Phenotype associated with TAF2 biallelic mutations: a clinical description of four individuals and review of the literature

Marion Lesieur-Sebellin, Yline Capri, Margot Grisval, Thomas Courtin, Augustine Burtz, Julien Thevenon, Julien Buratti, Elodie Lejeune, Laurence Faivre, Boris Keren

Phenotype associated with *TAF2* biallelic mutations: a clinical description of four individuals and review of the literature

Authors and affiliations

Marion Lesieur-Sebellin[a], Yline Capri[b], Margot Grisval[c], Thomas Courtin[a], Augustine Burtz[b], Julien Thevenon[c,d,e], Julien Buratti[a], Elodie Lejeune[a], Laurence Faivre[c,d], Boris Keren[a]

[a] *APHP, Département de Génétique, Centre de Référence Déficiences Intellectuelles de Causes Rares, Groupe Hospitalier Pitié Salpêtrière et GHUEP Hôpital Trousseau, Sorbonne Université, GRC "Déficience Intellectuelle et Autisme", Paris, France*

[b] *Service de Génétique Clinique, CHU Robert Debré, Paris Cedex, France*

[c] *Fédération Hospitalo-Universitaire Médecine Translationnelle et Anomalies du Développement (TRANSLAD), Centre Hospitalier Universitaire Dijon, Dijon, France/Centre de Génétique et Centre de Référence Anomalies du Développement et Syndromes Malformatifs de l'Interrégion Est, Centre Hospitalier Universitaire Dijon, Dijon, France*

[d] *UMR-Inserm 1231 GAD team, Génétique des Anomalies du développement, Université de Bourgogne Franche-Comté, F-21000 Dijon, France*

[e] *Laboratoire de Génétique chromosomique et moléculaire, UF Innovation en diagnostic génomique des maladies rares, Centre Hospitalier Universitaire de Dijon, Dijon, France*

Corresponding author:

Boris Keren, MD, PHD

E-mail address: boris.keren@aphp.fr

Full postal address: Département de Génétique, Unité Fonctionnelle de Génomique du Développement, Hôpital Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris

Telephone number : +33 (0)1 42 17 78 98 (France)
Fax number : +33 (0)1 42 17 76 00 (France)

Abstract

Transcription factor IID is a multimeric protein complex that is essential for the initiation of transcription by RNA polymerase II. One of its critical components, the TATA-binding protein-associated factor 2, is encoded by the gene *TAF2.* Pathogenic variants of this gene have been shown to be responsible for the Mental retardation, autosomal recessive 40 syndrome. This syndrome is characterized by severe intellectual disability, postnatal microcephaly, pyramidal signs and thin corpus callosum. Until now, only three families have been reported separately. Here we report four individuals, from two unrelated families, who present with severe intellectual disability and global developmental delay, postnatal microcephaly, feet deformities and thin corpus callosum and who carry homozygous *TAF2* missense variants detected by Exome Sequencing. Taken together, our findings and those of previously reported subjects allow us to further delineate the clinical phenotype associated with *TAF2* biallelic mutations.

Key Words

TAF2, intellectual disability, neurodevelopmental disorder, autosomal recessive

Introduction

The initiation of transcription by RNA polymerase II requires the action of several general transcription factors. One of them, the transcription factor IID (TFIID), is a multimeric protein complex that plays a key role in the recruitment of additional general transcription factors and RNA polymerase II to the core promoter (Kaufmann et al., 1998). It is composed of TATA-binding protein (TBP) and 13 TBP-associated factors (from TAF1 to TAF13) (Feigerle and Weil, 2016). One of its critical components, TAF2, stabilizes TFIID binding to core promoter (Louder et al., 2016; Martinez et al., 1998). It is encoded by the gene *TATA-Box Binding Protein Associated Factor 2 (TAF2).*

Pathogenic homozygous variants in *TAF2* have been associated with the Mental retardation, autosomal recessive 40 syndrome (OMIM#615599). This very rare syndrome is associated with severe intellectual disability (ID), pyramidal signs, postnatal microcephaly and thin corpus callosum. To date, only three unrelated families have been reported separately with a total of seven affected individuals. Four of them have been thoroughly clinically described in two articles (Halevy et al., 2012; Hellman-Aharony et al., 2013).Three additional individuals were diagnosed in the context of large Exome Sequencing (ES) diagnostic series (Najmabadi et al., 2011; Thevenon et al., 2016) and unfortunately lacked detailed clinical descriptions. So far, no large series have been described.

Here, we report a novel homozygous *TAF2* variant c.2380T>A p.(Tyr794Asn) detected by ES in a subject with severe ID and global developmental delay, postnatal microcephaly, feet deformities, severe hypotonia, thin corpus callosum and delayed myelination of the brain. We also describe two new subjects, siblings from a previously published proband (Thevenon et al., 2016) as well as an extensive clinical description of the proband. Finally, we review

clinical features of previously published individuals in order to further delineate the clinical phenotype associated with *TAF2* biallelic mutations.

Clinical reports

Written informed consent for genetic analysis and photographs publication with blurred eyes (for subject I) was obtained from the parents for clinical testing and research use. Clinical and molecular features of our subjects and of those previously reported are summarized in table 1.

Subject I

Subject I is a female born from consanguineous healthy parents who came from North Africa (figure 1A). At the time of birth, maternal age was 28 years old (yo) and paternal age was 34 yo. She was born after an uneventful pregnancy. Birth measurements were in the normal range (Birth Weight (BW): 3360 g (0.5 SD); Birth Length (BL): 50 cm (0 SD); Birth Occipitofrontal Circumference (OFC): 43,5 cm (- 1 SD)) according to the OMS Z-score. From the first weeks of life, she had suction difficulties that required artificial nutrition. At around 3 months old (mo) she presented with hypotonia and was diagnosed with laryngomalacia. At 2 yo she presented with microcephaly (OFC: 43.5 cm (- 4 SD)) and severe ID without dysmorphic features (photographs are presented in figure 1B). Weight and length were in the normal range. Cognitive and motor developments were delayed as she babbled, could roll over but had no head control. She had severe axial hypotonia. She did not have any pyramidal signs. Microcephaly persisted at 2.5 yo (-4 SD) and at 4 yo (OFC: 46 cm (-4 SD)). Brain Magnetic Resonance Imaging (MRI) revealed a short and thin corpus callosum with diffuse and asymmetrical white matter abnormalities. Metabolic laboratory explorations and electroretinography were normal. Initial genetic investigations (Chromosomal Microarray Analysis (CMA), leucodystrophy genes panel, intellectual disability genes panel (including 450 genes), 15q11.2 methylation studies) did not show any abnormalities.

Subjects II:1, II:2 and II:4

Subjects II:1, II:2 and II:4 are siblings born from two healthy first cousin parents who came from North Africa (figure 1C).

II:1 is a male born in a context of perinatal distress. BW was in the normal range (3200 g). Unfortunately, we were not able to retrieve BL and birth OFC. At his arrival in France at 7 yo, he presented with severe ID and poor social interactions. Motor and cognitive developments were delayed as he did not walk, sit or rise and did not talk. Clinical examination showed microcephaly (OFC was not retrieved), congenital convergent strabismus and nystagmus without cataract or amblyopia, bilateral equinovarus of the feet and severe thoracolumbar scoliosis (+ 120°) that required arthrodesis. He had hand stereotypies and spastic tetraplegia that quickly deteriorated from birth. In addition, he presented with dysphagia and severe malnutrition that required a gastrostomy at 22 yo and he suffered from multiple aspiration pneumonias and chronic pulmonary congestion that necessitated tracheotomy at 25 yo. Brain MRI revealed a thin corpus callosum. He died at 27 yo from acute respiratory failure.

II:2 is a male who had a neurological presentation similar to that of his brother with severe ID and spastic tetraplegia quickly deteriorating from birth. Unfortunately, we could not retrieve birth parameters but he presented with microcephaly at 18 yo (OFC: 49cm (-3 SD)). Motor and cognitive developments were delayed as he did not walk nor talk. Clinical examination showed some distinctive craniofacial features (long face, mandibular prognathism, macrostomia and superior incisor's diastema) but similar to his non affected brother (II:3), bilateral equinovarus of the feet and onset of scoliosis. Neurological examination revealed severe limb amyotrophia and an absence of lower limb reflexes. He suffered from severe malnutrition due to early dysphagia and esophagitis due to severe gastroesophageal reflux that necessitated Nissen fundoplication and gastrostomy at 11 yo. In addition, he presented with

clinical hypogonadism (cryptorchidism, micro penis and poor pubic hairiness), he suffered from left hip congenial dysplasia that required hip replacement at 24 yo and he had multiple aspiration pneumonias with infections. Brain MRI revealed complete corpus callosum agenesis. Laboratory explorations, including karyotype and CMA, did not show any abnormalities.

II:4 is a female with the same clinical presentation as her brothers (II:1 and II:2) with the exception that she had more social interactions (eye contact, smiles). Unfortunately, we could not retrieve birth parameters but she presented with microcephaly at 8 yo (OFC: 46cm (-3 SD)). From birth she had feeding difficulties with hypotonia, dysphagia and severe gastroesophageal reflux that necessitated gastrostomy and Nissen fundoplication during the first months of life. At 11 yo she suffered from iterative acute bleeding due to esophageal ulcerations that led to hemorrhagic shock. Clinical examination showed some distinctive craniofacial features (long eyelashes, synophrys, macrostomia and protruding central incisors), convergent left strabismus, severe scoliosis (+ 100°) that required arthrodesis at 13 yo, severe distortions of pelvis and ankles and bilateral clubfeet. She had hand stereotypies. She suffered from iterative bronchiolitis and aspiration pneumonias and presented with early puberty. Brain MRI revealed a thin corpus callosum. Laboratory explorations, including karyotype, did not show any abnormalities.

Exome Sequencing Results

In subject I, ES trio analysis revealed a homozygous missense variant in *TAF2*: NM_003184.4:c.2380T>A p.(Tyr794Asn). Both parents are heterozygous carriers. The variant falls on a highly conserved amino acid (exon 19/26) in an Armadillo-type fold protein domain. It is absent in general population alleles in the Genome Aggregation Database (gnomAD, http://gnomad.broadinstitute.org/). It is predicted deleterious by *in silico* prediction

tools (SIFT score: 0; Poly-Phen 2 score: 0.989; PHRED-like scaled CADD: 31; REVEL score: 0.715). According to the ACMG criteria (Richards et al., 2015), this variant is classified as probably pathogenic (PM1, PM2, PP2, PP3). The PP2 criterion was used because *TAF2* has a positive gnomAD missense constraint Z score = 2.78, and is therefore more intolerant to variation. In addition, the variant is localized in a position predicted intolerant to mutations (MetaDome tool, https://stuart.radboudumc.nl/metadome/). No additional rare variants were detected in genes involved so far in neurodevelopmental diseases with our analysis criteria; however, a double diagnosis cannot be formally excluded.

In subject II:4, ES solo analysis revealed a homozygous missense variant in *TAF2*: NM_003184.4:c.2531C>T p.(Pro844Leu). Familial segregation using Sanger sequencing revealed that subjects II:1 and II:2 are homozygous as well whereas both parents and the unaffected sibling II:3 are heterozygous carriers. The variant falls on a highly conserved amino acid (exon 19/26) in an Armadillo-type fold protein domain. Allele frequency (AF) in general population is very low according to the gnomAD database: AF= 0.00003583. It is predicted deleterious by *in silico* prediction tools (SIFT score: 0; Poly-Phen 2 score: 0.973; PHRED-like scaled CADD score: 28.1; REVEL score: 0.611). According to the ACMG criteria, this variant is classified as probably pathogenic (PM1, PM2, PP1, PP2, PP3). It was previously reported (Thevenon et al., 2016). No additional rare variants were detected in genes involved so far in neurodevelopmental diseases with our analysis criteria; however, a double diagnosis cannot be formally excluded.

Discussion

So far, only three families with individuals carrying pathogenic homozygous variants in *TAF2* had been reported separately. In 2011, Najmabadi et al identified 50 novel genes responsible for recessive cognitive disorders by using ES in consanguineous families. They detected a

TAF2 homozygous missense variant in two siblings with moderate to severe ID, postnatal microcephaly and feet deformities. This variant was considered probably pathogenic. In 2012, Halevy et al described four individuals from three interrelated consanguineous families who presented with autosomal recessive inheritance of moderate to severe ID, global developmental delay and postnatal microcephaly, pyramidal signs and thin corpus callosum. By using homozygosity mapping, they mapped the disease at locus 8q23.2q24.12. In 2013, Hellman-Aharony et al pursued investigations in these individuals and identified two shared homozygous missense variants in *TAF2*. Both variants were predicted to impact protein features, thus they could not ascertain which was the causative one or if both affected the function of the protein. In 2016, Thevenon et al performed ES on 43 individuals with ID and/or epileptic encephalopathy. They detected a *TAF2* homozygous missense variant in a subject from a consanguineous family who presented with severe ID and microcephaly but did not provide a full clinical description. In total, the report of these three affected families delineated a new autosomal recessive mental retardation syndrome (OMIM# 615599) caused by biallelic *TAF2* mutations. However, no large series have been described so far and additional reports were needed to further delineate mutational spectrum and clinical features associated with this very rare syndrome.

TAF2 protein is a subunit of TFIID which is critical for the initiation of transcription. Thus, alteration of its structure could be deleterious on various developmental processes. Here we report a novel *TAF2* homozygous missense variant c.2380T>A p.(Tyr794Asn) in a subject with a strongly concordant phenotype. All *TAF2* mutations that have been reported so far, as well as the one in our subject, are biallelic changes with missense effect on translation. Biallelic loss of function mutations have never been reported to this day, either in general population (gnomAD database) or in affected individuals. It might be possible that biallelic loss of function mutations are too deleterious for survival. However, although it is very

unlikely as this mechanism has rarely been described, we cannot eliminate the possibility that biallelic mutations of *TAF2* would result in a gain of function of the protein.

Moderate to severe ID and postnatal microcephaly were observed in all ten subjects. Global developmental delay was reported for 8/10 subjects but could have been present in all as there was no detailed clinical description for the remaining ones (Najmabadi et al., 2011). Pyramidal signs were observed in 7/10 subjects, absent in subject I and undocumented for the two subjects from Najmabadi et al. Feeding difficulties were reported for 5/10 subjects, visual impairments for 4/10 and feet deformities for 5/10. Notably, 8/10 subjects presented with corpus callosum abnormalities on brain MRI and 4/10 (from two unrelated families) with delayed myelination of the brain. Unfortunately, this information was not documented for the family reported by Najmabadi et al and we were not able to retrieve this family's medical history in order to precise clinical features shared with our subjects.

Clinically, subjects I, II:1, II:2 and II:4 presented with a strongly overlapping phenotype with the individuals previously reported. Subject I had severe ID, global developmental delay, postnatal microcephaly, hypotonia and feet deformities associated with a thin corpus callosum and delayed myelination. In her case pyramidal signs were not observed. In this article we also describe two new subjects (II:1 and II:2), siblings from the previously published proband in Thevenon et al, 2016 (II:4) as well as an extensive clinical description of the proband. The three siblings share a common phenotype with severe ID, global developmental delay, postnatal microcephaly, spasticity, feet deformities and severe feeding difficulties associated with a thin corpus callosum. All in all, the clinical description of these four subjects allowed us to precise clinical features of the Mental retardation, autosomal recessive 40 syndrome.

In summary, we report a detailed clinical description of four individuals with mental retardation due to *TAF2* biallelic mutations. While awaiting a better understanding of the

pathological process involved, we were able to better delineate the clinical features associated with this very rare syndrome.

Acknowledgements

We thank the families for the agreement to publish their medical history. We are grateful to the laboratory technicians who performed the assays in Dijon and La Pitié-Salpêtrière hospitals.

Accession numbers

Variants have been submitted to the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/). NM_003184.4:c.2380T>A can be found using accession number SCV001571233. NM_003184.4:c.2531C>T can be found using accession number RCV000824867.1.

Figure 1. Family trees of the four subjects and pictures of subject I. A : Family tree of subject I **B:** Photographs of subject I at 3 years old. Dysmorphic features were not observed. **C :** Family tree of siblings II:1, II:2 and II:4

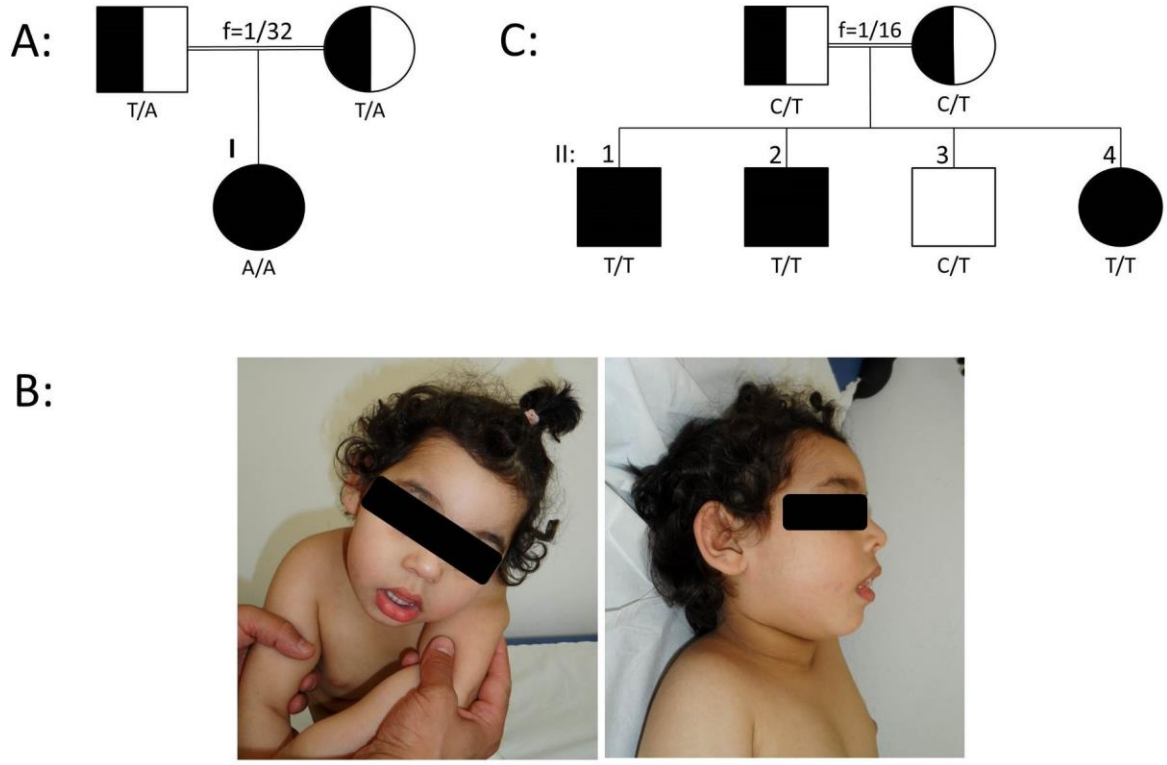

Table 1. Clinical and molecular features of subjects with *TAF2* pathogenic biallelic mutations.

Abbreviations: F, female; M, male; yo, years old; ND, information not documented; Hmz, homozygous; |, when two variants are reported they are separated by |; gnomAD AF, general population allele frequency in gnomAD database; OFC, occipitofrontal circumference; CCS, congenital convergent strabismus; IAP, iterative aspiration pneumonia; HCD: hip congenital dysplasia; MRI: magnetic resonance imaging; CC, corpus callosum; DM, delayed myelination

Features	Subject I	Subject II.1	Subject II.2	Subject II.4 Thevenon et al (2016)	Patient 1 Halevy et al. (2012)	Patient 2 Halevy et al. (2012)	Patient 3 Halevy et al. (2012)	Patient 4 Halevy et al. (2012)	Family M177 Najmabadi et al. (2011)	Family M177 Najmabadi et al. (2011)
Gender	F	M	M	F	F	F	M	M	ND	ND
Age at last evaluation (yo)	4	27	25	15	7	6	4	3	ND	ND
Consanguinity	+	+	+	+	+	+	+	+	+	+
Variant status	Hmz	Hmz	Hmz	Hmz	Hmz|Hmz	Hmz|Hmz	Hmz|Hmz	Hmz|Hmz	Hmz	Hmz
cDNA (NM_003184.4)	c.2380T>A	c.2531C>T	c.2531C>T	c.2531C>T	c.557C>G| c.1247C>A	c.557C>G| c.1247C>A	c.557C>G| c.1247C>A	c.557C>G| c.1247C>A	c.1945T>C	c.1945T>C
Genomic coordinates Chr8(GRCh37)	g.120774833A>T	g.120774682G>A	g.120774682G>A	g.120774682G>A	g.120816121G>C| g.120805636G>T	g.120816121G>C| g.120805636G>T	g.120816121G>C| g.120805636G>T	g.120816121G>C| g.120805636G>T	g.120795788A>G	g.120795788A>G
Predicted protein	p.(Tyr794Asn)	p.(Pro844Leu)	p.(Pro844Leu)	p.(Pro844Leu)	p.(Thr186Arg)| p.(Pro416His)	p.(Thr186Arg)| p.(Pro416His)	p.(Thr186Arg)| p.(Pro416His)	p.(Thr186Arg)| p.(Pro416His)	p.(Trp649Arg)	p.(Trp649Arg)
Exon	19	19	19	19	5|10	5|10	5|10	5|10	16	16
GnomAD AF	0	0.00003583	0.00003583	0.00003583	0|0	0|0	0|0	0|0	0	0
SIFT score	0	0	0	0	0|0	0|0	0|0	0|0	0	0
Poly-Phen 2 score	0.989	0.973	0.973	0.973	0.770|0.744	0.770|0.744	0.770|0.744	0.770|0.744	0.996	0.996
PHRED-like scaled CADD score	31	28.1	28.1	28.1	28.5|24.2	28.5|24.2	28.5|24.2	28.5|24.2	28	28
REVEL score	0.715	0.611	0.611	0.611	0.432|0.411	0.432|0.411	0.432|0.411	0.432|0.411	0.678	0.678
OFC (cm)	At birth: 33 (-0.75 SD) At 23 mo: 43,5 (-4 SD) At 2 y 9 mo: -4 SD At 4 y 3 mo: 46 (-4 SD)	Microcephaly (but OFC not available)	At 18 yo: 49 (-3 SD)	At 8 yo: 46 (-3 SD)	At birth: 40 (+4 SD) At 2 yo: 45,2 (-2 SD)	At birth: 33.5 (-0.5 SD) At 3 mo: -2 SD At 9 mo: -3 SD	At 9 mo: - 2 SD	At birth: 32.1 (-2 SD) At 9 mo: - 5,5 SD	Microcephaly (but OFC not available)	Microcephaly (but OFC not available)
Global developmental delay	+	+	+	+	+	+	+	+	ND	ND
Intellectual disability	Severe	Severe	Severe	Severe	Severe	Severe	Moderate-Severe	Moderate	Moderate-Severe	Moderate-Severe

Feeding difficulties	+	+	+	+	ND	+	ND	ND	ND	ND
Spasticity	-	+	+	+	+	+	+	+	ND	ND
Visual impairment	-	CCS	-	CCS	ND	ND	Strabismus, mild pallor of the fundi without retinal pigmentary changes	Horizontal nystagmus, mildly pale fundi, diffuse retinal pigmentary changes	ND	ND
Feet deformities	Bilateral equinovarus	Bilateral equinovarus	Bilateral equinovarus	Bilateral clubfoot	ND	ND	ND	ND	Yes (but no details available)	Yes (but no details available)
Additional signs	Global hypotonia Laryngomalacy	Scoliosis IAP	Scoliosis HCD Limbs amyotrophia IAP Clinical hypogonadism	Scoliosis Distortion of ankles and pelvis Early puberty	ND	Bicuspid aortic valve	ND	ND	ND	ND
Brain MRI	Short and thin CC Diffuse DM	Thin CC	CC agenesis	Thin CC	Thin CC Hydrocephalus	Thin CC Mildly DM Mild cerebral atrophy	Thin CC Mildly DM	Thin CC Mildly DM	ND	ND

References

Feigerle, J.T., Weil, P.A., 2016. The C Terminus of the RNA Polymerase II Transcription Factor IID (TFIID) Subunit Taf2 Mediates Stable Association of Subunit Taf14 into the Yeast TFIID Complex. Journal of Biological Chemistry 291, 22721–22740. https://doi.org/10.1074/jbc.M116.751107

Halevy, A., Basel-Vanagaite, L., Shuper, A., Helman, S., Har-Zahav, A., Birk, E., Maya, I., Kornreich, L., Inbar, D., Nürnberg, G., Nürnberg, P., Steinberg, T., Straussberg, R., 2012. Microcephaly-thin corpus callosum syndrome maps to 8q23.2-q24.12. Pediatr Neurol 46, 363–368. https://doi.org/10.1016/j.pediatrneurol.2012.03.014

Hellman-Aharony, S., Smirin-Yosef, P., Halevy, A., Pasmanik-Chor, M., Yeheskel, A., Har-Zahav, A., Maya, I., Straussberg, R., Dahary, D., Haviv, A., Shohat, M., Basel-Vanagaite, L., 2013. Microcephaly Thin Corpus Callosum Intellectual Disability Syndrome Caused by Mutated TAF2. Pediatric Neurology 49, 411-416.e1. https://doi.org/10.1016/j.pediatrneurol.2013.07.017

Kaufmann, J., Ahrens, K., Koop, R., Smale, S.T., Müller, R., 1998. CIF150, a Human Cofactor for Transcription Factor IID-Dependent Initiator Function. Mol. Cell. Biol. 18, 233–239. https://doi.org/10.1128/MCB.18.1.233

Louder, R.K., He, Y., López-Blanco, J.R., Fang, J., Chacón, P., Nogales, E., 2016. Structure of promoter-bound TFIID and model of human pre-initiation complex assembly. Nature 531, 604–609. https://doi.org/10.1038/nature17394

Martinez, E., Ge, H., Tao, Y., Yuan, C.-X., Palhan, V., Roeder, R.G., 1998. Novel Cofactors and TFIIA Mediate Functional Core Promoter Selectivity by the Human TAFII150-Containing TFIID Complex. Mol. Cell. Biol. 18, 6571–6583. https://doi.org/10.1128/MCB.18.11.6571

Najmabadi, H., Hu, H., Garshasbi, M., Zemojtel, T., Abedini, S.S., Chen, W., Hosseini, M., Behjati, F., Haas, S., Jamali, P., Zecha, A., Mohseni, M., Püttmann, L., Vahid, L.N., Jensen, C., Moheb, L.A., Bienek, M., Larti, F., Mueller, I., Weissmann, R., Darvish, H., Wrogemann, K., Hadavi, V., Lipkowitz, B., Esmaeeli-Nieh, S., Wieczorek, D., Kariminejad, R., Firouzabadi, S.G., Cohen, M., Fattahi, Z., Rost, I., Mojahedi, F., Hertzberg, C., Dehghan, A., Rajab, A., Banavandi, M.J.S., Hoffer, J., Falah, M., Musante, L., Kalscheuer, V., Ullmann, R., Kuss, A.W., Tzschach, A., Kahrizi, K., Ropers, H.H., 2011. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. Nature 478, 57–63. https://doi.org/10.1038/nature10423

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., Grody, W.W., Hegde, M., Lyon, E., Spector, E., Voelkerding, K., Rehm, H.L., ACMG Laboratory Quality Assurance Committee, 2015. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 17, 405–424. https://doi.org/10.1038/gim.2015.30

Thevenon, J., Duffourd, Y., Masurel-Paulet, A., Lefebvre, M., Feillet, F., El Chehadeh-Djebbar, S., St-Onge, J., Steinmetz, A., Huet, F., Chouchane, M., Darmency-Stamboul, V., Callier, P., Thauvin-Robinet, C., Faivre, L., Rivière, J.B., 2016. Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test: Diagnostic odyssey in severe neurodevelopmental disorders. Clin Genet 89, 700–707. https://doi.org/10.1111/cge.12732