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RESEARCH REVIEW

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The 22q11.2 deletion syndrome: Cancer predisposition, platelet abnormalities and cytopenias

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The 22q11.2 deletion syndrome (DS) is associated with variable phenotypic expression as findings range from severely affected individuals with the classical triad of DiGeorge and velocardiofacial syndromes, including congenital heart disease, immunodeficiency, hypocalcemia, and palatal abnormalities, to subtly affected adults who only come to attention following the diagnosis of a more severely affected child. The multiple manifestations can affect all organ systems, including the hematologic system resulting in baseline lower platelet counts for individuals with 22q11.2DS and increased platelet size. In addition, there may be an associated increased risk of bleeding. Individuals with 22q11.2DS are also at increased risk of autoimmune cytopenias that can complicate the evaluation or management of other manifestations. Finally, there may be an increased risk of malignancy, although the mechanism for this risk is not fully understood. This review summarizes the currently available data on hematologic/oncologic manifestations of 22q11.2DS and reports on our findings within a large cohort of individuals with the deletion.

1 | INTRODUCTION

The 22q11.2 Deletion Syndrome (22q11.2DS) is the most frequent chromosomal microdeletion syndrome with prevalence estimated to be between one per 3,000–6,000 live births and one per 1,000 unselected fetuses (Botto et al., 2003; Grati et al., 2015; Tezenas Du Montcel et al., 1996). The majority of newly identified patients have de novo deletions, and most patients have the classical LCR22A-LCR22D deletion (McDonald-McGinn et al., 2015). Hypernasal speech due to palatal abnormalities, congenital cardiac defects, nasopharyngeal reflux, hypocalcemia, feeding difficulties, developmental and language delays, short stature, skeletal differences, renal abnormalities, and thyroid function abnormalities, may all be seen in children with the deletion. Immunodeficiency is common, affecting up to 75% of children with 22q11.2DS (Jyonouchi et al., 2009; Lawrence, McDonald-McGinn, Zackai, & Sullivan, 2003), and may predispose to the development of autoimmune cytopenias, including Immune thrombocytopenia (ITP) (Lawrence et al., 2003), autoimmune hemolytic anemia (AIHA) (Kratz et al., 2003), and Evans syndrome (Kratz et al., 2003). Some reports have suggested lower baseline platelet counts in patients with 22q11.2DS (Lawrence et al., 2003) and there are reports of associated Bernard Soulier Syndrome (BSS), a severe platelet disorder caused by abnormal expression of the GP1b-IX-V complex on platelets (Budarf et al., 1995). Platelet abnormalities, and even bleeding predisposition, would be anticipated given the involvement of the critical platelet gene *GPIBB* by the classical deletion (McDonald-McGinn et al., 2015). However, increased risk of bleeding (in general) has not been reported for the majority of patients with 22q11.2DS except for one recent report of increased transfusion needs in the setting of cardiac surgery (Brenner et al., 2016), and one report of cerebral microbleeds in an individual with 22q11.2DS (Bonati et al., 2016). There are also reports of dysplastic changes in peripheral blood (Ozbek, Derbent, Olcay, Yilmaz, & Tokel, 2004) and malignancy in several individuals with 22q11.2DS, including atypical teratoid/rhabdoid tumors, lymphoma, neuroblastoma, acute lymphoblastic leukemia, osteosarcoma, Wilms tumor, thyroid carcinoma, and

hepatoblastoma (Bosse et al., 2014; Chakrapani et al., 2012; Finch, Pivnick, Furman, & Odom, 2011; Forest et al., 2012; Itoh, Ohno, Kakizaki, & Ichinohasama, 2011; McDonald-McGinn et al., 2006; Murray et al., 2011; Mussai et al., 2008; Pongpruttipan, Cook, Reyes-Mugica, Spahr, & Swerdlow, 2012). In this review, we summarize the current available data regarding the hematological/oncological manifestations of 22q11.2DS and describe our results with a large cohort of primarily pediatric patients with 22q11.2DS.

2 | METHODS

2.1 | Literature review

Review of the literature was performed for English language journals utilizing PubMed and EBSCO and the search terms: DiGeorge, 22q, hematology, bleeding, platelets, Evans syndrome, autoimmune cytopenia, ITP, and immune thrombocytopenia in various combinations. The resultant articles were then reviewed and additional references gleaned from those articles.

2.2 | Patients

After Institutional Review Board approval, patients with a confirmed 22q11.2 deletion by fluorescent in situ hybridization, multiplex ligation probe amplification, comparative genomic hybridization, or SNP microarray, evaluated in the 22q and You Center at the Children's Hospital of Philadelphia (CHOP) were enrolled in an ongoing registry organized to understand phenotype and genotype interactions in individuals with abnormalities of chromosome 22q11.2. After identification of the patients, information on platelet parameters (Mean Platelet Volume — MPV-, platelet count and if available, immature platelet fraction — IPF), age and hospitalization status was collected. Once obtained, only outpatient platelet parameters were used in determination of ranges. Descriptive statistics were used for analysis of data. The control population was the laboratory reference population obtained from routine outpatient evaluations. Data was collected retrospectively over 5 years. All of the platelet parameters were obtained from clinical samples run on a Sysmex XN system. Malignancy information was also collected through the registry when patients reported the malignancy to investigators or presented to the hospital for evaluation/treatment of the malignancy.

3 | RESULTS AND LITERATURE REVIEW

3.1 | Patient cohort

Five hundred and sixty four patients had complete blood count data available for at least one occasion that was not an inpatient visit. The control cohort consisted of 326 pediatric samples evaluated by the laboratory for validation of hematology assays and consisted of otherwise healthy children without significant underlying medical conditions who presented for routine well child care. There were 312 males (55.3%) in the 22q11.2DS cohort.

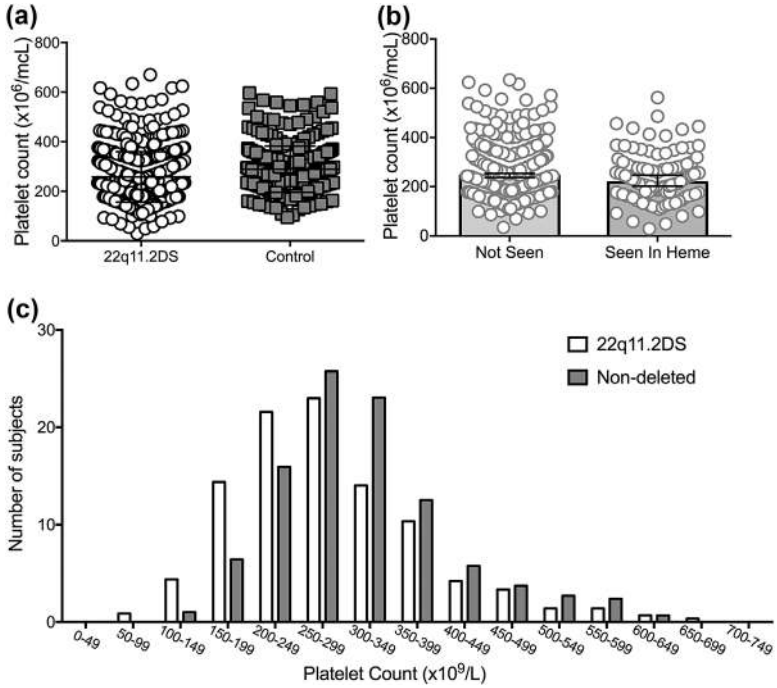

FIGURE 1 Platelet counts in individuals with 22q11.2DS versus control. (a) Platelet counts in the two cohorts of patients followed at CHOP. (b) same as (a) but displayed as a those patients seen in hematology clinic versus those who have not been evaluated by hematology. (c) same as (a) but a histogram of distribution of platelet counts demonstrating a clear skewing towards lower platelet counts in 22q11.2DS individuals relative to control population

3.2 | Hematologic manifestations

The frequency of thrombocytopenia in children with 22q11.2DS is postulated to occur as a result of the deletion of the *GPIBB* gene. The protein encoded for by this gene is GPIbβ, which is an integral part of the platelet receptor GPIb-IX-V, which bind to von Willebrand factor and allows for initial adhesion of platelets to damaged endothelium and for recruitment of additional platelets to sites of injury. Lack of GPIb-IX-V expression, or severe deficiency or dysfunction, leads to BSS, a rare, severe autosomal recessive bleeding disorder with macro-thrombocytopenia and significant mucosal bleeding characterized by abnormal platelet aggregation to ristocetin (Berndt & Andrews, 2011; Kunishima, Kamiya, & Saito, 2002). Individuals with BSS have a lifelong bleeding risk and generally present with bleeding manifestations early in life. The deletion of the *GPIBB* gene in 22q11.2DS has resulted in BSS in a few individuals (to date six patients have been reported) who have concomitantly inherited a hypomorphic or dysfunctional allele for *GPIBB* on the other chromosome (Budarf et al., 1995; Hillmann et al., 2002; Kunishima et al., 2013; Ludlow et al., 1996; Tang et al., 2004). However, decreased expression of GPIb-IX-V on platelet surfaces is associated with increased platelet size, decreased platelet number and, in some individuals, decreased function as demonstrated for families harboring variants responsible for BSS and Autosomal Dominant Macrothrombocytopenia (Bragadottir et al., 2015; Savoia et al., 2001, 2011). For this reason, one might expect that some individuals with 22q11.2DS would have a predisposition to bleeding. One report has examined the bleeding risk in children with the deletion (neonates), by examining transfusion requirement in surgery for congenital heart disease in deleted versus non-deleted individuals (Brenner et al., 2016). This study suggested an increased bleeding risk, as reflected in increased transfusion requirements, in individuals with the deletion. An additional report describes cerebral microbleeds in an individual with 22q11.2DS and *DGRC8* hemizygosity who had documented platelet dysfunction at the time of her presentation with loss of consciousness resulting in the discovery of the cerebral microbleeds (Bonati et al., 2016). Further study is required to better document and evaluate the underlying bleeding risk of individuals with the 22q11.2DS, and studies are ongoing at CHOP and other institutions to further investigate this risk. However, the presence of epistaxis is quite common in individuals with 22q11.2DS, perhaps exacerbated by velopharyngeal insufficiency and chronic nasal irritation. In a substudy of our 22q11.2DS cohort, 174 patients were evaluated separately by hematology and of these, 47/174 (27%) reported epistaxis. Most of these individuals did not have significant thrombocytopenia at the time of evaluation, and there was no difference in the platelet counts between those patients seen in hematology clinic versus those who were not (Figure 1b). The prevalence of epistaxis in the general population is difficult to estimate, but all of these individuals were referred because another practitioner felt the degree/duration/frequency of epistaxis was excessive.

Of the 564 individuals with 22q11.2DS evaluated at CHOP and assessed for hematologic manifestations, the mean platelet count was 257 ($\pm 102 \times 10^9$/L) and the mean platelet count in the control population was 289 ($\pm 93 \times 10^9$/L) ($p < 0.0001$) (Figure 1a) with a clear skewing of the distribution of platelet counts to lower numbers

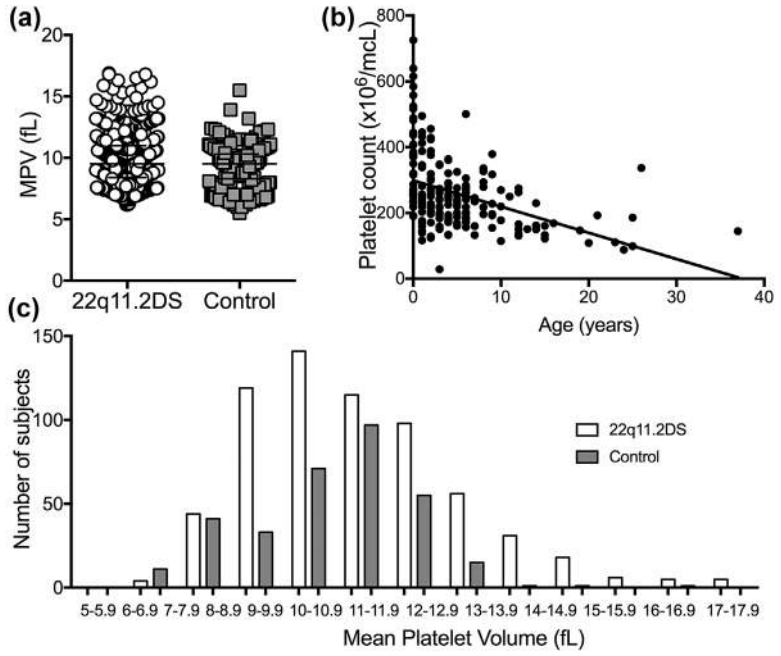

FIGURE 2 Mean platelet volume (MPV) in individuals with 22q11.2DS over time and versus control. (a) MPV in 22q11.2DS individuals versus control showing no difference in mean, but a difference in distribution with wider distribution in 22q11.2DS. (b) Comparison of platelet count versus age in 22q11.2DS showing that platelet count decreases with age. (c) same as (a) but histogram of the distribution showing a non-gaussian distribution of MPV in 22q11.2DS compared to controls with more individuals with both low and high MPV in individuals with 22q11.2DS

TABLE 1 Reported malignancies in 22q11.2DS

Pt.	Twin v. Singleton	Malignancy	Pathologic details	Gender and age at onset	Laboratory methodology	Other phenotypic features
1	Monozygotic twin	Invasive squamous carcinoma of the tongue	Squamous epithelium infiltrating fibrovascular stroma	M/29 years	FISH	Submucosal cleft palate; hypocalcaemia; chronic otitis media, hearing loss; clubfoot; idiopathic seizures; learning disability
2	Monozygotic twin	Papillary thyroid carcinoma	Diffuse sclerosing variant; multifocal; infiltrative	M/10 years	MLPA StandardA-D ^{Deletion}	VSD, coarctation of the aorta; low IgA, transient hypoglycemia, hypocalcemia; hearing loss; developmental and behavioral differences
3[a]	Monozygotic twin	Hepatoblastoma	Mixed type; left lobe of liver	M/3 months	MLPA StandardA-D ^{Deletion}	Myoclonic seizure disorder; hearing loss; developmental delay; anxiety
4	Dizygotic twin	Vulvar melanoma	Atypical melanocytic proliferation of the labia minora inferior; severely atypical junctional melanocytic proliferation of the labia superior	F/9 years	Microarray StandardA-D ^{Deletion}	VPI; low T-cells; GERD; hearing loss; developmental delay
5	Singleton	B lymphoblastic leukemia	High hyperdiploid with structural abnormality and subclonal deletion of CREBBP	M/18 years	FISH	IAA type B; submucousal cleft palate with bifid uvula and VPI; hypothyroid; juvenile rheumatoid arthritis, thrombocytopenia; LD
6[a]	Singleton	Acute Lymphoblastic Leukemia B-cell lineage	CD10+,CD19+, CD34+, DR+, TdT+, CALLA+	F/8 years	FISH	Submucousal cleft palate; single kidney; idiopathic seizures, hypotonia
7[a]	Singleton	Neuroblastoma	Celiac ganglion, stroma poor, undifferentiated	M/Congenital	FISH	Aortic atresia, ventricular septal defect; hypocalcemia

[a]Previously reported in McDonald-McGinn et al. (2006).

(Figure 1c). The MPV between the two groups was not statistically different, but there was a significant difference in the standard deviation between the two populations with the 22q11.2DS population having more individuals with both lower and higher MPV ($p < 0.007$ by Mann-Whitney test comparing the distributions, Figures 2a and 2c). Patients with the highest platelet count were young and platelet count decreased with age (Figure 2b). It is possible that this difference in MPV is related to the "acute phase reactant" nature of platelet counts, which can be elevated in the setting of infection/inflammatory response given that the frequency of infection in young children is higher than in older individuals. Further study is needed to better understand the underlying reasons for changes in platelet count/MPV over time in patients with 22q11.2DS. Previous studies suggest that thrombocytopenia is more common in 22q11.2DS even in the absence of obvious bleeding symptoms and/or immune thrombocytopenia (Lawrence et al., 2003). This thrombocytopenia is not related to development of idiopathic thrombocytopenia (ITP) and does not appear to be related to the underlying cardiac defect (Kato et al., 2003). Kato and colleagues examined the frequency of thrombocytopenia in children with 22q11.2DS and cardiac defects and compared the platelet counts and parameters to age and lesion matched non-deleted patients and found that there was an increased risk of thrombocytopenia in the deleted individuals (relative risk, RR, 1.9; confidence interval (CI), 1.24–2.93, $p < 0.05$). Naqvi et al. (2011) have suggested that evaluation of the MPV in children with cardiac defects can predict the presence of 22q11.2DS. They examined 166 individuals with congenital heart disease and found that 12% of their population had the 22q11.2 deletion. In that cohort, an MPV of >10 fL had a sensitivity of 80% and specificity of 89.7% with a negative predictive value of 97% (Naqvi et al., 2011). Another small study (34 patients) examined MPV and its correlation with immune dysfunction and conotruncal cardiac anomalies, demonstrating that the platelet abnormalities were independent of other findings (Latger-Cannard et al., 2004).

The other reported hematologic manifestations in children with 22q11.2DS are autoimmune cytopenias. The first report of ITP in association with AIHA was in 1990 by Shetty and colleagues in the form of an abstract. The deletion was diagnosed by chromosome analysis in this original report. Subsequently additional cases with both AIHA and ITP have been described, (Akar & Adekile, 2007; Davies, Telfer, Cavenagh, Foot, & Neat, 2003; DePiero et al., 1997) and at least one report describes these patients as having Evans syndrome (both AIHA and ITP) (Kratz et al., 2003). The incidence of ITP may be as much as 200 times higher in individuals with 22q11.2DS (Davies et al., 2003; Jawad, McDonald-Mcginn, Zackai E, & Sullivan, 2001), however, this may be inflated due to the high frequency of mildly low platelet counts in this population in general and the lack of specific diagnostic tests that can identify (definitively) ITP. Generally, reports suggest that the risk of recurrence of cytopenias is increased in patients with 22q11.2DS, although management is generally the same as for non-deleted individuals (Maggadottir & Sullivan, 2013). Individuals with recurrent autoimmune cytopenias should be investigated for the presence of a 22q11.2 deletion as this has important implications for

other potential complications and for the use of significant immunosuppression.

3.3 | Oncologic manifestations

Many case reports have discussed individuals with 22q11.2DS and malignancy, most prevalently (and recently), the association of atypical teratoid/rhabdoid tumor with *SMARCB1* variants and concurrent 22q11.22 distal deletions germline (Bosse et al., 2014; Chakrapani et al., 2012). We have identified seven cases of malignancy over the last 10 years in patients with typical 22q11.2 deletions, with an overall prevalence of malignancy of ~5.7 per 1,000 individuals (5.7%) in our cohort of individuals with 22q11.2DS. Four of seven were previously reported (Table 1) (McDonald-McGinn et al., 2006). Compared to SEER reported age-adjusted general population estimates (3.141%), the prevalence in our cohort appears to be increased compared to the population of patients that is not known to be deleted. We also examined whether there was an association between twins and malignancy in 22q11.2DS and found that of the seven patients with malignancy, four were part of a twin set, three as one of a monozygotic twin set and one from a dizygotic twin set. During this same period of time, CHOP followed a total of seven monozygotic twin sets and 21 individuals with 22q11.2DS that were part of a dizygotic twin pair. Thus, notably the prevalence of malignancy in our 22q11.2 DS cohort is 42.8% for monozygotic twins and 4.76% for dizygotic twins with an overall prevalence of 143/1000 (14.3%) in same-sex twins. Previous studies suggest that the prevalence of malignancy is greater than in singleton pregnancies and that for twins it is approximately 0.979% (Neale, Mineau, Whiteman, Brownbill, Murphy, 2005). Our data is limited by our ability to identify malignancy in individuals in our registry, especially if that diagnosis of malignancy is not made at our institution or is not reported to our investigators. Therefore, the prevalence of malignancy may actually be higher in our cohort.

Several genes within the deleted region may play a role in increased incidence of malignancy. Additionally, immunodeficiency (seen in up to 75% of infants with 22q11.2DS) (Kobrynski & Sullivan, 2007) may predispose to hematologic malignancy (lymphoma/leukemia) due to aberrant immune surveillance (the ability of the immune system to identify early cellular changes that can develop into malignancy). Other literature suggests that *COMT*, located within the deleted region and playing a role in detoxification of carcinogens may play a role (McDonald-McGinn et al., 2006). Atypical deletions downstream of the classical LCR22A-LCR22D deletion include the *SMARCB1* tumor suppressor gene known to play an important role in rhabdoid tumors (Bosse et al., 2014). Finally, *DGCR8*, located within the deleted region, haploinsufficiency leads to abnormal levels of miRNA, (Sellier et al., 2014) and abnormal miRNA levels may predispose to development of malignancy (Gregory & Shiekhattar, 2005). Further studies are needed to identify the mechanisms by which individuals with 22q11.2DS may have an increased risk of malignancy and to determine what the true incidence and prevalence is within this patient population. These data suggest that large, registry studies that enroll all individuals with 22q11.2DS regardless of the reason or age at diagnosis would be helpful in defining the full phenotype, especially given the variable cancer types reported in order to better define the issue and to begin to understand the mechanisms.

4 | SUMMARY/CONCLUSIONS

Hematologic/Oncologic manifestations in individuals with 22q11.2DS are frequent, most often consisting of baseline thrombocytopenia with increased MPV (macrothrombocytopenia). There is also an increased risk of autoimmune cytopenias, which tend to be recurrent, although management recommendations at this time do not recommend different treatment for individuals with 22q11.2DS and autoimmune cytopenias. Individuals with recurrent cytopenias should be evaluated for 22q11.2DS given the likelihood of more recurrent disease in this patient population and the phenotypic heterogeneity of 22q11.2DS with some individuals very mildly affected. Finally, there appears to be an increased prevalence of malignancy in individuals with 22q11.2DS. Whether this is due to the deletion and which genes are responsible are still not clear, and further investigation in this area is urgently needed.

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REFERENCES

Akar, N. A., & Adekile, A. D. (2007). Chromosome 22q11.2 deletion presenting with immune-mediated cytopenias, macrothrombocytopenia and platelet dysfunction. *Medical Principles and Practice*, *16*(4), 318–320.

Berndt, M. C., & Andrews, R. K. (2011). Bernard-Soulier syndrome. *Haematologica*, *96*(3), 355–359.

Bonati, M. T., Vanelli, C., Sangalli, D., Sina, C., Giardino, D., Sassone, J., … Ciammola, A. (2016). Cerebral microble eds A new presenting feature of chromosome 22q11. 2 deletion syndrome. *Journal of the Neurological Sciences*, *368*, 300–303.

Bosse, K. R., Shukla, A. R., Pawel, B., Chikwava, K. R., Santi, M., Tooke, L., … Bagatell, R. (2014). Malignant rhabdoid tumor of the bladder and ganglioglioma in a 14 year-old male with a germline 22q11.2 deletion. *Cancer Genetics*, *207*(9), 415–419.

Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S. A., … Campbell, R. M. (2003). A population-based study of the 22q11.2 deletion: Phenotype, incidence, and contribution to major birth defects in the population. *Pediatrics*, *112*(1 Pt 1), 101–107.

Bragadottir, G., Birgisdottir, E. R., Gudmundsdottir, B. R., Hilmarsdottir, B., Vidarsson, B., Magnusson, M. K., … Onundarson, P. T. (2015). Clinical phenotype in heterozygote and biallelic Bernard-Soulier syndrome-a case control study. *American Journal of Hematology*, *90*(2), 149–155.

Brenner, M. K., Clarke, S., Mahnke, D. K., Simpson, P., Bercovitz, R. S., Tomita-Mitchell, A., … Newman, D. K. (2016). Effect of 22q11.2 deletion on bleeding and transfusion utilization in children with

congenital heart disease undergoing cardiac surgery. *Pediatric Research*, *79*(2), 318–324.

Budarf, M. L., Konkle, B. A., Ludlow, L. B., Michaud, D., Li, M., Yamashiro, D. J., … Driscoll, D. A. (1995). Identification of a patient with Bernard-Soulier syndrome and a deletion in the DiGeorge/velo-cardio-facial chromosomal region in 22q11.2. *Human Molecular Genetics*, *4*(4), 763–766.

Chakrapani, A. L., White, C. R., Korcheva, V., White, K., Lofgren, S., Zonana, J., … Mansoor, A. (2012). Congenital extrarenal malignant rhabdoid tumor in an infant with distal 22q11.2 deletion syndrome: The importance of SMARCB1. *The American Journal of Dermatopathology*, *34*(6), e77–e80.

Davies, J. K., Telfer, P., Cavenagh, J. D., Foot, N., & Neat, M. (2003). Autoimmune cytopenias in the 22q11.2 deletion syndrome. *Clinical and Laboratory Haematology*, *25*(3), 195–197.

DePiero, A. D., Lourie, E. M., Berman, B. W., Robin, N. H., Zinn, A. B., & Hostoffer, R. W. (1997). Recurrent immune cytopenias in two patients with DiGeorge/velocardiofacial syndrome. *Journal of Pediatrics*, *131*(3), 484–486.

Finch, P. T., Pivnick, E. K., Furman, W., & Odom, C. C. (2011). Wilms tumor in a patient with 22q11.2 microdeletion. *American Journal of Medical Genetics Part A*, *155A*(5), 1162–1164.

Forest, F., David, A., Arrufat, S., Pierron, G., Ranchere-Vince, D., Stephan, J. L., … Bourdeaut, F. (2012). Conventional chondrosarcoma in a survivor of rhabdoid tumor: Enlarging the spectrum of tumors associated with SMARCB1 germline mutations. *The American Journal of Surgical Pathology*, *36*(12), 1892–1896.

Grati, F. R., Molina Gomes, D., Ferreira, J. C., Dupont, C., Alesi, V., Gouas, L., … Vialard, F. (2015). Prevalence of recurrent pathogenic micro-deletions and microduplications in over 9500 pregnancies.. *Prenatal Diagnosis*, *35*(8), 801–809.

Gregory, R. I., & Shiekhattar, R. (2005). MicroRNA biogenesis and cancer. *Cancer Research*, *65*(9), 3509–3512.

Hillmann, A., Nurden, A., Nurden, P., Combrie, R., Claeyssens, S., Moran, N., & Kenny, D. (2002). A novel hemizygous Bernard-Soulier Syndrome (BSS) mutation in the amino terminal domain of glycoprotein (GP) Ibbeta–platelet characterization and transfection studies. *Thrombosis and Haemostasis*, *88*(6), 1026–1032.

Itoh, S., Ohno, T., Kakizaki, S., & Ichinohasama, R. (2011). Epstein-Barr virus-positive T-cell lymphoma cells having chromosome 22q11.2 deletion: An autopsy report of DiGeorge syndrome. *Human Pathology*, *42*(12), 2037–2041.

Jawad, A. F., McDonald-Mcginn, D. M., Zackai, E., & Sullivan, K. E. (2001). Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Journal of Pediatrics*, *139*(5), 715–723.

Jyonouchi, S., McDonald-McGinn, D. M., Bale, S., Zackai, E. H., & Sullivan, K. E. (2009). CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, ear anomalies/deafness) syndrome and chromosome 22q11.2 deletion syndrome: A comparison of immunologic and nonimmunologic phenotypic features. *Pediatrics*, *123*(5), e871–e877.

Kato, T., Kosaka, K., Kimura, M., Imamura, S., Yamada, O., Iwai, K., … Matsuoka, R. (2003). Thrombocytopenia in patients with 22q11.2 deletion syndrome and its association with glycoprotein Ib-beta. *Genetics in Medicine*, *5*(2), 113–119.

Kobrynski, L. J., & Sullivan, K. E. (2007). Velocardiofacial syndrome, DiGeorge syndrome: The chromosome 22q11.2 deletion syndromes. *Lancet*, *370*(9596), 1443–1452.

Kratz, C. P., Niehues, T., Lyding, S., Heusch, A., Janssen, G., & Gobel, U. (2003). Evans syndrome in a patient with chromosome 22q11.2 deletion syndrome: A case report. *Pediatric Hematology and Oncology*, *20*(2), 167–172.

Kunishima, S., Imai, T., Kobayashi, R., Kato, M., Ogawa, S., & Saito, H. (2013). Bernard-Soulier syndrome caused by a hemizygous GPIbbeta mutation and 22q11.2 deletion. *Pediatrics International*, *55*(4), 434–437.

Kunishima, S., Kamiya, T., & Saito, H. (2002). Genetic abnormalities of Bernard-Soulier syndrome. *International Journal of Hematology*, *76*(4), 319–327.

Latger-Cannard, V., Bensoussan, D., Gregoire, M. J., Marcon, F., Cloez, J. L., Leheup, B., … Bordigoni, P. (2004). Frequency of thrombocytopenia and large platelets correlates neither with conotruncal cardiac anomalies nor immunological features in the chromosome 22q11.2 deletion syndrome. *European Journal of Pediatrics*, *163*(6), 327–328.

Lawrence, S., McDonald-McGinn, D. M., Zackai, E., & Sullivan, K. E. (2003). Thrombocytopenia in patients with chromosome 22q11.2 deletion syndrome. *Journal of Pediatrics*, *143*(2), 277–278.

Ludlow, L. B., Schick, B. P., Budarf, M. L., Driscoll, D. A., Zackai, E. H., Cohen, A., & Konkle, B. A. (1996). Identification of a mutation in a GATA binding site of the platelet glycoprotein Ibbeta promoter resulting in the Bernard-Soulier syndrome. *The Journal of Biological Chemistry*, *271*(36), 22076–22080.

Maggadottir, S. M., & Sullivan, K. E. (2013). The diverse clinical features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome). *The Journal of Allergy and Clinical Immunology. In Practice*, *1*(6), 589–594.

McDonald-McGinn, D. M., Reilly, A., Wallgren-Pettersson, C., Hoyme, H. E., Yang, S. P., Adam, M. P., … Sullivan, K. E. (2006). Malignancy in chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *American Journal of Medical Genetics Part A*, *140*(8), 906–909.

McDonald-McGinn, D. M., Sullivan, K. E., Marino, B., Philip, N., Swillen, A., Vorstman, J. A., … Bassett, A. S. (2015). 22q11.2 deletion syndrome. *Nature Reviews. Disease Primers*, *1*, 15071.

Murray, J. C., Donahue, D. J., Malik, S. I., Dzurik, Y. B., Braly, E. Z., Dougherty, M. J., … Biegel, J. A. (2011). Temporal lobe pleomorphic xanthoastrocytoma and acquired BRAF mutation in an adolescent with the constitutional 22q11.2 deletion syndrome. *Journal of Neuro-Oncology*, *102*(3), 509–514.

Mussai, F. J., Cunningham, L. C., Rezvani, G., Stratakis, C. A., Reynolds, J. C., Nesterova, G., … Kim, S. Y. (2008). Hypocalcemia in a patient with osteosarcoma and 22q11.2 deletion syndrome. *Journal of Pediatric Hematology/Oncology*, *30*(8), 612–617.

Naqvi, N., Davidson, S. J., Wong, D., Cullinan, P., Roughton, M., Doughty, V. L., … Daubeney, P. E. (2011). Predicting 22q11.2 deletion syndrome: A novel method using the routine full blood count. *International Journal of Cardiology*, *150*(1), 50–53.

Neale, R. E., Mineau, G., Whiteman, D. C., Brownbill, P. A., & Murphy, M. F. (2005). Childhood and adult cancer in twins: Evidence from the Utah genealogy. *Cancer Epidemiology, Biomarkers & Prevention*, *14*(5), 1236–1240.

Ozbek, N., Derbent, M., Olcay, L., Yilmaz, Z., & Tokel, K. (2004). Dysplastic changes in the peripheral blood of children with microdeletion 22q11.2. *American Journal Of Hematology*, *77*(2), 126–131.

Pongpruttipan, T., Cook, J. R., Reyes-Mugica, M., Spahr, J. E., & Swerdlow, S. H. (2012). Pulmonary extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue associated with granulomatous inflammation in a child with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome). *Journal of Pediatrics*, *161*(5), 954–958.

Savoia, A., Balduini, C. L., Savino, M., Noris, P., Del Vecchio, M., Perrotta, S., … Iolascon, A. (2001). Autosomal dominant macrothrombocytopenia in Italy is most frequently a type of heterozygous Bernard-Soulier syndrome. *Blood*, *97*(5), 1330–1335.

Savoia, A., Pastore, A., De Rocco, D., Civaschi, E., Di Stazio, M., Bottega, R., … Noris, P. (2011). Clinical and genetic aspects of Bernard-Soulier syndrome: Searching for genotype/phenotype correlations. *Haematologica*, *96*(3), 417–423.

Sellier, C., Hwang, V. J., Dandekar, R., Durbin-Johnson, B., Charlet-Berguerand, N., … Tassone, F. (2014). Decreased DGCR8 expression and miRNA dysregulation in individuals with 22q11.2 deletion syndrome. *PLoS ONE*, *9*(8), e103884.

Tang, J., Stern-Nezer, S., Liu, P. C., Matyakhina, L., Riordan, M., Luban, N. L., ... Kaler, S. G. (2004). Mutation in the leucine-rich repeat C-flanking region of platelet glycoprotein Ib beta impairs assembly of von Willebrand factor receptor. *Thrombosis and Haemostasis*, *92*(1), 75–88.

Tezenas Du Montcel, S., Mendizabai, H., Ayme, S., Levy, A., & Philip, N. (1996). Prevalence of 22q11 microdeletion. *Journal of Medical Genetics*, *33*(8), 719.

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