


# DiGeorge-like syndrome in a child with a 3p12.3 deletion involving MIR4273 gene born to a mother with gestational diabetes mellitus

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Chromosome 22q11.2 deletion is the most common chromosomal alteration associated with DiGeorge syndrome (DGS), even though this is not the only underlying cause of DGS. In rare patients, mutations in a single gene, *TBX1*, have been described resulting in a DGS phenotype. Recently, it has been reported that at least part of the *TBX1* mutant phenotype is due to excessive bone morphogenetic proteins (BMP) signaling. Evidence suggests that miRNA may modulate the expression of critical T-box transcriptional regulators during midface development and Bmp-signaling. We report on a 7-year-old Caucasian male born to a mother affected with gestational diabetes (GDM) who had a 371Kb-interstitial deletion of 3p12.3 identified by array CGH, involving the *ZNF717*, *MIR1243*, and *4273* genes. The child presented with a DiGeorge anomaly (DGA) associated with unilateral renal agenesis and language delay. The immunological evaluation revealed a severe reduction and impairment of T lymphocytes. FISH analysis and *TBX1* sequencing were negative. Among the miRNA-4273 predicted target genes, we found *BMP3*, which is involved in several steps of embryogenesis including kidney and lung organogenesis and in insulin gene expression. Since, DGA is not commonly found in newborns of diabetic mothers, we hypothesize that the pathogenesis of DGA associated with GDM is multifactorial, involving both genetic and/or epigenetic cofactors.

## KEYWORDS

3p12.3 deletion, array-CGH, DiGeorge syndrome, miRNA, rare genetic syndromes

## 1 | INTRODUCTION

DiGeorge syndrome (DGS), also known as 22q11.2 deletion syndrome (22q11.2 DS) was first described in the 1960s and classically comprises facial anomalies, hypoparathyroidism, cardiac malformations, developmental, and speech delay, and mild to moderate immune deficiency related to thymic a/hypoplasia (Cancrini et al., 2014). Chromosome 22q11.2 deletion is the most common chromosomal alteration associated with DGS, occurring in approximately 1:4,000 live births (Cirillo et al., 2014; Tezenas Du Montcel, Mendizabai, Ayme, Levy, & Philip, 1996). However, a small number of patients affected with other genetic syndromes share a few clinical features with the 22q11 spectrum, including Opitz G/BBB (McDonald-MCGinn et al., 1995;

Robin, Opitz, & Muenke, 1996) and CHARGE syndrome (Devriendt, Fryns, Mortier, van Thienen, & Keymolen, 1998), and other chromosomal deletions as 16p11.2, 10p13, 17p13, 4q34.1q35.2 (Ballif et al., 2007; Cuturilo et al., 2011; Greenberg, Elder, Haffner, Northrup, & Ledbetter, 1988; Pignata et al., 1996).

Teratogenic influences such as maternal diabetes (Wilson et al., 1993) or prenatal exposure to retinoic acid or alcohol may also lead to a DiGeorge anomaly (DGA). However, only a minority of newborns of diabetic mothers have a DGA, thus implying the requirement for multiple factors for the expression of this anomaly. In rare patients with a DGS phenotype but without the 22q11.2 deletion, mutations in the single T-box (*TBX1*) gene, which plays an important role in regulating the expression of several transcription factors, have been

described (Yagi et al., 2003). However, in some patients with a presumed diagnosis of DGS, the underlying etiology cannot be identified (Rope, Cragun, Saal, & Hopkin, 2009). Chromosomal microarray analysis has been advocated as a first-line diagnostic approach for patients with multiple congenital anomalies, including patients with a phenotype suggestive of 22q11.2 DS and normal fluorescent in situ hybridization (FISH) (Busse et al., 2010).

We report on a child born to a mother with gestational diabetes mellitus (GDM) affected with a DGA, associated with a 3p12.3 deletion, involving the *ZNF717*, *MIR1243*, and *4273* genes, which have a role in the regulation of embryogenesis. Among the miRNA-4273 predicted target genes, there is the bone morphogenetic protein-3 (*BMP3*), which is involved in several steps of embryogenesis, including kidney and lung. We hypothesize that this alteration may act as a genetic cofactor in favoring the clinical expression of the DGA in newborns of diabetic mothers.

## 2 | CLINICAL REPORT

The proband is a 7-year-old Caucasian male referred to our Immunodeficiency Center at the age of 25 months because of recurrent upper respiratory infections (URIs), hypoparathyroidism, unilateral renal agenesis diagnosed during fetal life and language delay. He was the third child of non-consanguineous parents. The family history was unremarkable except for a maternal aunt, affected with type 2 diabetes, who died of kidney cancer, and the paternal grandfather who was affected with coronary artery disease. No further chronic or genetic diseases were reported in other family members. The proband was born to a 36-year-old female with GDM after a 36 week gestation. Delivery was by caesarean section. The mother has had GDM with each of her previous two pregnancies; during this pregnancy, she took subcutaneous insulin twice daily, monitored blood sugar four times per day, and denied worsening of her hyperglycemia during the pregnancy. There was no exposure to alcohol, tobacco, or other teratogenic factors. No additional health problems such as hypertension, obesity, or type 2 diabetes were reported in the mother. Fetal movements were reported as normal. The birth weight was 4.2 kg (>90th centile). The child had a short period of hypoglycemia and received a glucose infusion. He was discharged on the third day of life. On the fourth day of life he was re-admitted due to hyperbilirubinemia and tremors of the upper and lower right limbs. Serum calcium levels were 5.2 mg/dl (normal value: 9–11 mg/dl) and the electrolytes were normal. Therapy with calcium and alpha-calcidol was successfully started. An echocardiogram showed a patent oval foramen. Cerebral ultrasonography revealed a cyst of the septum pellucidum.

At 24 months, growth and head circumference were normal. Dysmorphic features included long face, a small nose with a normal bridge, long philtrum, highly arched palate, and dental enamel dysplasia (Figure 1a,b). No other craniofacial findings such as, bulbous nasal tip and prominent nasal root, hypoplastic alae nasae, hooded eyelids, cupped and protuberant ears, preauricular pits or tags, or

craniosynostosis, which are frequently reported in children with 22q11.2DS, were detected in the patient.

The chest and abdominal examination was normal. A speech delay was observed during the first years of life. At the age of 4 years, expressive language was characterized by a sporadic use of short sentences consisting of 2–3 words, with oculomotor difficulties and abnormalities of perceptual organization. The language impairment was associated with an inhibited temperament and signs of anxiety. However, comprehensive language was appropriate for age. Psychomotor development assessed by Griffith Mental Developmental Scale-Extended Revised (GMDS-ER) was normal (IQ = 86). The patient received psychomotor and speech therapy, resulting in a progressive improvement of the expressive language, even though it remained poorly structured.

Since, the age of 15 months, the patient had recurrent and frequent episodes of URIs. The ear-nose-throat evaluation did not reveal any hearing loss. Ophthalmologic examination was normal. G-banded chromosomal analysis on peripheral blood lymphocytes indicated a normal karyotype.

Fluorescent in situ hybridization performed to exclude a 22q11.2 deletion syndrome and *TBX1* sequencing were both negative.

## 3 | METHODOLOGY AND RESULTS

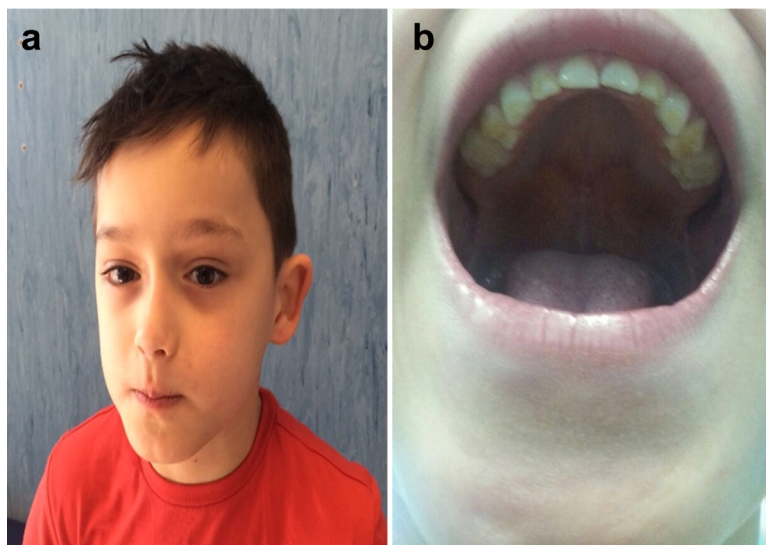
### 3.1 | Cytogenetic and molecular genetics

A 4 × 44 CytoChip™ array with ISCA design (BlueGnome Ltd; Cambridge, UK) was used in accordance with manufacturer's guidelines for genome screening. The arrays were scanned using the InnoScan 710 and analyzed using BlueFuse for Microarrays 3.5 software (BlueGnome, Cambridge, UK), referring to Hg19 Genome Assembly (NCBI Build GRCh37). Copy number variants were classified according to the Database of Genomic Variants, the DECIPHER Database and the UCSC Genome Browser. Oligo-array CGH analysis identified a 3p12.3 deletion, spanning approximately 317 kb (Figure 2) and overlaps three genes (*LOC401074*, *ZNF717*, *FLJ20518*), *MIR1243*, and *MIR4273* (National Center for Biotechnology Information, hg19). The result, according to the ISCN nomenclature, is: arr [hg19] (75, 571, 183–75, 888, 573 × 1).

The miRBase database available online at <http://microrna.sanger.ac.uk/> which provides integrated information about miRNAs and related predicted genes targets, was used to identify the potential genetic targets of the deleted miRNAs. The potential effects of the reduced dosage of the deleted miRNAs on gene targets were considered during the analysis. Among the miRNA-4273 predicted target genes, there are several genes, such as *BMP3*, which are involved in several steps of embryogenesis, such as kidney and lung organogenesis and in insulin gene expression.

### 3.2 | Immunological evaluation

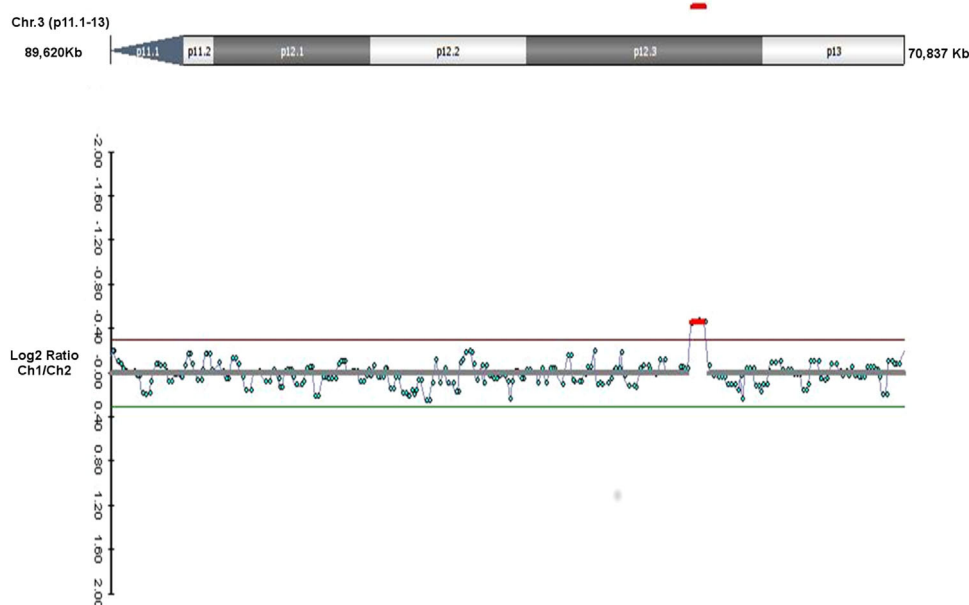
Initial immunological evaluation revealed leukopenia (median white blood cell count ± SD 4900 ± 1237 cells/μl; range over the time



**FIGURE 1** Proband's phenotype. a: Noted long face, long philtrum, and small nose with a normal bridge. b: Highly arched palate and dental enamel dysplasia. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

3780–7470) with moderate lymphopenia (median  $2577 \pm 662$  cells/ $\mu$ l; range 1170–2670), as illustrated in Table 1. At the diagnosis, the flow cytometric analysis of peripheral blood mononuclear cells (PBMCs) revealed a  $T^{\text{low}}B + NK+$  combined immunodeficiency (CID), characterized by a marked reduction of  $CD3+$  (373 cells/ $\mu$ l),  $CD4+$  (163 cells/ $\mu$ l), and  $CD8+$  (140 cells/ $\mu$ l) T cells. B lymphocytes were increased (1352 cells/ $\mu$ l), while  $CD56+$  were normal. In order to further investigate the T-cell phenotype and function in the context of a putative thymic  $\alpha$ /hypoplasia, we evaluated the naïve and memory subsets and the proliferative response to mitogens. As observed in

Figure 3, among  $CD3 + CD4 + T$  cells, a severe reduction of naïve  $CD45^{RA+}$  T cells and a prevalence of memory  $CD45^{RO+} CD4 + T$  cells were evident. On the contrary, although the number of  $CD3 + CD8+ T$  cells was lower than age-matched controls, the distribution of the naïve and memory phenotypes was normal. A reduction of  $CD4 + CD25+$ , which include Treg cells, paralleled the  $CD4+$  lymphopenia. The proliferative response to phytohemagglutinin (PHA) and pokeweed, evaluated by thymidine uptake from cultured cells pulsed with  $0.5 \mu\text{Ci}$  [ $^3\text{H}$ ] thymidine (Amersham International), was decreased, corresponding to the 45% and 39% of the control, respectively.



**FIGURE 2** The ideogram of chromosome 3. The red bar indicates the deletion of the 3p12.3 region identified in our patient. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 1** Immunological evaluation during the long term follow-up

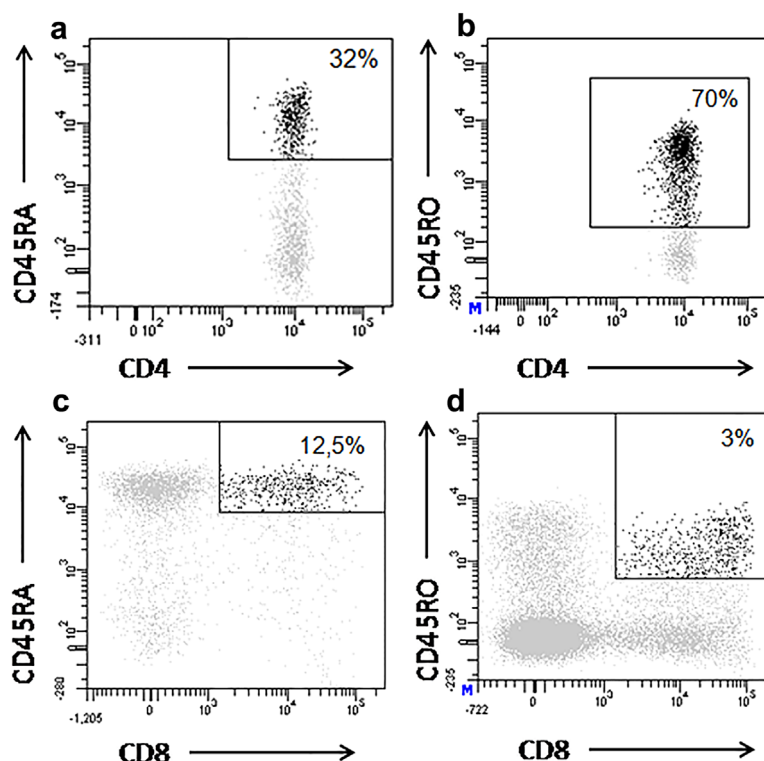
Age (y)	2	2.6	3	4.6	5	6
Serum Ig (mg/dl)						
IgG	605	ND	809	684	936	800
IgA	70.9	ND	94.3	51.7	94.7	91.6
IgM	85.4	ND	188	98	130	94
Leukocytes (cells/mm <sup>3</sup> )	5800	4100	7470	4000	4200	5160
Lymphocytes (cells/mm <sup>3</sup> )	2330	1320	2670	1590	1170	1370
T cells (CD3+)	373 (2100–6200)	396 (1400–3700)	881 (1400–3700)	700 (1400–3700)	526 (1400–3700)	698 (1400–3700)
CD3 + CD4+	163 (1300–3400)	198 (700–2200)	454 (700–2200)	318 (700–2200)	246 (700–2200)	233 (700–2200)
CD3 + CD8+	140 (620–2000)	145 (490–1300)	267 (490–1300)	366 (490–1300)	164 (490–1300)	192 (490–1300)
CD19	1351 (720–2600)	436 (1400–3700)	854 (1400–3700)	397 (1400–3700)	304 (1400–3700)	110 (1400–3700)
CD56	419 (180–920)	396 (130–720)	667 (130–720)	ND	316 (130–720)	507 (130–720)
CD4 + CD25 + %	1	ND	ND	ND	ND	1
TCRαβ%						31
TCRγδ%						20

The brackets indicate normal values for age; ND, not done.

During the 5 years of follow-up, despite a sporadic mild increase in the lymphocytes count at 3 years of age, a progressive further reduction of lymphocytes was documented.

Even though TCR αβ cells predominated, an increased number of TCR γδ T cells (20%), was detected at the age of 6 years. However,

despite the marked reduction of T cells, the patient did not suffer from severe episodes of bacteremia, systemic *C. albicans* infections, or other opportunistic and life-threatening infections. Furthermore, a normalization of the proliferative response to mitogens was observed at 3 years.



**FIGURE 3** Blood T cell subsets by flow cytometry at the age of two years. a: Naïve T cells (CD45RA +) represent the 32% of the CD4+ cells. b: Memory T cells (CD45RO +) represent the 70% of the CD4+ T cells. c, d: Normal distribution of the naïve and memory CD8+ T cells [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

Despite consistently normal serum levels of IgM, IgG, IgA, and IgE, the patient had an absent antibody specific production toward Hepatitis B. Autoantibodies to anti-thyroglobulin (TGB-Ab), anti-thyroid peroxidase (TPO-Ab), anti-nuclear (ANA), anti-double stranded DNA (dsDNA), and anti-transglutaminase were all negative.

## 4 | DISCUSSION

In this study, we report a novel association between a DGA characterized by a quantitative and qualitative immunodeficiency resembling a T<sup>low</sup>B + NK+ combined immunodeficiency in a child with a 3p12.3 deletion born to a mother with GDM.

Diabetic embryopathy encompasses a wide spectrum of congenital anomalies with a multifactorial pathogenesis (Castori, 2013). Holoprosencephaly, caudal dysgenesis, VACTERL association, and cardiovascular congenital abnormalities are the most common features associated with diabetic embryopathy. Furthermore, renal dysgenesis has been frequently reported in newborns of diabetic mothers. Moreover, DGA has also been reported in newborns of diabetic mothers (Dentici et al., 2013; Novak, Robert, & Robinson, 2005). In these patients, unilateral or bilateral renal agenesis has also been found, suggesting a non-random association between the two events.

To date, cytogenetic studies in patients with DGA born to diabetic mothers have either not been done or have failed to identify an underlying genetic alteration.

The etiology of diabetic embryopathy is multifactorial and results from the interplay between uterine microenvironment, parental and offspring genomes, and epigenetic regulation (Castori, 2013; Vrachnis et al., 2012). It has been hypothesized that alterations of the metabolic homeostasis associated with DM could profoundly affect several signal transduction pathways and morphogenetic processes (Castori, 2013), thus resulting in developmental field defects. Altered expression of developmental control genes, as *Pax3*, has been reported in mouse models of diabetic embryopathy. However, a molecular mechanism underlying the phenotypic spectrum of DM-associated structural anomalies in humans has not been reported yet. Of note, even though several studies documented a high teratogenic potential for women with pre-gestational DM type 1 (DM1) or 2 (DM2), pregnant women developing GDM have an overall very low risk for fetal congenital anomalies, suggesting the requirement of further pathogenetic cofactors (Balsells, Garcia-Patterson, Gich, & Corcoy, 2012). In our study, we found a novel interstitial deletion at 3p12.3 encompassing three genes, *ZNF717*, *MIR1243* and *MIR4273* in a patient with multiple congenital anomalies born to a mother whose pregnancy was complicated by GDM. MiRNAs are a family of small, non-coding RNAs that modulate gene expression by targeting messenger RNAs for degradation, translational repression or both. MiRNAs may affect a wide range of biological responses including proliferation, differentiation, apoptosis and cell metabolism, and are implicated in several processes, such as brain differentiation and function,

growth, and skeletal and cardiovascular development. Individual miRNAs can target multiple messenger RNAs, controlling the expression of several genes, and frequently their alterations can have a profound impact on cellular development and function (Zhang, Wang, & Gameinhardt, 2013). Furthermore, there is evidence for miRNA dysregulation and biogenesis having a role in the immunological, cardiac, endocrinological, and neurological phenotype of patients with 22q11.2 DS due to DiGeorge Critical Region Gene 8 (*DGCR8*) haploinsufficiency (de la Morena et al., 2013). *DGCR8* encodes a component of the microprocessor complex involved in miRNA biogenesis, which is deleted in the majority of patients with 22q11.2DS (Sellier et al., 2014). Furthermore, it has been recently demonstrated that the haploinsufficiency of miRNA-17-92 due to a germline hemizygous deletion of *MIR17HG* is responsible for several developmental abnormalities observed in some patients with microcephaly, short stature, and digital abnormalities (De Pontual et al., 2012).

Evidence also indicates that miRNAs may modulate the expression of critical T-box transcriptional regulators during midface development and the BMPs. Part of the *TBX1* mutant phenotype is due to excessive Bmp-signaling (Wang et al., 2013). Interestingly, *BMP3*, a member of the transforming growth factor  $\beta$  superfamily, which plays a key role during embryogenesis, and in particular, in the development of the organs that require an epithelial-mesenchymal interaction (such as the thymus and kidney) is among the miRNA-4273 predicted target genes (Takahashi & Ikeda, 1996). More recently, it has been reported that *BMP3* has a role in the regulation of insulin gene expression in pancreatic beta-cells as well (Bonner et al., 2011). However, a clear causative relationship between haploinsufficiency of *ZNF717* and the patient's clinical phenotype was not found.

In conclusion, we report for the first time on the association between a DGA in an infant born to a mother with GDM and a microdeletion of chromosome 3, involving the *MIR4273* gene. Even though the causal relationship between the two events remains to be proven, our report provides further support for the multifactorial pathogenesis of DGA associated with GDM.

## CONFLICTS OF INTEREST

None declared.

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