Received: 1 September 2021 | Revised: 20 October 2021 | Accepted: 12 November 2021

DOI: 10.1111/cge.14089

CLINICAL GENETICS WILEY

LETTER TO THE EDITOR

Early psychosis in Thauvin-Robinet-Faivre syndrome, a complication of the disease?

The authors would like to thank Ms. Guinot for helping with the results of the various cognitive assessments and Ms. Vachet for her assistance in writing this letter.

Thauvin-Robinet-Faivre syndrome (TROFAS) is an autosomal recessive disorder characterized by generalized overgrowth associated with mild to severe learning difficulties, facial features, large extremities, inconstant congenital heart defects, kidney and eye anomalies, and skeletal defects. An increased risk of developing Wilms' tumor is suspected.[1,2] These features have been explained by biallelic variants in the *FIBP* gene, belonging to the fibroblast growth factor (FGF) pathway.[1] Currently, only four cases have been described worldwide, three of which were siblings. The first case was reported in France in a 23-year-old patient born from consanguineous North African parents.[1] The next three cases were from the same sibship originating from the United Arab Emirates, and who were 14, 10, and 3 years old at the time of publication.

One year after publication, at the age of 24 years, the index patient presented with first episode psychosis (FEP). There was no family history of psychiatric conditions. The patient experienced acoustic-verbal hallucinations, delusions, disorganization syndrome, behavioral disturbances of psychomotor agitation, and hetero-aggressivity. The symptoms appeared in a context of stress secondary to difficulty with apprenticeship training. The patient was therefore hospitalized for 1 month in a psychiatry ward and antipsychotic treatment with aripiprazole was initiated. He was readmitted 4 months later for a recurrence of delusions and behavioral disorders after discontinuing treatment 1 week after discharge from the first hospitalization. It is in this context that he was referred to our early intervention center, which is specialized in early psychosis. His treatment with aripiprazole was reintroduced at the start of care in our center. Both the initial neurocognitive and social cognitive assessments were impaired (Table 1). In terms of patient management, he was provided with an individualized care project in case management for 3 years, which was associated with monthly medical consultations. In order to obtain better compliance, the patient was switched to injectable sustained-release antipsychotic treatment. He took part in a group therapeutic education program for the symptoms of psychosis and treatment. He also participated in a cognitive behavioral therapy (CBT) program (CBT psychosis), and a Positive Emotion Program for Schizophrenia (PEP'S). Regarding cognitive remediation, he benefited from the "RECOS,"[3] "MCT," and "RC2S"[4] programs. After cognitive remediation, neurocognitive, and social cognitive assessments showed partial improvement (Table 1). The symptoms observed at the end of the treatment were mainly negative symptoms, with persistent cognitive alterations as well as sexual compulsions with daily masturbatory practices. He was referred for classic follow-up after specific treatment. Four years after the second psychotic episode, there were no additional hospitalizations or psychotic relapses. Compliance with his medication (aripiprazole maintena 400 mg every 28 days) and treatment tolerance were good.

The vulnerability-stress-competence model has been used for many years to explain the etiology, risk, and protective factors for initial psychotic symptoms and relapses.[5] It is now recognized that certain genetic diseases such as de novo microdeletion of chromosome 22q11.2 may constitute a genetic vulnerability to the onset of psychiatric illness. Moreover, the onset of FEP most often begins at a pivotal age between adolescence and early adulthood, when stressors are numerous. Our proband is the oldest of the four reported cases with TROFAS, and so far he is the only one that developed early psychosis. Akawi et al. confirmed the expression of Fibp in the central nervous system at different stages of embryonic development in mice embryos.[2] Also, FGF signaling is known to play diverse roles in regulating the development of the nervous system since it is essential for early neurogenesis and adult neuronal precursor proliferation. For instance, knockout Fgfr1 and Fgfr2-deficient mice, which lack FGFRs during development, exhibit decreased hippocampal volume and variable learning and/or memory impairments.[1]

At this stage, there is no proof of an association between TROFAS and psychosis due to the rarity of this syndrome. But reporting this case can draw attention to this possible association in future cases.

TABLE 1 Neurocognitive and social cognitive assessment before and after cognitive remediation in the reported patient

Neuro-cognitive assessment before treatment (March 2018)	Neuro-cognitive assessment after treatment (March 2019)	Social cognition assessment before treatment (January 2019)	Social cognition assessment after treatment (July 2019)
Assessment of memory functioning	Assessment of memory functioning	Theory of mind	Theory of mind
-RL/RI (Grober & BUSCHKE) *Immediate recall*: 16 *Free recall* 1: 1 *Free recall* 2: 13 *Free recall* 3: 11 *Deferred free recall*: 9 *Acknowledgement* 16/16 *Total recall* 1: 15 *Total recall* 2: 16 *Total recall* 3: 14 *Total deferred recall*: 13 -REY's Figure (3 min): 17/36 -REY's Figure (30 min): 15/36 -Memory for numbers (WAIS-IV): *Span right side*: 4 *Span reverse side*: 3 *Crescent span*: 4	-RL/RI (Grober & BUSCHKE) *Immediate recall*: 15 *Free recall* 1: 14 *Free recall* 2: 15 *Free recall* 3: 15 *Deferred free recall*: 12 *Acknowledgement* 16/16 *Total recall* 1: 16 *Total recall* 2: 16 *Total recall* 3: 16 -Memory for numbers (WAIS-IV): *Span right side*: 5 *Span reverse side*: 4 *Crescent span*: 4	-MASC-VF (Dziobek) *ToM* 19 *Exc ToM*15 *Less ToM* 7 *No ToM* 4 *Limits* -ACSo Scale *Theory of mind* 12/20 Attributional style -AIHQ (Comb) *Hostility bias* 2.4/5 *Attribution of responsibility* 3.18/5 *Aggression bias* 1.8/5 -ACSo Scale *Attributional bias* 11/20	-MASC-VF (Dziobek) *ToM* 23 *Exc ToM* 12 *Less ToM* 9 *No ToM* 1 *Limits* -ACSo Scale *Theory of mind* 13/20 Attributional style -AIHQ (Comb) *Hostility bias* 2/5 *Attribution of responsibility* 2.63/5 *Aggression bias* 1.8/5 -ACSo Scale *Attributional bias* 8/20
Assessment of attentional functioning -Bell Test 35/35 Time 218 s Omission 0 -Symbols (WAIS-IV) 14/30 1 *omission* -Attention assessment test *Single auditory modality* 120 *(T39)* 8 *False (T34)* *Single visual modality*: *impossible* *Double auditory visual modality*: *impossible*	**Assessment of attentional functioning** -Bell Test 35/35 Time 158 s Omission 0 -Symbols (WAIS-IV) 11/30 4 *omissions* *Attention assessment test single auditory modality* 77 *(T50)* 11 *False (T31)* *Single visual modality*: *realized* *Double auditory visual modality*: *performed*	**Perception and social knowledge** -PerSo (GDR 3557) *Contextual fluency score* 66 *Interpretation Score* 21/24 *Social knowledge score* 4/4 -ACSo Scale *Perception and social knowledge* 11/20	**Perception and social knowledge** -PerSo (GDR 3557) *Contextual fluency score* 61 *Interpretation Score* 19/24 *Social knowledge score* 4/4 -ACSo Scale *Perception and social knowledge* 9/20
Evaluation of executive functioning *Verbal fluency* 20 *words* *categorical fluency animals* 19 *words* -Trail-making test (Tombaugh) *Part A*:67 s *Part B* 253 *s* *Part B-A* 186 s -Stroop (Grefex version) *Name* 83 s *Reading* 61 s *Interference* 156 s *Interference-Name* 73 s -Committee test 1 *logical error*, 1 *time error*, 1 *diversion*, 3 *errors in total* -Wisconsin card sorting test (Milner's version) *Number of categories completed* 1 *Number of items needed to complete the first category* 34 *Failure to maintain a strategy* 0 *Total number of perseverative errors* 22	**Evaluation of executive functioning** *Verbal fluency* 23 *words* *categorical fluency animals* 26 *words* -Trail-making test (Tombaugh) *Part A*: 53 s *Part B* 268 s *Part B-A* 215 s -Stroop (Grefex version) *Name* 74 s *Reading* 60 s *Interference* 118 s *Interference-name* 44 s -Committee test 2 *logical error*, 2 *time error*, 1 *diversions*, 5 *errors in total* -Wisconsin card sorting test (Milner's version) *Number of categories completed* 1 *Number of items needed to complete the first category* 31 *Failure to maintain a strategy* 4 *Total number of perseverative errors* 9	**Empathy** -Empathy Quotient (Baron-Cohen and Wheelwright) 15/80 **Emotional perception** -TREF (Gaudelus) *Total recognition score* 61.11% *Disgust score* 55.46% *Emotional attribution* 18,51. *Contempt score* 44.44% *Emotional attribution* 12.96 *Joy score* 88.89% *Emotional attribution* 14.81 *Fear score* 66.67% *Emotional attribution* 12.96 *Sadness score* 33.33% *Emotional attribution* 18.51 *Anger Score* 77.78% *Emotional attribution* 22.22 -ACSo Scale *Emotional Perception* 13/20 **Total ACSo Scale** 47/80	**Empathy** -Empathy Quotient (Baron-Cohen and Wheelwright) 22/80 **Emotional perception** -TREF (Gaudelus) *Total recognition score* 75.92% *Disgust score* 77.77% *Emotional attribution* 16.67 *Contempt score* 33.33% *Emotional attribution* 12.96 *Joy score* 100% *Emotional attribution* 22.22 *Fear score* 88.89% *Emotional attribution* 14.81 *Sadness score* 55.55% *Emotional attribution* 12.96 *Anger score* 100% *Emotional attribution* 20.37 -ACSo scale *Emotional Perception* 6/20 **Total ACSo Scale** 36/80

TABLE 1 (Continued)

Neuro-cognitive assessment before treatment (March 2018)	Neuro-cognitive assessment after treatment (March 2019)	Social cognition assessment before treatment (January 2019)	Social cognition assessment after treatment (July 2019)
Percentage of perseverative errors 26.82 -REY's Figure copy 32/36 -Matrices (WAIS-IV) 11/26 Similarities (WAIS-IV) 19/36	*Percentage of perseverative errors* 14,75% -Matrices (WAIS-IV) 12/26 Similarities (WAIS-IV) 19/36		

CONFLICT OF INTEREST

The authors declare no conflict of interest

REFERENCES

1. Thauvin-Robinet C, Duplomb-Jego L, Limoge F, et al. Homozygous FIBP nonsense variant responsible of syndromic overgrowth, with overgrowth, macrocephaly, retinal coloboma and learning disabilities. *Clin Genet*. 2015;89:e1-e4.
2. Akawi N, Ben-Salem S, Lahti L, Partanen J, Ali BR, al-Gazali L. A recessive syndrome of intellectual disability, moderate overgrowth, and renal dysplasia predisposing to Wilms tumor is caused by a mutation in FIBP gene. *Am J Med Genet*. 2016;170:2111-2118.
3. Franck N, Duboc C, Sundby C, et al. Specific vs general cognitive remediation for executive functioning in schizophrenia: a multicenter randomized trial. *Schizophr Res*. 2013;147:68-74.
4. Peyroux E, Franck N. Improving social cognition in people with schizophrenia with RC2S: two single-case studies. *Front Psych*. 2016;7:66.
5. Lecomte T, Potvin S, Samson C, et al. Predicting and preventing symptom onset and relapse in schizophrenia: a metareview of current empirical evidence. *J Abnorm Psychol*. 2019;128:850-854.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/cge.14089.

DATA AVAILABILITY STATEMENT

The authors declare that the data supporting the results of this study are available from the corresponding author upon reasonable request.

Yanni Andreou,[1] Christel Thauvin-Robinet,[2,3,4] Juliette Martin,[1] Laurence Faivre,[3,4,5] and Ophélie Granon,[1]

[1]*Centre Hospitalier La Chartreuse, Centre Référent de Réhabilitation Psychosocial de Bourgogne (C2RB) Centre d'Intervention Précoce (CIP), Dijon, France*

[2]*Centre de Génétique et Centre de référence « Déficiences Intellectuelles de Causes Rares », Hôpital d'Enfants, Centre Hospitalier Universitaire de Dijon, Dijon, France*

[3]*UMR-Inserm 1231 GAD, Génétique des Anomalies du Développement, Université de Bourgogne Franche-Comté, Dijon, France*

[4]*Fédération Hospitalo-Universitaire Médecine Translationnelle et Anomalies du Développement (FHU TRANSLAD), Centre Hospitalier Universitaire de Dijon et Université de Bourgogne Franche-Comté, Dijon, France*

[5]*Centre de Génétique et Centre de référence « Anomalies du Développement et Syndromes Malformatifs », Hôpital d'Enfants, Centre Hospitalier Universitaire de Dijon, Dijon, France*

ORCID

Yanni Andreou https://orcid.org/0000-0002-3001-6682