Received: 13 October 2022 | Revised: 1 February 2023 | Accepted: 21 February 2023

DOI: 10.1002/ajmg.a.63173

AMERICAN JOURNAL OF medical genetics PART A WILEY

RESEARCH LETTER

Developmental disorder and spastic paraparesis in two sisters with a *TCF7L2* truncating variant inherited from a mosaic mother

Beryl Royer-Bertrand[1] | Sébastien Lebon[2] | Ailsa Craig[1] | Johanna Maeder[2] | Laureane Mittaz-Crettol[1] | Heidi Fodstad[1] | Andrea Superti-Furga[1] | Jean-Marc Good[1]

[1]Division of Genetic Medicine, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland

[2]Unit of Pediatric Neurology and Neurorehabilitation, Department of Pediatrics, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland

Correspondence
Jean-Marc Good, Division of Genetic Medicine, Lausanne University Hospital (CHUV) and University of Lausanne, Av. Pierre Decker 5, 1011 Lausanne, Switzerland.
Email: jean-marc.good@chuv.ch

To the Editor,

The Wnt signaling pathway has a key role in controlling numerous biological processes including cell proliferation, differentiation, apoptosis as well as embryonic development (Augustin et al., 2012; Clevers et al., 2014; Lu et al., 2011; Polioudakis et al., 2019). Upon stimulation by Wnt proteins, beta-catenin is released from its repressive complex, allowing it to translocate to the nucleus where it binds to transcription factors, including TCF7L2 (Transcription Factor 7-Like 2), to initiate gene expression (Castrop et al., 1992; Polakis, 2000; Yang et al., 2016). Numerous genome-wide association studies have found robust associations between common intronic variants in the *TFC7L2* gene and type-2 diabetes, suggesting a role of this gene in glucose metabolism (Cauchi et al., 2006; Del Bosque-Plata et al., 2021; Del Bosque-Plata et al., 2022; Grant et al., 2006; Tong et al., 2009). More recently, experiments on murine models revealed a critical role of *Tcf7l2* in neurogenesis and neural connectivity in the developing brain (Chodelkova et al., 2018; Lee et al., 2017). In consistence with these findings, de novo *TCF7L2* variants were identified as a potential cause of neurodevelopmental phenotype in large-scale exome sequencing studies (Iossifov et al., 2014; Lelieveld et al., 2016). More recently, Dias et al. (2021) provided a phenotypic description of a new neurodevelopmental disorder by reporting 11 individuals carrying de novo missense or truncating variants in the *TCF7L2* gene. Soon after, the *TCF7L2*-related Neurodevelopmental Disorder network (trndnetwork.org) was created to support patients and families, as well as to promote research and collaborations.

We report here two sisters with a developmental phenotype carrying a novel *TCF7L2* variant originating from maternal mosaicism. In addition to the developmental delay typical of *TCF7L2*-related Neurodevelopmental Disorder, pyramidal signs of lower limbs compatible with spastic paraparesis as well as periventricular white matter lesions were noted in both of them, and the eldest one developed diabetes mellitus type 1 at age 9 years.

The proband (II-3, Figure 1a) is a 7-year-old girl born at term to healthy unrelated parents. Birth was uneventful and her neonatal adaptation was good (Apgar score: 9/10/10). She had a mild global developmental delay with severe speech and language disorder and suspicion of childhood apraxia of speech. Toe walking was noticed as soon as she started to walk independently at around 15 months of age. The neurological assessment revealed pyramidal signs of the lower limbs. Brain Magnetic resonance imaging (MRI) at age 4 showed small periventricular white matter lesions (Figure 1c) as well as a thin isthmus of the corpus callosum. At age 5, she was unable to pronounce sounds and syllables accurately, resulting in unintelligible speech, and she receives special education. A recent neuropsychological assessment revealed a severe oral language impairment and childhood apraxia of speech with a preserved nonverbal intelligence. Attention deficit, poor executive control, as well as weak graphomotor performances were also reported (Wechsler Intelligence Scale for Children V (WISC-V): Full-Scale intellectual quotient (IQ): 68, General Ability Index (GAI): 76, Non Verbal Index (NVI): 78, Cognitive

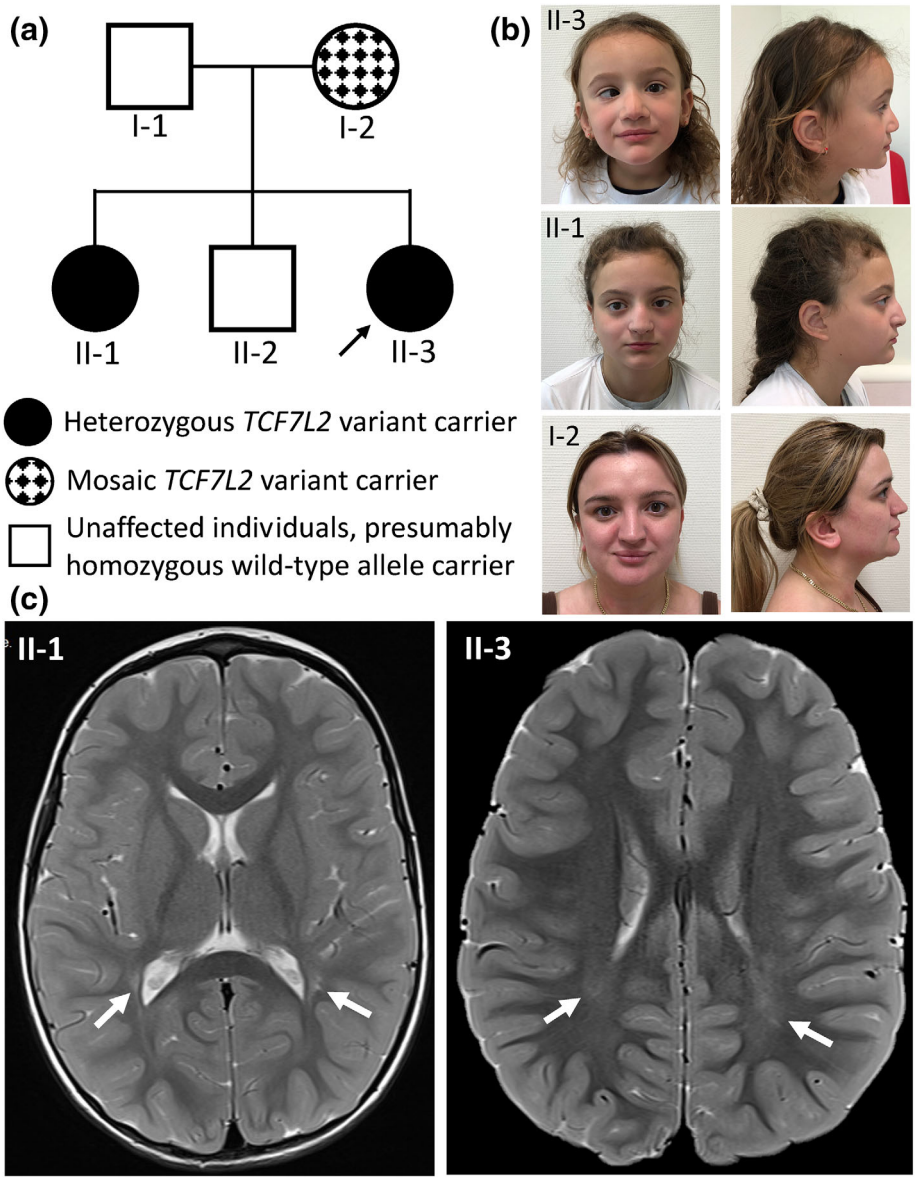

FIGURE 1 (a). Family pedigree. (b). Face and profile pictures of the proband II-3, her sister II-1, and their mother I-2. (c). Brain MRI axial T2-weighted images. On the left panel (II-1): punctate periventricular hyperintensities. On the right panel (II-3): mild periventricular hyperintensities compatible with terminal zones of myelination.

Proficiency Index (CPI): 73, Snijders-Oomen nonverbal intelligence test (SON-R): reasoning 103). Ophthalmological examination at age one revealed strabismus and myopia of −6 diopters in both eyes. The proband currently still has −6 diopters in the left eye, and − 7.25 in the right eye, as well as astigmatism in both eyes, +2.50 diopters at 3° and + 2.75 diopter at 10° in the left and right eye, respectively. Clinical evaluation revealed distinctive facial features including a prominent forehead, a wide-based nose with a wide nasal ridge and a pointed chin (Figure 1b). The growth parameters were within normal limits.

The older sister of the proband (II-1, Figure 1a) had been born at term after a premature rupture of membranes, and her neonatal adaptation was good (Apgar score of 7/9/9). At age 2, a similar developmental phenotype predominantly affecting expressive language was noticed. A brain MRI at age 2 showed moderate posterior periventricular hyperintensities with white matter thinning, first interpreted as periventricular leukomalacia (Figure 1c). Regarding her motor development, "stiffness" with limitation of hip abduction was noticed soon after birth and she started to walk at age 18 months. Neurologic evaluation revealed mild spastic diparesis that improved over time. At 7 years of age, she had brisk deep tendon reflexes and mild distal hypertonia of lower limbs. The neuropsychological assessment at age 6½ years was suggestive of a moderate intellectual disability but the cooperation of the child was considered suboptimal. Currently aged 14, she receives special education but has been making progress and expresses herself clearly, using sentences. A subsequent neuropsychological evaluation revealed a mild intellectual disability with poor executive functioning and graphomotor skills, as well as learning disorders (WISC-V: Total IQ 68, GAI: 74, NVI: 73, CPI: 60). She also developed moderate myopia as early as age one, and had surgery to correct strabismus. The last ophthalmological evaluation revealed myopia of −5 diopters and astigmatism of +5.25 at 3° in the right eye, and myopia of −5.50 and astigmatism of +3.25 at 171° in the left eye. During childhood, she also suffered from recurrent serous otitis media that

were treated with tympanostomy tubes. At age 9, she developed diabetes mellitus type 1 with positive Islet Antigen 2 antibodies: 997 U/mL (N < 15). No other family members suffer from glucose metabolism disorder. Clinical evaluation revealed mild eversion of inferior eyelids, a wide nasal ridge and tip with a prominent nasal bridge, as well as a slightly low-hanging columella and a pointed chin (Figure 1b).

The proband's mother (I-2, Figure 1a,b) describes herself as having some difficulties at school mainly due to absenteeism in the context of chronic migraines, but no developmental delay or cognitive disorders have been documented. She is known for myopia since age 6, and has currently −7 diopters in the right eye and −7.50 diopters in the left with mild astigmatism in both eyes.

With appropriate informed consent of the parents, exome sequencing was carried out on NextSeq 500 sequencing from Illumina using the Comprehensible library from Twist Biosciences®, on genomic DNA extracted from leukocytes of the proband and processed as previously described (Royer-Bertrand et al., 2021). The targeted analysis of virtual gene panels for neurodevelopmental disorders (1832 genes) and hereditary spastic paraplegia (147 genes) allowed the identification of the heterozygous variant c.565_566dup, p.Pro190Arg*fs**13, NM_030756.5, (chr10:114901022->CA, GRCh37) in the Exon 5 of the *TCF7L2* gene (Supplementary Figure S1), leading to a frameshift and a truncation of the protein. The *TCF7L2* variant is absent from public databases of control cohort (gnomAD v2.1.1 database; Karczewski et al., 2020), as well as from our in-house patient's database (n = 1465). *TCF7L2* is predicted to be associated with dominant disorders (DOMINO score of 1; Quinodoz et al., 2017) and is also predicted to be highly intolerant to loss-of-function, as calculated in GnomAD constraint (pLI = 1). Familial segregation analysis was performed by Sanger sequencing on DNA extracted from leukocytes. It revealed that the proband's sister was also carrying the duplication (Figure 2), while both parents were homozygous for the wild-type allele. For these reasons, the p.Pro190Arg*fs**13 variant was classified as "pathogenic" according to ACMG criteria, and considered causative of the neurodevelopmental phenotype of the proband and her sister. Because of the recurrence of a seemingly de novo mutation, parental mosaicism was suspected. Sanger sequencing was performed on DNA extracted from buccal swab from the parents, confirming this hypothesis by showing a small signal for the *TCF7L2* variant in the mother (I-2; Figure 2). To better characterize the mosaicism, we performed an additional analysis by exome sequencing on the mother's DNA. Consistently with the result of the Sanger sequencing, the c.565_566dup variant was present in the buccal swab's DNA with a fraction of 9.6% (11 out of 115 reads) while it was undetectable in leucocytes, as represented with Integrative Genomics Viewer in Supplementary Figure S1 (Robinson et al., 2017).

Phenotypic descriptions of *TCF7L2*-related Neurodevelopmental Disorder are limited to the 11 patients recently documented by Dias et al. (2021). Here, we report two additional patients carrying an undescribed truncating variant, further supporting a causative role of *TCF7L2* haploinsufficiency in this neurodevelopmental condition. The proband and her sister's clinical features, in particular the developmental delay with speech and language disorders, myopia, and strabismus, correspond well to the previously documented patients (Table 1). Dias et al. (2021) reported 2/11 patients with hypertonia, but motor aspects of *TCF7L2*-related Neurodevelopmental Disorder have otherwise not been well documented. Here, we describe a phenotype of spastic paraparesis in both patients and a specific brain MRI

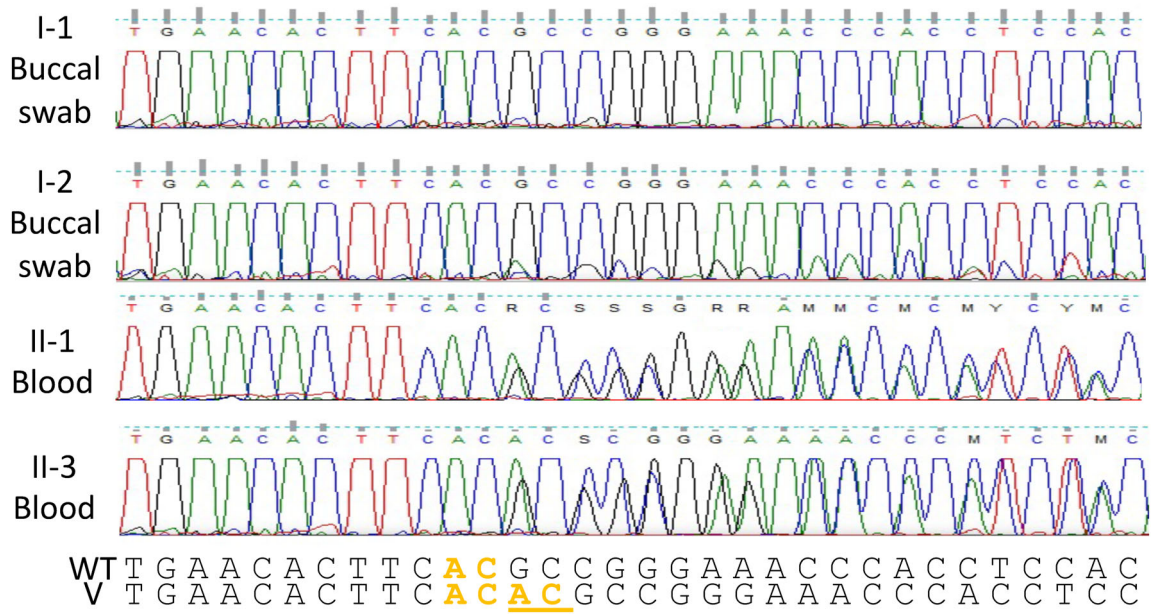

FIGURE 2 Familial segregation by Sanger sequencing of the variant c.565_566dup in *TCF7L2*, confirming a heterozygous state in the proband (II-3) and her sister (II-1) (DNA extracted from leukocytes), and revealing a mosaic pattern in the mother (I-2), the father (I-1) being homozygous for the wild-type allele (DNA extracted from buccal swabs). V, variant c.565_566dup. WT, wild-type allele. The duplicated bases are indicated in orange.

TABLE 1 Clinical features of patients with pathogenic variants in *TCF7L2*.

SIS	II-3	II-1	Dias et al. (2021) 11 cases
Variant (NM_030756.5)	c.565_566dup, p.Pro190Arg*fs**13	c.565_566dup, p.Pro190Arg*fs**13	
Inheritance	From mosaic mother	From mosaic mother	De novo (11/11)
Gender (M[Male]/F [Female])	F	F	M:8, F:3
Age at evaluation	5 y	11 y	Mean 9 y (3–18 y)
Pregnancy	Normal	Normal	Complications (2/10)
Delivery	Term	Term	Term (10/10)
Perinatal complications	No. Good neonatal adaptation (APGAR score: 9–10-10)	Premature rupture of membranes, good neonatal adaptation (APGAR score: 7–9-9)	Yes (4/10)
Development			
Global developmental delay	Mild	Mild	Motor delay: 8/11. Speech delay: 11/11
Age at walking	15 months	18 months	Mean: 16 months (12 months – 24 months)
Speech delay?	Yes. Significant expressive language disorder	Yes. Expressive language disorder	11/11
Intellectual disability	Mild. FSIQ: 68. Normal nonverbal intelligence.	Mild. FSIQ: 68	5/11 Mean IQ (when IQ stated): 85
Craniofacial features			
Craniofacial dysmorphic features	Prominent forehead, wide-based nose with a wide nasal ridge and tip, pointed chin	Mild eversion of inferior eyelids, wide nasal ridge and tip, prominent nasal bridge, slightly low-hanging columella, pointed chin	8/11
Skeletal /extremities anomalies	No	No	5/11
Growth at evaluation			
Height	105 cm (25%–50%)	148 cm (50%–75%)	Within normal range[a] (9/9)
Weight	18 kg (50%–75%)	48 kg (75%–90%)	Within normal range[a] (8/10)
Head circumference	51.5 cm (75%)	54.5 cm (75%–90%)	Within normal range[a] (10/11)
Behavioral features			
Autism spectrum disorder	No	No	4/11
ADHD	Attention deficit without hyperactivity	No	4/11
Neurological features			
Tone abnormalities	Pyramidal signs of the lower limbs	Mild spastic diparesis	Hypertonia (2/11) Hypotonia in infancy (1/11)
Epilepsy	No	No	2/11
Ophthalmology findings	Strabismus, myopia, astigmatism	Strabismus, myopia, astigmatism	Myopia (6/11), Strabismus (3/11)
Otorhinolaryngology/ hearing	Recurrent otitis media	Recurrent otitis media	Ears infections (2/10)
Diabetes	No	Diabetes mellitus type 1 at age 9 y	0/7
Brain MRI	Small periventricular white matter lesions, thin isthmus of the corpus callosum	Posterior periventricular hyperintensities with white matter thinning	Abnormal (5/10)
Additional genetic findings	Heterozygous carrier of c.2881C > T, p.Arg961* in *SACS* (ClinVar ID: 640122)	N/A	

[a]Normal range is defined as the central 95% of the population.

Abbreviations: %, percentile; ADHD, attention deficit hyperactivity disorder; IQ, intellectual quotient; cm, centimeters; FSIQ, full-scale intellectual quotient; kg, kilograms; N/A, not available; y, year.

pattern with periventricular hyperintensities in the T2-weighted sequences. This association, together with strabismus and developmental delay, led first to the misdiagnosis of cerebral palsy due to periventricular leukomalacia in the proband's sister. The latter condition usually affects premature infants, which was not the case of the two sisters (Schneider & Miller, 2019). Of note, this radiological phenotype has not been reported by Dias et al., except in one patient with prominent ventricles and frontal periventricular leukomalacia, who indeed suffered from perinatal asphyxia and was excluded from the cohort for this reason. The study of larger series of patients will help to determine whether the spasticity and brain MRI findings indeed belong to the phenotypic features of *TCF7L2*-related Neurodevelopmental Disorder. Interestingly, the proband's sister developed diabetes type 1 at age 9. The causality between this phenotype and *TCF7L2* haploinsufficiency remains unclear. None of the 11 patients in the cohort from Dias et al. (2021) developed diabetes, even if the majority of the patients in that series are still very young. Moreover, no association between the presence of diabetes type 1 and *TCF7L2* variants was ever reported, albeit some single nucleotide polymorphisms were shown to be linked to certain characteristics of diabetes type 1, including the level of C-peptide and the pattern of antibodies (Ergur et al., 2022; Redondo, Geyer, et al., 2018; Redondo, Steck, et al., 2018). All documented cases of *TCF7L2*-related Neurodevelopmental Disorder were described as occurring in a de novo manner (Dias et al., 2021). The observation of two siblings carrying a *TCF7L2* variant inherited from a mosaic mother adds to the list of neurodevelopmental disorders in which mosaicism has been observed. Importantly, prenatal diagnosis should be an option offered to pregnant mothers with a first affected child, even when due to an apparently de novo variant in *TCF7L2*.

AUTHOR CONTRIBUTIONS

Conceptualization: Beryl Royer-Bertrand and Jean-Marc Good. *Molecular analysis*: Beryl Royer-Bertrand, Laureane Mittaz-Crettol, and Heidi Fodstad. *Clinical aspects*: Jean-Marc Good, Ailsa Craig, Johanna Maeder, Andrea Superti-Furga, and Sebastien Lebon. *Preparation of the original draft*: Beryl Royer Bertrand, Ailsa Craig, Laureane Mittaz-Crettol, and Jean-Marc Good. *Writing, reviewing and editing*: Beryl Royer-Bertrand, Sebastien Lebon, Johanna Maeder, Laureane Mittaz-Créttol, Heidi Fodstad, Andrea Superti-Furga, and Jean-Marc Good. All authors participated in revision and approval of the article.

ACKNOWLEDGMENTS

The authors are grateful to the patients and their parents for their participation in this study.

CONFLICT OF INTEREST STATEMENT

The authors declared that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this report are available upon reasonable request, from the corresponding author.

ORCID

Beryl Royer-Bertrand https://orcid.org/0000-0002-7971-1862
Sébastien Lebon https://orcid.org/0000-0002-1666-1124
Andrea Superti-Furga https://orcid.org/0000-0002-3543-7531
Jean-Marc Good https://orcid.org/0000-0001-9491-7597

REFERENCES

Augustin, I., Goidts, V., Bongers, A., Kerr, G., Vollert, G., Radlwimmer, B., Hartmann, C., Herold-Mende, C., Reifenberger, G., von Deimling, A., & Boutros, M. (2012). The Wnt secretion protein Evi/Gpr177 promotes glioma tumourigenesis. *EMBO Molecular Medicine*, *4*(1), 38–51. https://doi.org/10.1002/emmm.201100186

Castrop, J., van Norren, K., & Clevers, H. (1992). A gene family of HMG-box transcription factors with homology to TCF-1. *Nucleic Acids Research*, *20*(3), 611. https://doi.org/10.1093/nar/20.3.611

Cauchi, S., Meyre, D., Dina, C., Choquet, H., Samson, C., Gallina, S., Balkau, B., Charpentier, G., Pattou, F., Stetsyuk, V., Scharfmann, R., Staels, B., Frühbeck, G., & Froguel, P. (2006). Transcription factor TCF7L2 genetic study in the French population: Expression in human beta-cells and adipose tissue and strong association with type 2 diabetes. *Diabetes*, *55*(10), 2903–2908. https://doi.org/10.2337/db06-0474

Chodelkova, O., Masek, J., Korinek, V., Kozmik, Z., & Machon, O. (2018). Tcf7L2 is essential for neurogenesis in the developing mouse neocortex. *Neural Development*, *13*(1), 8. https://doi.org/10.1186/s13064-018-0107-8

Clevers, H., Loh, K. M., & Nusse, R. (2014). Stem cell signaling. An integral program for tissue renewal and regeneration: Wnt signaling and stem cell control. *Science*, *346*(6205), 1248012. https://doi.org/10.1126/science.1248012

Del Bosque-Plata, L., Hernandez-Cortes, E. P., & Gragnoli, C. (2022). The broad pathogenetic role of TCF7L2 in human diseases beyond type 2 diabetes. *Journal of Cellular Physiology*, *237*(1), 301–312. https://doi.org/10.1002/jcp.30581

Del Bosque-Plata, L., Martinez-Martinez, E., Espinoza-Camacho, M. A., & Gragnoli, C. (2021). The role of TCF7L2 in type 2 diabetes. *Diabetes*, *70*(6), 1220–1228. https://doi.org/10.2337/db20-0573

Dias, C., Pfundt, R., Kleefstra, T., Shuurs-Hoeijmakers, J., Boon, E. M. J., van Hagen, J. M., Zwijnenburg, P., Weiss, M. M., Keren, B., Mignot, C., Isapof, A., Weiss, K., Hershkovitz, T., Iascone, M., Maitz, S., Feichtinger, R. G., Kotzot, D., Mayr, J. A., Ben-Omran, T., … Rodan, L. H. (2021). De novo variants in TCF7L2 are associated with a syndromic neurodevelopmental disorder. *American Journal of Medical Genetics Part A*, *185*(8), 2384–2390. https://doi.org/10.1002/ajmg.a.62254

Ergur, E., Ergur, E., Alnek, K., Metskula, K., Peet, A., Lubi, M., Heilman, K., & Uibo, R. (2022). Clinical signs of type 1 diabetes are associated with type 2 diabetes marker transcription factor 7-like 2 polymorphism. *Journal of Diabetes Investigation*, *14*, 221–229. https://doi.org/10.1111/jdi.13933

Grant, S. F., Thorleifsson, G., Reynisdottir, I., Benediktsson, R., Manolescu, A., Sainz, J., Helgason, A., Stefansson, H., Emilsson, V., Helgadottir, A., Styrkarsdottir, U., Magnusson, K. P., Walters, G. B., Palsdottir, E., Jonsdottir, T., Gudmundsdottir, T., Gylfason, A., Saemundsdottir, J., Wilensky, R. L., … Stefansson, K. (2006). Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nature Genetics*, *38*(3), 320–323. https://doi.org/10.1038/ng1732

Iossifov, I., O'Roak, B. J., Sanders, S. J., Ronemus, M., Krumm, N., Levy, D., Stessman, H. A., Witherspoon, K. T., Vives, L., Patterson, K. E., Smith, J. D., Paeper, B., Nickerson, D. A., Dea, J., Dong, S., Gonzalez, L. E., Mandell, J. D., Mane, S. M., Murtha, M. T., … Wigler, M. (2014). The contribution of de novo coding mutations to

autism spectrum disorder. *Nature*, *515*(7526), 216–221. https://doi.org/10.1038/nature13908

Karczewski, K. J., Francioli, L. C., Tiao, G., Cummings, B. B., Alfoldi, J., Wang, Q., Collins, R. L., Laricchia, K. M., Ganna, A., Birnbaum, D. P., Gauthier, L. D., Brand, H., Solomonson, M., Watts, N. A., Rhodes, D., Singer-Berk, M., England, E. M., Seaby, E. G., Kosmicki, J. A., … MacArthur, D. G. (2020). The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature*, *581*(7809), 434–443. https://doi.org/10.1038/s41586-020-2308-7

Lee, M., Yoon, J., Song, H., Lee, B., Lam, D. T., Yoon, J., Baek, K., Clevers, H., & Jeong, Y. (2017). Tcf7l2 plays crucial roles in forebrain development through regulation of thalamic and habenular neuron identity and connectivity. *Developmental Biology*, *424*(1), 62–76. https://doi.org/10.1016/j.ydbio.2017.02.010

Lelieveld, S. H., Reijnders, M. R., Pfundt, R., Yntema, H. G., Kamsteeg, E. J., de Vries, P., de Vries, B. B., Willemsen, M. H., Kleefstra, T., Löhner, K., Vreeburg, M., Stevens, S. J., van der Burgt, I., Bongers, E. M., Stegmann, A. P., Rump, P., Rinne, T., Nelen, M. R., Veltman, J. A., … Gilissen, C. (2016). Meta-analysis of 2,104 trios provides support for 10 new genes for intellectual disability. *Nature Neuroscience*, *19*(9), 1194–1196. https://doi.org/10.1038/nn.4352

Lu, D., Choi, M. Y., Yu, J., Castro, J. E., Kipps, T. J., & Carson, D. A. (2011). Salinomycin inhibits Wnt signaling and selectively induces apoptosis in chronic lymphocytic leukemia cells. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(32), 13253–13257. https://doi.org/10.1073/pnas.1110431108

Polakis, P. (2000). Wnt signaling and cancer. *Genes & Development*, *14*(15), 1837–1851.

Polioudakis, D., de la Torre-Ubieta, L., Langerman, J., Elkins, A. G., Shi, X., Stein, J. L., Vuong, C. K., Nichterwitz, S., Gevorgian, M., Opland, C. K., Lu, D., Connell, W., Ruzzo, E. K., Lowe, J. K., Hadzic, T., Hinz, F. I., Sabri, S., Lowry, W. E., Gerstein, M. B., … Geschwind, D. H. (2019). A single-cell transcriptomic atlas of human neocortical development during mid-gestation. *Neuron*, *103*(5), 785–801 e788. https://doi.org/10.1016/j.neuron.2019.06.011

Quinodoz, M., Royer-Bertrand, B., Cisarova, K., Di Gioia, S. A., Superti-Furga, A., & Rivolta, C. (2017). DOMINO: Using machine learning to predict genes associated with dominant disorders. *American Journal of Human Genetics*, *101*(4), 623–629. https://doi.org/10.1016/j.ajhg.2017.09.001

Redondo, M. J., Geyer, S., Steck, A. K., Sosenko, J., Anderson, M., Antinozzi, P., Michels, A., Wentworth, J., Xu, P., Pugliese, A., & Type 1 Diabetes TrialNet Study Group. (2018). TCF7L2 genetic variants contribute to phenotypic heterogeneity of type 1 diabetes. *Diabetes Care*, *41*(2), 311–317. https://doi.org/10.2337/dc17-0961

Redondo, M. J., Steck, A. K., Sosenko, J., Anderson, M., Antinozzi, P., Michels, A., Wentworth, J. M., Atkinson, M. A., Pugliese, A., Geyer, S., & Type 1 Diabetes TrialNet Study Group. (2018). Transcription factor 7-like 2 (TCF7L2) gene polymorphism and progression from single to multiple autoantibody positivity in individuals at risk for type 1 diabetes. *Diabetes Care*, *41*(12), 2480–2486. https://doi.org/10.2337/dc18-0861

Robinson, J. T., Thorvaldsdottir, H., Wenger, A. M., Zehir, A., & Mesirov, J. P. (2017). Variant review with the integrative genomics viewer. *Cancer Research*, *77*(21), e31–e34. https://doi.org/10.1158/0008-5472.CAN-17-0337

Royer-Bertrand, B., Cisarova, K., Niel-Butschi, F., Mittaz-Crettol, L., Fodstad, H., & Superti-Furga, A. (2021). CNV detection from exome sequencing data in routine diagnostics of rare genetic disorders: Opportunities and limitations. *Genes (Basel)*, *12*(9), 1427. https://doi.org/10.3390/genes12091427

Schneider, J., & Miller, S. P. (2019). Preterm brain injury: White matter injury. *Handbook of Clinical Neurology*, *162*, 155–172. https://doi.org/10.1016/B978-0-444-64029-1.00007-2

Tong, Y., Lin, Y., Zhang, Y., Yang, J., Zhang, Y., Liu, H., & Zhang, B. (2009). Association between TCF7L2 gene polymorphisms and susceptibility to type 2 diabetes mellitus: A large human genome epidemiology (HuGE) review and meta-analysis. *BMC Medical Genetics*, *10*, 15. https://doi.org/10.1186/1471-2350-10-15

Yang, K., Wang, X., Zhang, H., Wang, Z., Nan, G., Li, Y., Zhang, F., Mohammed, M. K., Haydon, R. C., Luu, H. H., Bi, Y., & He, T. C. (2016). The evolving roles of canonical WNT signaling in stem cells and tumorigenesis: Implications in targeted cancer therapies. *Laboratory Investigation*, *96*(2), 116–136. https://doi.org/10.1038/labinvest.2015.144

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Royer-Bertrand, B., Lebon, S., Craig, A., Maeder, J., Mittaz-Crettol, L., Fodstad, H., Superti-Furga, A., & Good, J.-M. (2023). Developmental disorder and spastic paraparesis in two sisters with a *TCF7L2* truncating variant inherited from a mosaic mother. *American Journal of Medical Genetics Part A*, *191*A:1658–1663. https://doi.org/10.1002/ajmg.a.63173