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Early Initiation of B-vitamin Supplementation May Reduce Symptoms and Explain Intrafamilial Variability: Insights from Two Sibling Pairs from the TANGO2 Natural History Study

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Abstract

TANGO2-deficiency disorder (TDD) is an autosomal recessive condition arising from pathogenic biallelic variants in the *TANGO2* gene. TDD is characterized by symptoms typically beginning in late infancy including delayed developmental milestones, cognitive impairment, dysarthria, expressive language deficits, and gait abnormalities. There is wide phenotypic variability where some are severely affected whileothers have mild symptoms. This variability has been documented even among sibling pairs who share the same genotype, but reasons for this variability have not been well understood. Emerging data suggest a potential link between B-complex or multivitamin supplementation and decreased metabolic crises in TDD. In this report we describe two unrelated sibling pairs diagnosed with TDD with marked differences in symptoms. In both families, the older siblings suffered multiple metabolic crises and are clinically more affected than their younger siblings who have very mild to no symptoms; they are the least impaired among 70 other patients in our ongoing international natural history study. Unlike their older siblings, the two younger siblings started taking B-complex vitamins early between 9 and 16 months. This report delineates the mildest presentation of TDD in two families. These data may support a role

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for early diagnosis and initiation of vitamin supplementation to not only prevent metabolic crises but also improve neurologic outcomes in this life-threatening disorder.

Keywords

TANGO2; multivitamins; B-complex; treatment; arrhythmia; management; supplement

Introduction

TANGO2 Deficiency Disorder (MIM # 616878) was first described in 2016 as an autosomal recessive disease associated with chronic neuro-developmental and cognitive deficits (Kremer et al., 2016; Lalani et al., 2016). Characteristic of TANGO2 Deficiency Disorder (TDD) is episodic metabolic crisis associated with rhabdomyolysis triggered by metabolic stressors such as illness or prolonged fasting (Berat et al., 2021; Dines et al., 2019; Jennions et al., 2019; Lalani et al., 2016; Mingirulli et al., 2020; Miyake, Lay, et al., 2022; Miyake, et al., 2022; Powell et al., 2021; Schymick et al., 2022). The exact function of TANGO2 remains unknown, however, ongoing studies suggest it may be involved in lipid homeostasis and endoplasmic reticulum to Golgi transport, with secondary effects on mitochondrial energy metabolism.(Asadi et al., 2022; Heiman et al., 2022; Jennions et al., 2019; Lujan et al., 2022; Milev et al., 2021; Mingirulli et al., 2020) Multiple case reports and series describe similar phenotypes among all affected patients; yet there appears to be marked heterogeneity in the degree of symptoms even among sibling pairs sharing the same TANGO2 genotype.(Berat et al., 2021; Dines et al., 2019; Jennions et al., 2019; Miyake, et al., 2022; Powell et al., 2021; Schymick et al., 2022)

A natural history study of TDD, supported by the TANGO2 Research Foundation was launched in 2019 (ClinicalTrials.gov Identifier: NCT05374616). Using extensive parental interviews and review of medical records, our team identified a potential effect of multivitamins or B-complex supplementation (MVI-B) on disease morbidity.(Miyake, et al., 2022). Specifically, we noted a significant decrease in the incident rate of metabolic crisis events among patients taking MVI-B.(Miyake, et al., 2022) During inpatient metabolic crises, patients initiated on nutritional support containing MVI-B also seemed less likely to develop lethal cardiac arrhythmias and cardiomyopathy.(Miyake, Lay, et al., 2022)

From the ongoing natural history study, we identified two unrelated sibling pairs where both younger siblings demonstrated very mild to no TDD symptoms. Indeed, in both cases, features of TDD were not recognizable upon evaluation. In this report, we discuss the clinical course and findings of the two sibling pairs and the interesting observation that both younger siblings were initiated on B-complex vitamins early in childhood. The study was approved by the Institutional Review Board (IRB, H-43240) of Baylor College of Medicine and with written consent by both families. These findings support our previous data.(Miyake,et al., 2022) Specifically, B-vitamin supplementation may not only reduce the risk of serious metabolic crises but may lead to improved neurologic outcomes if initiated early.

Clinical report

Sibling pair 1.—An 8.5-year-old male (S1–1) and his 7.0-year-old younger sister (S1–2) were born at term to unrelated parents of Italian and Indian descent and were diagnosed with TDD at age 2.5 years and 13 months, respectively. Both siblings harbor compound heterozygous TANGO2 variants (c.262C>T, p.(Arg88*) and c.338delG, p.(Gly113Alafs*10) [NM_152906.7]). The older brother was breastfed until 9 months of age, then used formula until he transitioned to whole milk at age 12 months. He was noted to have delayed developmental milestones, sitting at 8 months and rolling over at 9 months. His first metabolic crisis, triggered by a viral illness, occurred at the age of 13 months and resulted in a 2-month hospitalization. During this crisis, he was diagnosed with rhabdomyolysis (highest CK 220,000 IU/L), hypothyroidism, prolonged QTc, and cardiomyopathy with mildly reduced systolic ejection fraction. He was treated with IVIG, prednisone, levothyroxine, carnitine, CoQ10, riboflavin, and was started on iron and folic acid for anemia. Folic acid and iron were discontinued 10 days after discharge. At the age of 22 months, all supplements were discontinued, as no diagnosis had been identified. He was continued on levothyroxine only.

He slowly regained strength and began to crawl at 18 months and by 24 months he was able to stand with support and say a few words. Five months later, at age 27 months, he fell ill again with a fever and poor oral intake triggering his second crisis (highest CK 226,844 IU/L) which was again associated with mild cardiomyopathy. He was restarted on CoQ10, carnitine, thiamine, and riboflavin. Total parenteral nutrition (TPN) was also initiated. By hospital day #28 his CK levels had normalized (147 IU/L) and he was scheduled for discharge when he developed another fever. He tested positive for parainfluenza virus and was found to have line infection. All lines were removed and TPN was discontinued. He had poor oral intake and stopped eating. His CK began to rise again (54,000 IU/L) triggering his 3rd crisis at age 28 months. On hospital day #34 he went into cardiogenic shock with severe cardiac dysfunction requiring inotropic support in the intensive care unit. Six weeks later, he was discharged home on daily carnitine 500mg, CoQ10 50mg, Vitamin D, riboflavin (90mg daily), and thiamine (200mg daily). Around 2.5 years, his parents started him on ½ tab daily Solaray brand B-Complex-50 (doses shown in Table 1). He has not had a subsequent crisis since. A timeline of his metabolic crises events and vitamin supplementation is shown in Figure 1. His current supplements include L-carnitine (450mg twice daily) and CoQ10 (100mg daily), Ubidecarenone (2.5mg daily), thiamine (130mg), riboflavin (120mg daily), Vitamin D drops (6ml of 10,000u/mL solution), and 365 Whole Foods brand B-50 complex. Individual B-vitamin doses are shown in Table 1. He learned to walk for the first time at 4.8 years of age. At 8.4 years of age, his growth parameters and percentiles were as follows: length 123 cm (15th centile); weight 25 kg (38th centile); and head circumference 52 cm (46th centile). Presently, he can walk and run independently although with a wide-based gait (Supplemental video 1). He can speak full sentences and there has been gradual improvement in articulation over the past two years, although it is still difficult to understand him. Although he cannot read, he can write letters of the alphabet. He understands well by parental report and memorizes enough to recite books by memory.

His younger sister (S1–2) was diagnosed with TDD at the age of 13 months. She was breastfed for 3 months, then formula fed (Humana Anticolic) until age 9 months and then transitioned to whole milk around age 12 months. She met all developmental milestones on time, rolling over at 4 months, sitting at 6 months and walking at 14 months. She said her first words at 10 months. Between the ages of 13–16 months, she was started on carnitine followed by one half tablet of Nature's Made Super B-complex vitamins (individual B vitamin doses shown in Table 1; this complex also contains Vitamin C). CoQ10 and Vitamin D were then added. A timeline of her vitamin supplementation is shown in Figure 1. She has consistently taken these supplements. She has no recognizable symptoms of TDD, can run (see Supplemental video 2) and speaks fluently in full sentences. A formal psychomotor assessment at age 5.8 years was normal for age. She has no evidence of cognitive delays although she has never undergone a formal IQ test. She is currently taking 1 tablet of the B-complex daily, carnitine (300mg every morning, 200mg every evening), Ubidecarone (2.5mg daily), and vitamin D (4 drops of 10,000U/ml solution daily). Her growth parameters and percentiles at 6.9 years of age were as follows: length 116 cm (18^{th} centile); weight 20 kg (21^{st} centile); and head circumference 52 cm (70^{th} centile).

To assess potential differences in developmental skills, both siblings underwent evaluation using the Developmental Profile-4 (DP-4). The DP-4 is a standardized test that measures a child's development (from birth to 21 years 11 months) in five areas: physical, adaptive behavior, social-emotional, cognitive, and communication. This test consists of a series of yes or no questions administered by a physician and answered by parents. The answers are tabulated and a standardized score is provided, comparing the child with age-matched peers. Scores in each section provide general assessment of the child compared to peers as 1) above average, average, or delayed, 2) their percentile rank, 3) and age-equivalent abilities. In addition to scores for each area of development, the DP-4 also provides a general developmental score which comprehensively measures development across all five areas. The older brother (S1–1) was tested at age 8 years 4 months. His overall general developmental score categorized him as delayed, ranking him in the 2^{nd} centile for his age. Age equivalent scores were as follows: physical (4:0–4:5 years), adaptive behavior (5:6–5:11 years), social-emotional (6:6–6:11 years), cognitive (3:6–3:11 years) and communication (4:6–4:11 years). His younger sister (S1–2) underwent testing at age 6 years 11 months. Her overall general development score was categorized as average, ranking her in the 63^{rd} centile for age. Age equivalent scores were as follows: physical (7:0–7:11 years), adaptive behavior (8:0–8:11 years), social-emotional (8:0–8:11 years), cognitive (7:0–7:11 years) and communication (6:6–6:11 years). All scores are shown in Table 2.

Sibling Pair 2—A 29-year-old non-Hispanic White female (S2–1) and her 13-year-old younger brother (S2–2) who were born at term were diagnosed with TDD at age 24 years and 9 years, respectively. Their mother and father are distantly related. Both siblings harbor homozygous *TANGO2* exon 3–9 deletions.

The older sister was formula fed from birth and transitioned to whole milk at age 12 months. At 6 months of age, her parents noted her eyes would "drift". At 9 months, she started to sleep through the night without a nighttime feed and the parents first noted seizure-like activity upon waking from sleep or naps. These "seizures" occurred approximately twice

weekly and were described as whole-body continuous jerking with eye blinking lasting 1 minute followed by crying. Within 30 minutes, these episodes abated without post-ictal fatigue or confusion. From a developmental standpoint she met early milestones on time except for walking. Between 12–16 months of age, she developed episodes of lethargy, ataxia, and drooling. Myringotomy tubes were placed at 12 months due to recurrent ear infections and to potentially address the ataxia but it remained unchanged. A neurologic evaluation revealed multiple normal EEGs between the ages of 12 months and 13 years. At approximately 16 months, she had a normal brain MRI.

Her first metabolic crisis was triggered by a viral illness at age 16 months. This episode was associated with severe hypoglycemia and unresponsiveness with encephalopathy, and she was admitted to the intensive care unit (ICU) where she remained for 2 weeks. No cardiac arrhythmias were noted during that admission. She was discharged home on carnitine 300mg three times daily, thiamine 200mg once daily, and biotin 10mg once daily. Subsequently, each time she became ill, she required hospitalizations due to poor oral intake, (CK levels >64,000 U/L). Around 2 years of age, her parents were taught how to place a nasogastric tube (NGT) and she was given Pediasure whenever she fell ill or wasn't eating. This helped significantly decrease hospital admissions. At the age of 3 years, she was admitted when persistent vomiting prevented their ability to maintain the NGT. She also had a seizure and was started on levetiracetam. By age 4 years, she had been diagnosed with hypothyroidism and was taking levothyroxine in addition to B1 (thiamine 100mg daily), B2 (riboflavin 100mg daily), B7 (biotin 10mg daily), carnitine (500mg three times daily), and CoQ10 (120mg twice daily). Her parents reported persistent symptoms until around 5 years of age when febrile illness seemed to stop and she went for years without any cold or viral illnesses.

She learned to walk at age 5 years. At 16 years of age, hand tremors were noted and treated with levetiracetam and clonazepam. It was at this time that her parents had decided to start both she and her brother on B100-complex (believed to be Walmart brand, Spring Valley, doses shown in Table 1). The complex was chosen to minimize the number of separate B-vitamin pills being taken. A timeline of her metabolic crises events and vitamin supplementation is shown in Figure 1.

At the age of 24, she developed seizures again, unresponsive to levetiracetam. She was switched to topiramate and has not had a seizure in one year. She walks with support and is able to speak and answer questions although her speech is not as clear (Supplemental video 3). Her growth parameters at 29 years of age were length: 152.4 cm (5^{th} centile) and weight: 101.5 kg (>99^{th} centile) and head circumference 56.1 cm (95 centile). Her current medications and supplements include: Now brand B-100 complex 1 tab twice daily (doses in Table 1), L-carnitine (1500mg twice daily), omega-3 Fish Oil (1200mg EPA + 900mg DHA twice daily), topiramate (100mg twice daily), clonazepam 0.5mg twice daily, levothyroxine (112mcg once daily), ethinylestradiol/levonorgestrel, sertraline (200mg daily), cetirizine once daily, pantoprazole 40mg daily, docusate sodium daily, and propranolol HCL 60mg daily.

The younger brother (S2–2) was not diagnosed with TDD until 9 years of age. He was born full term at 8 pounds, 1 ounce. He was breastfed but at 3 days of life he was admitted for lethargy. Given his sister's history, a CK level was sent and was normal however his ammonia level was elevated at 243 μmol/L, lactic acid was 6.1 mmol/L, and glucose was "low". He was put on intravenous fluids and switched to formula feeds and laboratory derangements resolved. He was discharged home on carnitor 250mg twice daily and biotin 2.5mg daily. At 9 months of age, he first started sleeping through the night without a night-time feed. At this time, he began to demonstrate truncal dystonia, leaning towards one side in a way reminiscent of his sister. Due to parental concern that he may have the same suspected mitochondrial condition as his sister, his parents decided on their own to start him on a full tablet of B-100 complex at age 9 months (Spring Valley, doses shown in Table 1). In addition, night-time feeds were resumed and his symptoms resolved. At age 12 months he transitioned to whole milk. At age 3 years, he underwent myringotomy tube placement as his only other hospitalization. At approximately 5–6 years of age, the family was told there was no evidence B-vitamins were helping and they briefly stopped the B-vitamins but continued the carnitine and CoQ10. Within 2 days, he was drooling, leaning to one side, his speech became unclear and he became lethargic. His parents immediately restarted the daily B complex vitamins and within 1–2 days, they noted complete resolution of symptoms. The patient has not missed any subsequent doses. A timeline of his vitamin supplementation is shown in Figure 1. At age 5 years, he was thought to have attention deficit hyperactivity disorder (ADHD). About 1 year later he was diagnosed with anxiety.

From a motor-developmental standpoint, his parents do not report any overt deficits, though he has never undergone any formal developmental testing. He is able to walk and run and can participate in sports activities. He has some learning difficulties predominantly with concentrating, longer term memory recall, and higher-level executive processing but he can do math that his sister cannot (Supplemental video 4). There are other family members not affected by TDD, with learning difficulties.

He is in 7th grade currently, can read and write, and speaks fluently. While his parents have not noticed any speech issues, they do indicate that he mumbles (Supplemental video 4). He is enrolled in some regular classes, such as social studies, in which he can ask for help if needed. He is in a separate special education class for English and Math. In these classes, he works at his own pace to complete the same assignments as all other students in regular classes.

His growth parameters at 13 years of age were length: 158 cm (34th centile), weight: 53.5 kg (66th centile), and head circumference 55 cm (62nd centile). His current medications include L-Carnitine (1g daily), CoQ10, Omega-3 Fish Oil 1200mg EPA + 900mg DHA daily, Now brand B-100 Complex 1 capsule twice daily (See Table 1), pantothenic acid (B5) 500mg twice daily, lisdexamfetamine daily, sertraline 50mg daily, clonidine for sleep (0.1mg nightly), and Amazon brand stool softener twice weekly.

Both siblings underwent Developmental Profile-4 testing (Table 2). Of note, the DP-4 is standardized for testing up to 21 years 11 months. The older sister (S2–1) underwent testing at age 28 years 8 months. Her overall general development score was categorized as delayed,

ranking her in the <0.1 centile for age. Age equivalent scores were as follows: physical (2:0–2:3 years), adaptive behavior (2:4–2:7 years), social-emotional (4:0–4:5 years), cognitive (3:0–3:5 years) and communication (2:8–2:11 years). Her younger brother (S2–2) underwent testing at age 13 years 3 months. His overall general development score was categorized as average, ranking him in the 45th centile for age. Age equivalent scores were as follows: physical (11:0–12:11 years), adaptive behavior (10:0–10:11 years), social-emotional (10:0–10:11 years), cognitive (13:0–16:11 years) and communication (17:0–21:11 years).

Discussion

TANGO2 Deficiency Disorder is a newly discovered disease associated with characteristic symptoms that affect nearly all patients.(Berat et al., 2021; Dines et al., 2019; Frey et al., 2022; Jennions et al., 2019; Kremer et al., 2016; Lalani et al., 2016; Mingirulli et al., 2020; Miyake, et al., 2022; Powell et al., 2021; Schymick et al., 2022) Metabolic crises are common, affecting 65% of patients and among those that experience crises, mortality is as high as 24%.(Miyake, et al., 2022) Notably, some patients have milder symptoms, and some have never experienced a metabolic crisis. Data from an ongoing natural history study has identified a potential link between multivitamin or B-complex use and decreased incidence of metabolic crisis.(Miyake, et al., 2022)

In this report we describe two different sibling pairs that reflect significant intrafamilial phenotypic heterogeneity that has been previously described in nearly all studies.(Berat et al., 2021; Dines et al., 2019; Jennions et al., 2019; Miyake, et al., 2022; Powell et al., 2021; Schymick et al., 2022) Specifically, the younger siblings in this report are not only significantly less affected than their older siblings but also represent two of the least affected patients among all affected TDD patients in an ongoing worldwide natural history study.

Our observations suggest B-vitamin supplementation may be explain the differences seen in these two sibling pairs and the phenotypic heterogeneity reported in other studies. Specifically, B-vitamin supplementation may not only reduce the risk of serious metabolic crises but may lead to improved neurologic outcomes if initiated early. Our data are supported by the recent work of Asadi et al., showing that vitamin B5, a coenzyme A (CoA) precursor rescues membrane trafficking defects in Tango2 *Drosophila* model.(Asadi et al., 2022) Whether the benefits observed in younger siblings in this report are related to these vitamins specifically or other supplements within MVI-B is not yet known.

In our report, the 7-year-old younger sister (S1–2) is the only known patient with no symptoms of TDD. She was started on B-complex before any symptoms occurred. The 13-year-old younger brother (S2–2) was started on B-complex vitamins at 9 months, the youngest age to be started on B-complex among all patients in the natural history study. He only has mild learning difficulties when compared to other TDD affected patients. In contrast, both older siblings did not initiate B-complex vitamins until after they had suffered multiple metabolic crises. Use of carnitine and CoQ10 is not associated with decreased crisis from our prior study.(Miyake, Lay, Soler-Alfonso, et al., 2022) However, as has been previously reported, after starting B-complex vitamins, neither older sibling had a subsequent metabolic crisis.(Miyake, et al., 2022) Nevertheless, both older siblings

have persistent TDD-related symptoms such as difficulty walking, dysarthria, and cognitive delays. When comparing developmental profiles of both siblings, the two younger siblings were found to be average, scoring in ranges that would be similar to their age-matched peers while their older siblings were delayed, both scoring less than the 3rd centile.

While further data are required, these observations may suggest an important role of early B-vitamin supplementation in TDD prior to the onset of any symptoms or crises. Whether genetic modifiers further modulate the disease course remains to be investigated. The mechanism behind the potential benefit and dose of B-vitamin supplementation in TDD remains unknown and requires further investigation.

While B-vitamins are water soluble with most having no risk, high-doses of pyridoxine (B6) can lead to peripheral neuropathy. The current recommendation is to take at least a minimum of recommended daily allowance under physician supervision. (Miyake, et al., 2022) Well-designed prospective studies are needed to confirm our findings and delineate the role of vitamin supplementation in the pathophysiology of TDD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing and Data Accessibility:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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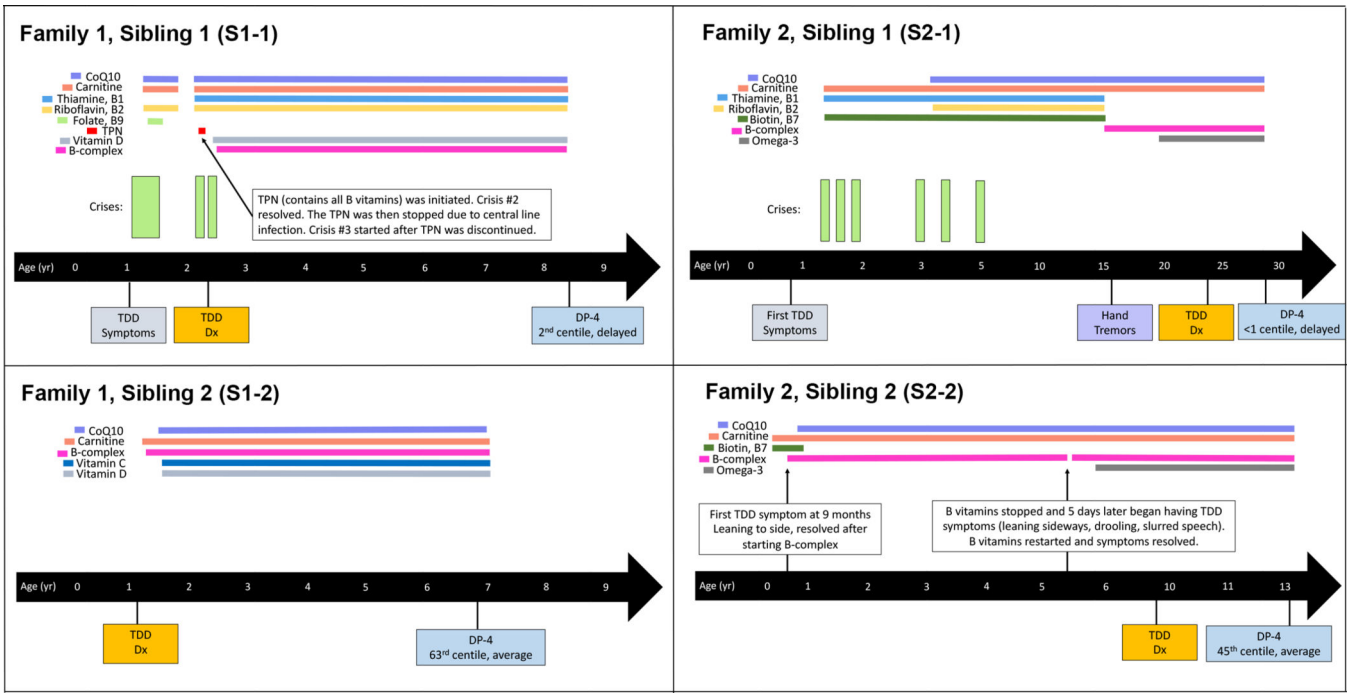

Figure 1.

Graphical Timeline of Metabolic Crises and Supplements

CoQ10-Coenzyme Q10, TPN- total parenteral nutrition, TDD – TANGO2 Deficiency Disorder, Dx – diagnosis, DP-4- Developmental Profile 4.

Table 1.

B-complex supplementation: Doses at initiation and current

		Family 1				Family 2			
		Sibling (S1–1)		Sibling (S1–2)		Sibling (S2–1)		Sibling (S2–2)	
	Unit	2.5y	8.5y	17m	7.0y	16y	29y	9m	13y
Thiamine, B1	mg	225†	180†	50	100	100	200	100	200
Riboflavin, B2	mg	115†	170†	10	20	100	200	100	200
Niacin, B3	mg	25	55	12.5	25	100	200	100	200
Pantothenic acid, B5	mg	25	100	2.75	5.5	100	1200†	100	1200†
Pyridoxine, B6	mg	25	50	1	2	100	200	100	200
Biotin, B7	mcg	25	300	15	30	100	200	100	200
Folate, B9	mcg‡	200	400	200	400	400	800	400	800
Cyanocobalamin, B12	mcg	25	50	7.5	15	100	200	100	200

Ages reflect times at which full B-complex was first initiated and current doses.

† doses include additional supplement being taken in addition to B-complex.

‡ as folic acid.

Table 2.

Developmental Profile-4 Testing

Family 1	**Older Sibling (S1–1) Age 8 years, 4 months**			**Younger Sibling (S1–2) Age 6 years, 11 months**		
	centile	**Descriptive range**	**Age equivalent**	**centile**	**Descriptive range**	**Age equivalent**
General Developmental Score	2	delayed	NA	63	average	NA
Physical	2	delayed	4:0 – 4:5	61	average	7:0 – 7:11
Adaptive Behavior	9	below average	5:6 – 5:11	81	average	8:0 – 8:11
Social-Emotional	34	average	6:6 – 6:11	73	average	8:0 – 8:11
Cognitive	0.1	delayed	3:6 – 3:11	82	average	7:0 – 7:11
Communication	0.5	delayed	4:6 – 4:11	50	average	6:6 – 6:11
Family 2	**Older Sibling (S2–1) Age 28 years, 9months†**			**Younger Sibling (S2–2) Age 13 years, 3months**		
General Developmental Score	<0.1	delayed	NA	45	average	NA
Physical	<0.1	delayed	2:0 – 2:3	53	average	11:0 – 12:11
Adaptive Behavior	<0.1	delayed	2:4 – 2:7	39	average	10:0 – 10:11
Social-Emotional	1	delayed	4:0 – 4:5	42	average	10:0 – 10:11
Cognitive	<0.1	delayed	3:0 – 3:5	55	average	13:0 – 16:11
Communication	0.1	delayed	2:8 – 2:11	75	average	17:0 – 21:11

† DP-4 administration is standardized for ages 21 years.