2.1 Mb pathogenic microdeletion of chr22: 18,889,490-21,025,732, analyzed using the UCSC Human Genome Browser.

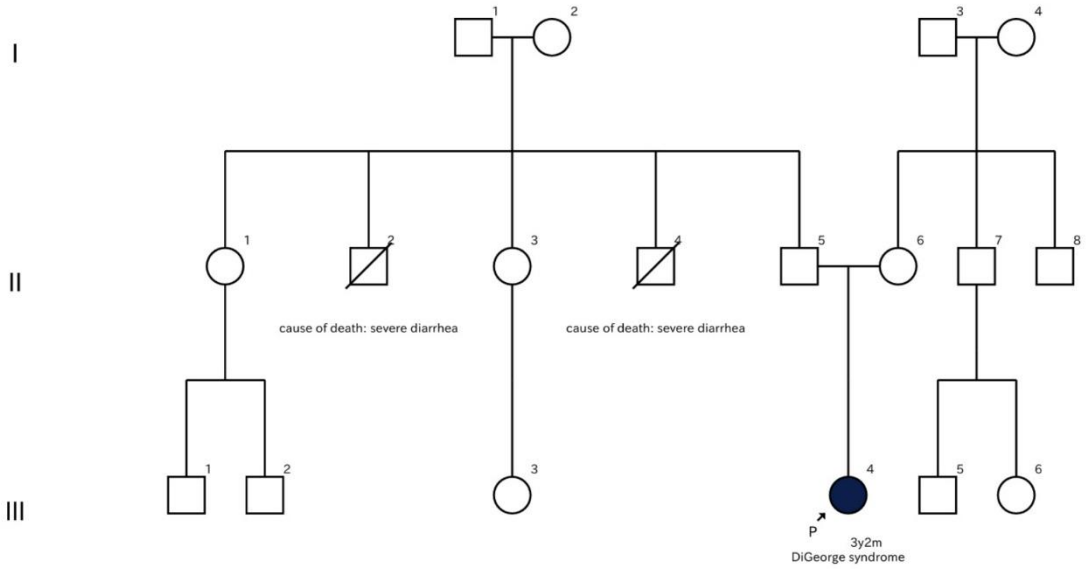

Figure 4 Three-generation pedigree analysis of patient 1 showed a de novo inheritance pattern (pedigree built using f-treeGC application) [18].

2.2 Case 2

A female infant was delivered via normal vaginal delivery to a 28-year-old G4P4A0 mother in a regional hospital. Her birth weight was 2800 grams. Twelve hours after birth, she experienced two episodes of generalized tonic seizures (lasting 1 minute each) with fever and cyanotic spells. She was admitted to the neonatal intensive care unit (NICU) in the regional hospital for 1 month and 25 days due to recurrent episodes of seizure. As the seizures persisted, she was referred to the NICU at our center when she was 2 months old.

Upon admission to the NICU at our center, it was determined that the cause of her recurrent episode of seizure was hypocalcemia. Parathyroid hormone level was assessed, showing a normal parathyroid hormone level of 21.51 pg/mL (reference range: 10-65 pg/mL). An

electroencephalogram (EEG) revealed multifocal epileptogenic wave and diffuse electrophysiologic abnormality. She subsequently received treatment for hypocalcemia at the NICU, and the seizures resolved. The corrected total calcium level was 2.2 mmol/L (reference range: 2.12-2.52 mmol/L). Additionally, an echocardiogram was performed to investigate the possibility of a cyanotic heart defect, which confirmed the presence of tetralogy of Fallot and a patent foramen ovale. Upon discharge from the hospital, the patient was prescribed calcium supplementation and antiepileptic medication (phenobarbital), which she continued until the age of five months. Her antiepileptic treatment was subsequently switched to valproic acid and vitamin B6. She responded well to the medication, remaining seizure-free until the age of 11 months.

The patient was referred to a pediatric endocrinology clinic when she was 3 months of age for evaluation of hypothyroidism. Thyroid function tests conducted at that time demonstrated a high TSH level of 6.85 mIU/L (laboratory reference range 0.51-4.94 mIU/L) and a low free T4 (FT4) level of 10.38 pmol/L (laboratory reference range: 10.6-19.4 pmol/l), confirming hypothyroidism. At 5 months of age, the patient began experiencing episodes of acute otitis media, which later progressed to chronic suppurative otitis media. Consequently, she was referred to a pediatric otolaryngologist for routine evaluation and management of chronic suppurative otitis media.

At six months of age, the pediatric endocrinologist identified several dysmorphic features in the patient, including hypertelorism, down-slanting palpebral fissures, a bulbous nose, a small downturned mouth, low-set ears, a high-arched palate, and overfolded toes (see Figure 5). Based on the clinical combination of congenital heart defect, recurrent seizures associated with hypocalcemia, recurrent infections, and dysmorphic features, the pediatric endocrinologist suspected DiGeorge syndrome. Due to limitations in genetic testing facilities, the genetic confirmatory test for 22q11.2 deletion was delayed until the patient was 2 years old.

Figure 5 Craniofacial dysmorphic features observed in patient case 2 including down-slanting eyes (blurred because of confidentiality), bulbous nose, small downturned mouth, and low-set set-ears.

Anthropometric and developmental evaluation at the age of 8 months old indicated underweight status, short stature, and global developmental delay. Her body measurements were as follows: body weight 5.9 kg, body length 64 cm, and head circumference 42 cm. The corresponding Z-scores were WAZ -2.78 SD, WHZ -1.51 SD, HAZ -2.76 SD, and HC -1.5 SD. Her developmental milestones were elevating her head at 45 degrees, visual object tracking to 180 degrees, and babbling “aaa” and “no.” She had not yet been able to crawl, sit, grasp items, and laugh loudly. Appropriate interventions were implemented to address the growth and developmental problems.

At 11 months of age, she experienced generalized clonic seizures without fever lasting less than five minutes. Laboratory evaluations at that time showed normal electrolyte and calcium levels (total calcium level of 2.3 mmol/L). There was no adjustment in the epileptic medication following this seizure episode. At 1 year and 5 months old of age, she experienced recurrent episodes of seizure accompanied by a fever of 40°C and diarrhea, leading to admission to the NICU at our center for 20 days. Laboratory results revealed hypocalcemia (total calcium: 1.99 mmol/L) and hypokalemia. The chest X-ray showed a boot-shaped heart, consistent with tetralogy of Fallot, along with signs of bronchopneumonia. The chest X-ray did not clearly define the thymus size. A head MSCT scan was conducted to exclude brain structure abnormalities, but normal findings were obtained. An electroencephalogram conducted during this period revealed diffuse electrophysiology abnormality. After being discharged from the hospital, her anti-epileptic regimen remained unchanged, with continued administration of valproic acid and vitamin B6. Following this episode at 1 year and 5 months, the patient remained seizure-free.

The CMA result, obtained when the patient was 2 years and 2 months, confirmed 2.6 Mb pathogenic microdeletion of chromosome 22q11.2 (refer to Figure 6 and Figure 7). A three-generation pedigree history was constructed to investigate the inheritance pattern of DGS. There was no history of DGS and consanguinity marriage within the family (see Figure 8). Similar to the patient in Case 1, laboratory immunological parameters data were unavailable. By the age of 2 years, the patient had received the complete set of basic immunizations for her age, except live vaccines. As of this writing, she has not yet undergone cardiac surgical repair.

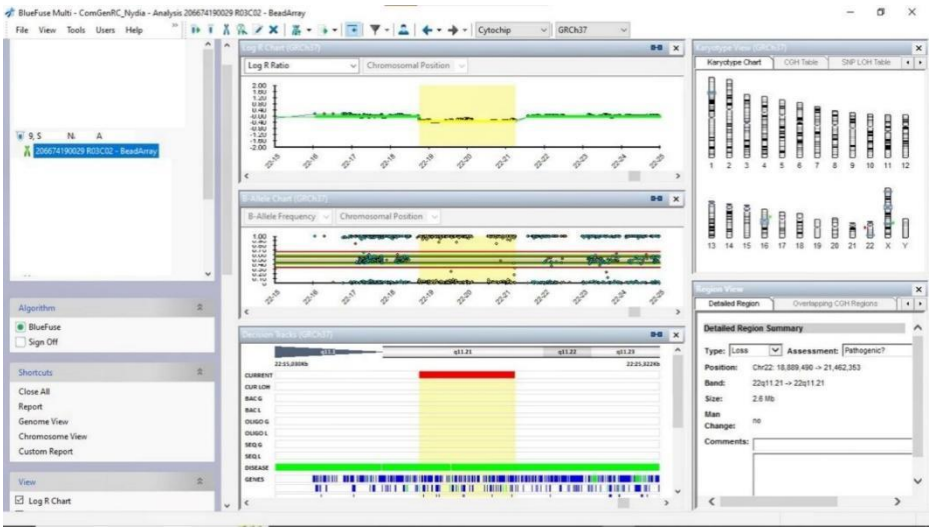

Figure 6 Chromosomal microarray analysis using the Human CytoSNP-850K Bead-Chip kit chromosomal microarray demonstrating 2.6 Mb pathogenic microdeletion of Chr22: 18,889,490-21,462,353.

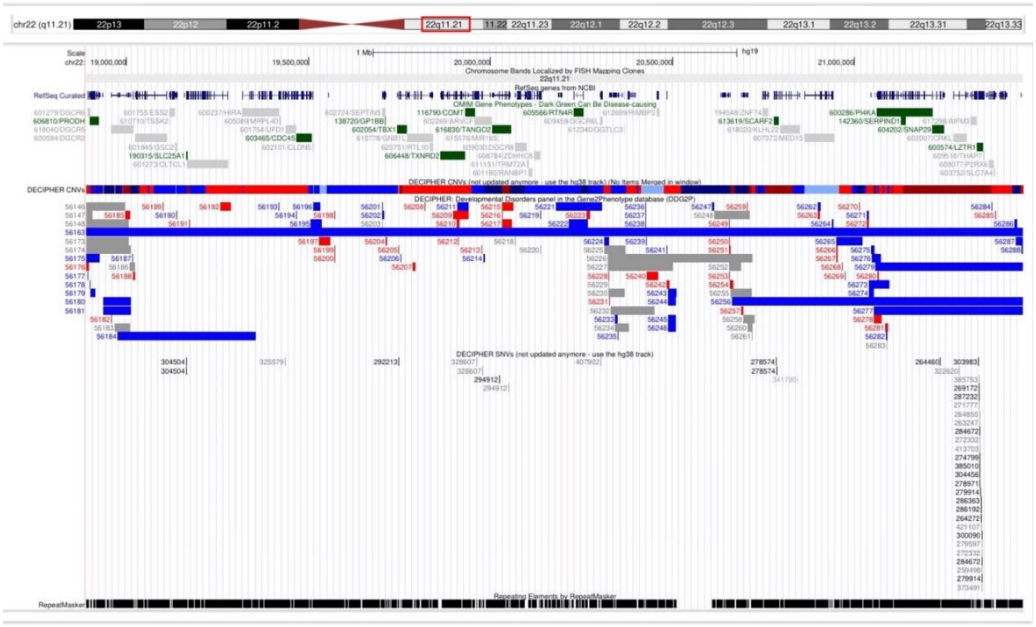

Figure 7 Genes involved in the 2.6 Mb pathogenic microdeletion of Chr22: 18,889,490-21,462,353, analyzed using UCSC Human Genome Browser.

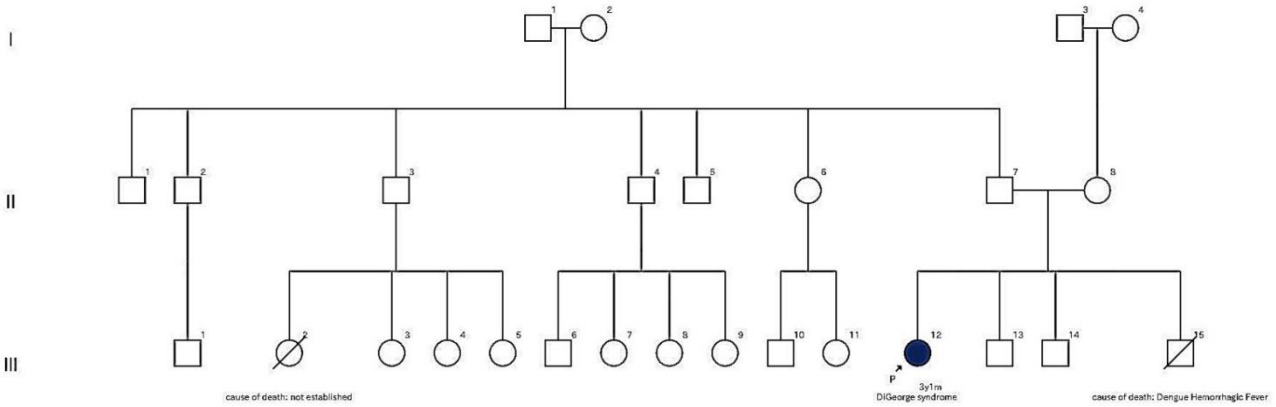

Figure 8 Three-generation pedigree of patient 2 showed a de novo inheritance pattern (pedigree built using f-treeGC application) [18].

2.3 Ethics Statement

This case report has been approved for publication by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Diponegoro, with reference number No. 298/EC/KEPK/FK-UNDIP/VIII/2021**.** Written informed consent for the sharing of data and publication of the report was obtained from the patient's parents.

3. Discussion

The patients in Cases 1 and 2 exhibit a similar constellation of clinical features associated with DiGeorge syndrome (DGS), including global developmental delay, dysmorphic features, signs of

immunodeficiency (e.g., recurrent infections), history of seizures, and hypothyroidism. These findings are consistent with the study on the clinical characteristics of DiGeorge syndrome (DGS) patients from diverse ethnic backgrounds globally and regionally. A study conducted by Méndez-Rosado et al identified that the most frequent combination of clinical manifestations of DGS in diverse populations (Cuba, South Asia, Morocco, and Europe) include congenital heart defects (68% of cases), dysmorphic features (61% of cases), neurodevelopmental disorders (43% of cases), and thymus aplasia/hypoplasia (32% of cases) [19]. Hypocalcemia and or hypoparathyroidism constituted 25% of cases [19]. Another study evaluating clinical characteristics of 22q11.2 deletion syndrome in Northern Thailand found that the most common clinical features in their cohorts were typical craniofacial dysmorphic features (91.2%), congenital heart defect (79.4%), history of hypocalcemia (64.7%), history of recurrent infections (50%), and intellectual disability (80%) [20].

Méndez-Rosado et al found that clinical features of DGS were recognized at different times during their lives. Within the group younger than 2 years old, the predominant clinical features were heart disease, dysmorphic features, hypocalcemia, and or hyperparathyroidism. Meanwhile, in the group older than 2 years old, the predominant clinical characteristics were dysmorphic features, congenital heart disease, intellectual disability, and immunological disorders [19]. These findings are consistent with the presented case reports. In Case 1, the patient was suspected of having DiGeorge syndrome (DGS) at an age older than 2 years based on a combination of clinical features, including dysmorphic features, developmental delay, and signs of immunodeficiency (recurrent upper respiratory tract infections). In contrast, the patient in Case 2 was suspected of DGS at a younger age of 6 months, based on a combination of clinical features, including tetralogy of Fallot, recurrent hypocalcemia, developmental delay, and recurrent infections.

The most common type of congenital heart defect in DiGeorge syndrome are conotruncal defects (tetralogy of Fallot, truncus arteriosus, interrupted aortic arch type, conoventricular and/or atrial septal defects, and aortic arch anomalies [21]. It is important to note that the proportion of tetralogy of Fallot in the cohort of DGS in the Asian population seems to be higher (56-72%) than in Western countries (13-43%) [20, 22-25]. It is also noteworthy that the presence of a congenital heart defect cannot be entirely excluded in the patient of Case 1 because she underwent echocardiography when she was 2 years and 1 month old, the time when a small congenital heart defect (such as a small ASD) may have closed spontaneously.

Both patients in the presented cases had a history of seizures. Méndez-Rosado et al found that a history of recurrent seizure was present in 15% of cohorts of DGS from diverse populations [19]. The most common type of seizure associated with DiGeorge syndrome is acute symptomatic seizures related to hypocalcemia due to hypoparathyroidism (71.8%) [15], while between 4.4%-36.8% have repeated unprovoked seizures (epilepsy) [15, 16, 26-28]. Characteristics of seizures associated with acute hypocalcemia are generalized tonic, generalized tonic-clonic, and focal seizures [29]. Among patients with DGS with epilepsy, the most common types include: genetic generalized epilepsy, focal seizures of unknown etiology, epilepsy due to malformation of cortical development, and epilepsy due to acquired structural changes [15].

The patient in Case 1 experienced a generalized tonic seizure. Her calcium level was normal at the age of 2 years old, and the EEG result showed no signs of slow wave or epileptic wave. This contrasts with the typical EEG abnormalities associated with hypocalcemia, which include slowing background rhythm with evolution from alpha through theta and diffuse increase in slow wave activity in the theta and delta range [30]. These findings suggest that the patient most likely has

genetic generalized epilepsy [16]. However, the possibility of transient hypocalcemia during the patient's seizure episode at 6 months of age cannot be definitively excluded, as the calcium level was not checked at that time. Hypocalcemia due to hypoparathyroidism can happen at a later onset in DGS patients. Therefore, further evaluation of parathyroid hormone levels and the parathyroid glands, along with routine monitoring of calcium levels, is essential.

The patient in Case 2 experienced recurrent generalized tonic seizures due to hypocalcemia during the neonatal period. At the age of 11 months old, she experienced generalized clonic seizures. Notably her calcium level was within normal range at this time. This observation suggests that, in addition to seizures due to hypocalcemia, the patient may also have genetic generalized epilepsy. Fever, recurrent episodes of infections, and structural brain anomalies may predispose to 22q11-associated epilepsy [31]. The patient's EEG findings were consistent with hypocalcemia-related seizures and generalized epilepsy [16, 30, 32].

Hypocalcemia can occur transiently in the neonatal period with seizure symptoms, mainly due to low parathyroid levels and abrupt cessation of maternal calcium supply after birth [33]. However, in Case 2, the patient's level of parathyroid hormone checked at 2 months of age exhibited normal results. This may suggest that the cause of neonatal hypocalcemia in this patient was vitamin D deficiency [34]. A comprehensive assessment of the underlying cause of hypocalcemia, including evaluation of parathyroid glands and vitamin D levels, is important, as it will guide the appropriate management of hypocalcemia. Hypocalcemia in DGS may improve over the first year of life as the parathyroid glands become hypertrophic [33]. This may account for the normal calcium levels observed when the patient was 11 months of age, despite the discontinuation of calcium supplementation at 5 months. However, hypoparathyroidism and subsequent hypocalcemia can recur during periods of increased metabolic demand and acute illness [33]. This is evidenced by the episode of recurrent seizure episodes precipitated by infections (high fever, diarrhea, and bronchopneumonia) when the patient was 1 year and 5 months old.

Both patients exhibited similar craniofacial dysmorphisms, including down-slanting palpebral fissure, small down-turned mouth, bulbous nose, and low-set ears. Additionally, the patient in Case 2 presented with other dysmorphic features, such as a high-arched palate and overfolded toes. According to McDonald-McGinn et al., there is no single facial phenotype that is pathognomonic for DGS; certain facial characteristics may become more evident with age, and ethnicity may influence the facial manifestations of the syndrome [35]. The most frequent craniofacial dysmorphisms in DGS patients are hypertelorism, down-slanting palpebral fissures, tubular nose or bulbous nose tip, short philtrum, small downturned mouth, cleft and or high arched palate, micrognathia, and low-set ears [6, 33, 36, 37]. Other dysmorphic features associated with DGS are tapering fingers and overfolded toes [38, 39]. Prominent nasal roots, hooded eyelids, and narrow palpebral fissures are common in Asians [40].

Hypothyroidism was also observed in both cases. A study of clinical characteristics of 22q11.2 deletion syndrome in Northern Thailand found that 17.6% of their cohort also experienced hypothyroidism [20]. Another study, also conducted in Northern Thailand found that hypothyroidism was observed in 30% of the cohort [22]. Although hypothyroidism is not pathognomonic for DiGeorge syndrome, and it does not guide the clinical suspicion of DGS, clinicians need to consider the evaluation of thyroid function in all DGS patients because of its relatively high incidence, particularly in the Asian population.

Besides some similarities, the presented cases also highlighted the clinical variability of DGS. The clinical variability observed in both cases includes the presence of congenital heart defects, the degree of recurrent infections, and the presence of hypocalcemia. High clinical variability and subtle clinical characteristics have led to the later onset of diagnosis of DGS. Oskarsdottir et al reported that the frequency of delayed diagnosis of DGS was 26% in the neonatal period, 17% in children aged 2-5 years old, 41% in children aged 6-12 years old, and 16% in adolescence (13-16 years old) [41]. Fomin et al. reported that only 28.5% of DGS patients are diagnosed younger than 4 years old [42].

A congenital heart defect is the most common instigating factor for clinical suspicion and diagnostic evaluation for DGS and thus is associated with earlier diagnosis [43]. This is exemplified by the early clinical suspicion of DGS for the patient in Case 2 (around 6 months old of age) compared to the patient in Case 2 and a case report from Taiwan (>2 years old) [33].

Immune system disorders in patients with 22q11.2DS are highly variable [44]. Immunodeficiency in children with DGS is mainly associated with thymus hypoplasia/aplasia, which affects the T cell count [45]. Laboratory facilities to assess immunological parameters (T cell immunity, immunoglobulin levels, and flow cytometry) were unavailable at our center. However, immunodeficiency can be indirectly inferred from the history of recurrent infections documented in both patients. Clinically, the patient in Case 1 exhibited a milder degree of immunodeficiency, i.e., recurrent upper respiratory infection and no adverse reaction even to live vaccines. The patient in Case 2 exhibited more remarkable signs of infections including chronic suppurative otitis media and a history of recurrent admission to the NICU due to the complication of infections. Imaging modalities to assess the size of the thymus gland may serve as an alternative approach to confirm immunodeficiency and support the diagnosis of DiGeorge syndrome. The thymus gland is often challenging to differentiate from the cardiac silhouette on frontal chest radiographs in young children [46]. Other imaging modalities may be more effective in evaluating the size and structure of the thymus gland, including ultrasound, CT scan, or MRI [46]. Recurrent infections in patients with DiGeorge syndrome (DGS) are not always associated with identifiable immune defects. This highlights the importance of other non-immunological factors that increase the risk of infections in DGS patients, such as heart defects and cleft palate [44]. In summary, evaluation of T cell immunity, the thymus gland, and other non-immunologic risk factors are important to determine the cause and subsequent appropriate management for recurrent infection in DGS patients.

Phenotypic variability observed in individuals with DiGeorge syndrome is not attributed to the size of the deletion but is primarily due to the specific genes involved [47]. It is also influenced by incomplete penetrance and variable expressivity [48]. In approximately 90% of patients with DGS, the deletion size is 3 Mb (encompasses over 40 genes), whereas the remaining range from 1.5 (encompasses 30 genes) to 2.5 Mb [49, 50].

DGS patients exhibit various deletion types and sizes in chromosome 22, classified as low-copy number repeat sequences (LCR22 [48]. Most individuals with DGS have LCR A-D, approximately 5% have LCR A-B, 2% have a deletion extending from LCR A-C, and 5% have a smaller atypical heterozygous deletion extending from LCR B-D or C-D [49]. Exact chromosomal locations of the different LCR22s in hg19 are as such: LCR22-A (chr22: 18,639,043-19,022,986); LCR22-B (chr22:20,128,537-20,731,921); LCR22-C: (chr22:21,021,564-21,092,560); and LCR22-D (chr22:21,363,668-21,916,380) [51]. The patient in case 1 has a heterozygous deletion that extends from LCR A-C, while the patient in case 2 exhibits a heterozygous deletion that extends from LCR A-

D. Table 1 and Figure 9 depict the deleted genes and the corresponding involved LCR region in the patients of Case 1 and Case 2 [48, 52].

Table 1 Genes involved in the microdeletion of 22q11.2 locus in Case 1 and Case 2.

Case 1	**Case 2**
DGCR6	*DGCR6*
PRODH	*PRODH*
DGCR5	*DGCR5*
DGCR2	*DGCR2*
ESS2	*ESS2*
TSSK2	*TSSK2*
CTCL1	*CTCL1*
GSC2	*GSC2*
SLC25A1	*SLC25A1*
HIRA	*HIRA*
MRPL40	*MRPL40*
UFD1	*UFD1*
CDC45	*CDC45*
CLDN5	*CLDN5*
SEPTIN5	*SEPTIN5*
GP1BB	*GP1BB*
TBX1	*TBX1*
GNB1L	*GNB1L*
RTL10	*RTL10*
TXNRD2	*TXNRD2*
COMT	*COMT*
ARVCF	*ARVCF*
TANGO2	*TANGO2*
MIR185	*MIR185*
DGCR8	*DGCR8*
TRMT2A	*TRMT2A*
RANBP1	*RANBP1*
ZDHHC8	*ZDHHC8*
RTN4R	*RTN4R*
DGCR6L	*DGCR6L*
GGTLC3	*GGTLC3*
RIMBP3	*RIMBP3*
ZNF74	*ZNF74*
SCARF2	*SCARF2*
KLH22	*KLH22*
MED15	*MED15*
	PI4KA
	SERPIND1

SNAP29
CRKL
AIFM3
LZTR1
THAP7
P2RX6
SLC7A4

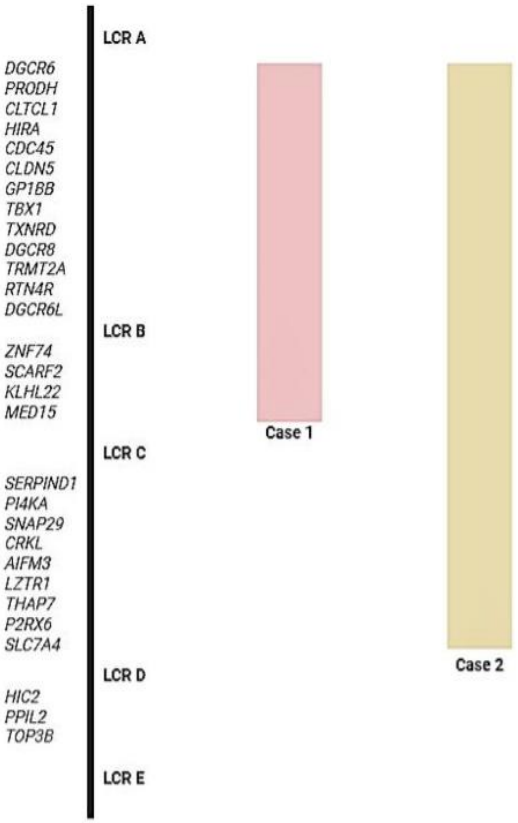

Figure 9 LCR involvement of the patients in Case 1 (LCR A-C) and Case 2 (LCR A-D).

LCR A-B was considered the critical region for phenotypes of DGS [49]. *TBX1*, located in the LCR A-B interval, is essential to 22q11DS cardiac, craniofacial, and otic phenotypes [53]. Other genes in this region that are considered potential contributors to heart anomalies in DGS include *PRODH, DGCR6, and DGCR8* [54, 55]. *TBX1* also correlates with neuromicrovascular anomalies, which may be responsible for the development delay seen in both patients [7].

The patient in Case 2 presented with conotruncal cardiac defect (tetralogy of Fallot), primarily due to the heterozygous LCR A-D deletion involving the *CRKL* gene, which is the main factor in conotruncal heart defects [56]. Immunodeficiency correlated with haploinsufficiency of LCR A-B [57]. The growth delay observed only in the patient of case 2 is likely due to the heterozygous deletion

that extends from LCR A-D. This observation concurs with a study by Gavril, et al., which found patients with deletion from LCR B-D exhibit growth delay [48].

Early clinical diagnosis of DGS can be made using European Society for Immunodeficiencies (ESID) criteria, particularly in settings where confirmatory genetic testing is limited [58]. A detailed clinical comparison based on ESID criteria between case 1 and case 2 compared to case reports of DGS from other Asian countries as described in Table 2. The patients in Case 1 and Case 2, along with those described in case reports from Malaysia, Iran, and South Korea did not meet the definitive clinical diagnostic criteria for DGS according to ESID, as the CD3+ T cell level was not assessed [58]. Only two case reports (Taiwan and Bangladesh) fulfilled the criteria for probable and definitive diagnosis of DGS according to ESID. However, all patients reported were confirmed to have 22q11.2 deletion syndrome by genetic testing. "DiGeorge syndrome" and "22q11.2 deletion syndrome" are often interchangeable. However, 22q11.2 deletion syndrome represents a broader category, encompassing the spectrum of associated syndromes, including DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome [4]. These syndromes often exhibited overlapping clinical features, making it challenging to distinguish them from one another. The term "DiGeorge syndrome" is now applied to those patients who present with clinical phenotypes consistent with 22q11.2 deletion syndrome in the absence of confirmatory genetic testing [52].

Table 2 ESID criteria fulfillment for DGS (22q11.2DS) between the presented cases and case reports from other Asian countries.

	ESID Criteria	**Case 1**	**Case 2**	**Malaysia [34]**	**Iran [59]**	**Taiwan [33]**	**South Korea [60]**	**Bangladesh [61]**
1.	Reduced CD3+T cells (less than 500-1500/mm^3) during the first three years of life	N/A	N/A	N/A	N/A	<1500/mm^3	N/A	<500/mm^3
2.	Conotruncal cardiac defect/cardiac defect	-	+	+	+	-	-	-
3.	Hypocalcemia	-	+	+	+	+	+	+
4.	Evidence of chromosome 22q11 deletion	+	+	+	+	+	+	+
5.	Dysmorphic facies or palatal abnormalities							
	Hypertelorism	-	+	-	-*	+	-	-
	Down-slanting palpebral fissure	+	+	-	-*	-	-	-

Short palpebral fissure	-	-	-	-*	-	-	-
Short philtrum	-	-	-	-*	+	-	-
Bulbous nose	+	+	-	-*	+	-	-
Micrognathia	-	-	-	-*	+	-	+
Small narrow mouth	+	+	-	-*	-	-	-
Low-set ears	+	+	-	-*	+	-	+
Cleft palate	-	-	-	-*	-	+	-
High-arched palate	-	+	-	-*	-	-	-
Asymmetric crying face	-	-	-	-*	-	-	+
Bifid uvula	-	-	-	-*	+	-	-
Diagnosis based on ESID criteria	**N/A**	**N/A**	**N/A**	**N/A**	**Probable DGS**	**N/A**	**Definitive DGS**

*Not described/reported.

Early diagnosis of DGS is important for early surveillance, treatment of associated conditions, and appropriate genetic counseling for the parents. One of the benefits of early diagnosis is that it will provide valuable insights into the global cognitive development specific to DGS patients. This information is essential for planning appropriate interventions, revising individualized educational plans, and ensuring ongoing neurodevelopmental follow-up [62].

Recognizing DGS early is also important for the evaluation of immune function and the subsequent management related to it, including early implementation of antibiotic prophylaxis, immunoglobulin replacement, and guiding the decision of live vaccine administration in children [43]. Evaluation of T cell function, particularly CD3+ T cells, is important to guide the immunization decision in children with DGS. Live vaccines are contraindicated in patients with CD3+ T cell counts <500 cells/mm^3, meanwhile some live vaccines can be administered to DGS patients with adequate T cell counts (≥500 and ≥200 CD3 and CD8 T cells/mm^3, respectively) with close monitoring of adverse reaction [63]. By 2 years old, the patient in Case 1 has received all basic vaccinations included in the national immunization program, including live vaccines. This occurred before clinical suspicion of DiGeorge syndrome (DGS) was raised by the clinicians. Notably, she did not experience any serious adverse reactions to immunization, which may indicate a mild degree of immunodeficiency. This observation is similar to a case report from Taiwan [33]. In contrast, for the patient in Case 2, because the clinical suspicion of DGS had been raised since she was 6 months old and the unavailability of the T-cell immunity laboratory tests at our center, the pediatrician opted to postpone the administration of live vaccines for this patient.

Another reason why it is important for early diagnosis of DGS is that DGS constitutes a three-fold increased risk for psychiatric diseases such as schizophrenia, attention deficit hyperactivity disorder, and anxiety disorder [1, 64]. Hoeffding, et al reported in their study, that the mean age at diagnosis for a psychiatric disorder was 12.4 years for individuals with DGS [64]. Early diagnosis of DGS enhances clinicians' awareness of psychiatric problems associated with it, enabling earlier routine follow-up for the detection of potential psychiatric disorders in DGS patients.

4. Conclusion

These two case reports provide valuable insight to healthcare practitioners, particularly in understanding the phenotype variability of DGS, and identify key clinical clues that can help them raise clinical suspicion for DGS, particularly for the Indonesian pediatric population. Due to the large phenotypic variability in DGS, early diagnosis requires a high degree of clinical suspicion. Clinicians can raise suspicion for DGS in the presence of congenital heart defects, recurrent infections, hypocalcemia, dysmorphic features, and developmental delay in children. The clinical criteria for diagnosing DGS (22q11.2 deletion syndrome) developed by ESID can help guide clinicians in diagnosing DGS, especially in developing country settings where genetic testing is still limited. Early diagnosis of DGS is important for early surveillance and treatment of associated conditions and appropriate genetic counseling for the parents. Further noteworthy aspect of these two case reports is that the phenotypic manifestation does not correlate with the size of the deletion, but is primarily associated with the gene involved in the microdeletion. Because the clinical phenotype of DGS can vary across populations, it would be beneficial for future studies to investigate a more comprehensive genotype-phenotype correlation in DiGeorge syndrome, especially in Indonesia and other Southeast Asian populations.

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Author Contributions

Joni Indah Sari wrote the initial draft of the case report; Nydia Rena Benita Sihombing collected and coordinated the figures; Nani Maharani and Tri Indah Winarni coordinated the writing; Agustini Utari did the clinical examinations and genetic counseling. Agustini Utari also coordinated the writing and finalized the report. All authors contributed to the revision of the draft and approved the final draft.

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Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

A list of genes involved in the deletion of patient case 1 and case 2 (Table 2) is available on the Human GRCh37/hg19 database on the UCSC Human Genome Browser website. Associated genes can be seen in link Case 1 and Case 2 respectively.

References

1. Kraus C, Vanicek T, Weidenauer A, Khanaqa T, Stamenkovic M, Lanzenberger R, et al. DiGeorge syndrome: Relevance of psychiatric symptoms in undiagnosed adult patients. Wien Klin Wochenschr. 2018; 130: 283-287.
2. Scambler PJ. The 22q11 deletion syndromes. Hum Mol Genet. 2000; 9: 2421-2426.
3. Jonas RK, Montojo CA, Bearden CE. The 22q11.2 Deletion syndrome as a window into complex neuropsychiatric disorders over the lifespan. Biol Psychiatry. 2014; 75: 351-360.
4. McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JA, et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers. 2015; 1: 15071.
5. Cortés-Martín J, Peñuela NL, Sánchez-García JC, Montiel-Troya M, Díaz-Rodríguez L, Rodríguez-Blanque R. Deletion syndrome 22q11.2: A systematic review. Children. 2022; 9: 1168.
6. Lackey A, Muzio M. DiGeorge syndrome. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2024 [cited date 2024 May 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549798/.
7. Cioffi S, Martucciello S, Fulcoli FG, Bilio M, Ferrentino R, Nusco E, et al. Tbx1 regulates brain vascularization. Hum Mol Genet. 2014; 23: 78-89.
8. Paylor R, Glaser B, Mupo A, Ataliotis P, Spencer C, Sobotka A, et al. Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: Implications for 22q11 deletion syndrome. Proc Natl Acad Sci U S A. 2006; 103: 7729-7734.
9. Baylis AL, Shriberg LD. Estimates of the prevalence of speech and motor speech disorders in youth with 22q11.2 deletion syndrome. Am J Speech Lang Pathol. 2019; 28: 53-82.
10. Soubry E, David K, Swillen A, Vergaelen E, Docx Op de Beeck M, Hulsmans M, et al. Endocrine manifestations in adults with 22q11.2 deletion syndrome: A retrospective single-center cohort study. J Endocrinol Invest. 2024; 47: 1827-1836.
11. Cheung EN, George SR, Costain GA, Andrade DM, Chow EW, Silversides CK, et al. Prevalence of hypocalcaemia and its associated features in 22q11·2 deletion syndrome. Clin Endocrinol. 2014; 81: 190-196.
12. Stagi S, Lapi E, Gambineri E, Salti R, Genuardi M, Colarusso G, et al. Thyroid function and morphology in subjects with microdeletion of chromosome 22q11 (del(22)(q11)). Clin Endocrinol. 2010; 72: 839-844.
13. Dyce O, McDonald-McGinn D, Kirschner RE, Zackai E, Young K, Jacobs IN. Otolaryngologic Manifestations of the 22q11.2 Deletion Syndrome. Arch Otolaryngol Head Neck Surg. 2002; 128: 1408.
14. Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, et al. Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: A European collaborative study. J Med Genet. 1997; 34: 798-804.

15. Wither RG, Borlot F, MacDonald A, Butcher NJ, Chow EW, Bassett AS, et al. 22q11.2 deletion syndrome lowers seizure threshold in adult patients without epilepsy. Epilepsia. 2017; 58: 1095-1101.
16. Strehlow V, Swinkels ME, Thomas RH, Rapps N, Syrbe S, Dorn T, et al. Generalized epilepsy and myoclonic seizures in 22q11.2 deletion syndrome. Mol Syndromol. 2016; 7: 239-246.
17. Boot E, Óskarsdóttir S, Loo JC, Crowley TB, Orchanian-Cheff A, Andrade DM, et al. Updated clinical practice recommendations for managing adults with 22q11.2 deletion syndrome. Genet Med. 2023; 25: 100344.
18. Tokutomi T, Fukushima A, Yamamoto K, Bansho Y, Hachiya T, Shimizu A. f-treeGC: A questionnaire-based family tree-creation software for genetic counseling and genome cohort studies. BMC Med Genet. 2017; 18: 71.
19. Méndez-Rosado LA, de León-Ojeda N, García A, Sheth F, Gaadi A, Bousfiha AA, et al. Clinical characterization of 72 patients with del(22)(q11.2q11.2) from different ethnic backgrounds. Egypt J Med Hum Genet. 2022; 23: 158.
20. Ua-areechit T, Varnado P, Tengsujaritkul M, Louthrenoo O, Pongprot Y, Lao-araya M. Clinical characteristics and immunological status of patients with 22q11.2 deletion syndrome in Northern Thailand. Asian Pac J Allergy Immunol. 2023; 41: 89-95.
21. Goldmuntz E. 22q11.2 deletion syndrome and congenital heart disease. Am J Med Genet C Semin Med Genet. 2020; 184: 64-72.
22. Wichajam K, Kampan J. Difference of clinical phenotypes and immunological features of 22q11.2 deletion syndrome in north-eastern Thai children compare to western countries. J Med Assoc Thai. 2014; 97: S59-S66.
23. Park IS, Ko JK, Kim YH, Yoo HW, Seo EJ, Choi JY, et al. Cardiovascular anomalies in patients with chromosome 22q11.2 deletion: A Korean multicenter study. Int J Cardiol. 2007; 114: 230-235.
24. Peyvandi S, Lupo PJ, Garbarini J, Woyciechowski S, Edman S, Emanuel BS, et al. 22q11.2 deletions in patients with conotruncal defects: Data from 1,610 consecutive cases. Pediatr Cardiol. 2013; 34: 1687-1694.
25. Botto LD, May K, Fernhoff PM, Correa A, Coleman K, Rasmussen SA, et al. A population-based study of the 22q11.2 deletion: Phenotype, incidence, and contribution to major birth defects in the population. Pediatrics. 2003; 112: 101-107.
26. Andrade DM, Krings T, Chow EW, Kiehl TR, Bassett AS. Hippocampal malrotation is associated with chromosome 22q11.2 microdeletion. Can J Neurol Sci. 2013; 40: 652-656.
27. Kim EH, Yum MS, Lee BH, Kim HW, Lee HJ, Kim GH, et al. Epilepsy and other neuropsychiatric manifestations in children and adolescents with 22q11.2 deletion syndrome. J Clin Neurol. 2016; 12: 85.
28. Olsen L, Sparsø T, Weinsheimer SM, Dos Santos MB, Mazin W, Rosengren A, et al. Prevalence of rearrangements in the 22q11.2 region and population-based risk of neuropsychiatric and developmental disorders in a Danish population: A case-cohort study. Lancet Psychiatry. 2018; 5: 573-580.
29. Riggs JE. Neurologic manifestations of electrolyte disturbances. Neurol Clin. 2002; 20: 227-239.
30. Nardone R, Brigo F, Trinka E. Acute symptomatic seizures caused by electrolyte disturbances. J Clin Neurol. 2016; 12: 21.

31. Kao A, Mariani J, McDonald-McGinn DM, Maisenbacher MK, Brooks-Kayal AR, Zackai EH, et al. Increased prevalence of unprovoked seizures in patients with a 22q11.2 deletion. Am J Med Genet A. 2004; 129: 29-34.
32. Kaplan PW. The EEG in metabolic encephalopathy and coma. J Clin Neurophysiol. 2004; 21: 307-318.
33. Fu CH, Leung C, Kao CH, Yeh SJ. Noncardiac DiGeorge syndrome diagnosed with multiplex ligation-dependent probe amplification: A case report. J Formos Med Assoc. 2015; 114: 769-773.
34. Sithra R, Sheila GK, Safwan N, Siah WP, Fadilah WI, Zurina Z. Early-onset neonatal hypocalcaemia secondary to maternal vitamin D deficiency in an infant with DiGeorge syndrome: A first case report in Malaysia. Med J Malaysia. 2022; 77: 271-273.
35. McDonald-McGinn DM, Minugh-Purvis N, Kirschner RE, Jawad A, Tonnesen MK, Catanzaro JR, et al. The 22q11.2 deletion in African-American patients: An underdiagnosed population? Am J Med Genet A. 2005; 134: 242-246.
36. Salehzadeh F, Bagheri A. Association of juvenile idiopathic arthritis and DiGeorge syndrome; a case report. Iran J Pediatr. 2014; 24: 334-336.
37. Candelo E, Estrada-Mesa MA, Jaramillo A, Martinez-Cajas CH, Osorio JC, Pachajoa H. The oral health of patients with DiGeorge syndrome (22q11) microdeletion: A case report. Appl Clin Genet. 2021; 14: 267-277.
38. Digilio M, Marino B, Capolino R, Dallapiccola B. Clinical manifestations of Deletion 22q11.2 syndrome (DiGeorge/Velo-Cardio-Facial syndrome). Images Paediatr Cardiol. 2005; 7: 23-34.
39. Rehman A, Dhamija R, Barrett M. 22q11.2 deletion syndrome presenting as Parkinson disease (P2.144). Neurology. 2015; 84: P2.144.
40. Kruszka P, Addissie YA, McGinn DE, Porras AR, Biggs E, Share M, et al. 22q11.2 deletion syndrome in diverse populations. Am J Med Genet A. 2017; 173: 879-888.
41. Oskarsdottir S. Incidence and prevalence of the 22q11 deletion syndrome: A population-based study in Western Sweden. Arch Dis Child. 2004; 89: 148-151.
42. Fomin AB, Pastorino AC, Kim CA, Pereira AC, Carneiro-Sampaio M, Abe Jacob CM. DiGeorge syndrome: A not so rare disease. Clinics. 2010; 65: 865-869.
43. Biggs SE, Gilchrist B, May KR. Chromosome 22q11.2 Deletion (DiGeorge Syndrome): Immunologic features, diagnosis, and management. Curr Allergy Asthma Rep. 2023; 23: 213-222.
44. Boyarchuk O, Volyanska L, Dmytrash L. Clinical variability of chromosome 22q11.2 deletion syndrome. Cent Eur J Immunol. 2017; 42: 412-417.
45. Kobrynski LJ, Sullivan KE. Velocardiofacial syndrome, DiGeorge syndrome: The chromosome 22q11.2 deletion syndromes. Lancet. 2007; 370: 1443-1452.
46. Manchanda S, Bhalla AS, Jana M, Gupta AK. Imaging of the pediatric thymus: Clinicoradiologic approach. World J Clin Pediatr. 2017; 6: 10.
47. Rozas MF, Benavides F, León L, Repetto GM. Association between phenotype and deletion size in 22q11.2 microdeletion syndrome: Systematic review and meta-analysis. Orphanet J Rare Dis. 2019; 14: 195.
48. Gavril EC, Popescu R, Nucă I, Ciobanu CG, Butnariu LI, Rusu C, et al. Different types of deletions created by low-copy repeats sequences location in 22q11.2 deletion syndrome: Genotype–phenotype correlation. Genes. 2022; 13: 2083.

49. Adeyinka A, Stockero KJ, Flynn HC, Lorentz CP, Ketterling RP, Jalal SM. Familial 22q11.2 deletions in DiGeorge/velocardiofacial syndrome are predominantly smaller than the commonly observed 3 Mb. Genet Med. 2004; 6: 517-520.
50. Gao S, Li X, Amendt BA. Understanding the role of Tbx1 as a candidate gene for 22q11.2 deletion syndrome. Curr Allergy Asthma Rep. 2013; 13: 613-621.
51. Vervoort L, Vermeesch JR. The 22q11.2 low copy repeats. Genes. 2022; 13: 2101.
52. Cillo F, Coppola E, Habetswallner F, Cecere F, Pignata L, Toriello E, et al. Understanding the variability of 22q11.2 deletion syndrome: The role of epigenetic factors. Genes. 2024; 15: 321.
53. Motahari Z, Moody SA, Maynard TM, LaMantia AS. In the line-up: Deleted genes associated with DiGeorge/22q11.2 deletion syndrome: Are they all suspects? J Neurodev Disord. 2019; 11: 7.
54. Carli D, Moroni A, Eleonora DG, Zonta A, Montin D, Licciardi F, et al. Atypical microdeletion 22q11.2 in a patient with tetralogy of Fallot. J Genet. 2021; 100: 5.
55. Gao W, Higaki T, Eguchi-Ishimae M, Iwabuki H, Wu Z, Yamamoto E, et al. DGCR6 at the proximal part of the DiGeorge critical region is involved in conotruncal heart defects. Hum Genome Var. 2015; 2: 15004.
56. Zhao Y, Diacou A, Johnston HR, Musfee FI, McDonald-McGinn DM, McGinn D, et al. Complete sequence of the 22q11.2 allele in 1,053 subjects with 22q11.2 deletion syndrome reveals modifiers of conotruncal heart defects. Am J Hum Genet. 2020; 106: 26-40.
57. Crowley B, Ruffner M, McDonald McGinn DM, Sullivan KE. Variable immune deficiency related to deletion size in chromosome 22q11.2 deletion syndrome. Am J Med Genet A. 2018; 176: 2082-2086.
58. European Society for Immunodeficiencies. DiGeorge syndrome diagnostic criteria [Internet]. ESID; 2024 [cited date 2024 May 4]. Available from: https://esid.org/diagnostic-criteria-pid/.
59. Asl SN, Masjedi HK, Sanati AR. DiGeorge syndrome presenting with seizures: A case report. J Neurol Res. 2017; 7: 94-96.
60. Kim G, Moon E, Park JM, Lee BD, Lee YM, Jeong HJ, et al. Various psychiatric manifestation in DiGeorge syndrome (22q11.2 Deletion Syndrome): A case report. Clin Psychopharmacol Neurosci. 2020; 18: 458-462
61. Begum N, Mohzin F, Sufian A, Islam N, Nahar J, Mollah M. DiGeorge syndrome presenting with seizure in neonatal period: A case report. Birdem Med J. 2021; 11: 128-132.
62. Swillen A, Moss E, Duijff S. Neurodevelopmental outcome in 22q11.2 deletion syndrome and management. Am J Med Genet A. 2018; 176: 2160-2166.
63. Lim SM, Shin JH, Baek JY, Lee JY, Kang JM, Ahn JG. Safety of Live Immunization in DiGeorge Syndrome: A Retrospective Single-Center Study in Korea, 2005–2021. Vaccines. 2022; 10: 2165.
64. Hoeffding LK, Trabjerg BB, Olsen L, Mazin W, Sparsø T, Vangkilde A, et al. Risk of psychiatric disorders among individuals with the 22q11.2 deletion or duplication. JAMA Psychiatry. 2017; 74: 282.