

## Short clinical report

## Bipolar affective disorder and early dementia onset in a male patient with *SHANK3* deletion

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## ABSTRACT

The *SHANK3* protein is a scaffold protein known to stabilize metabotropic glutamate receptor mGluR5 in the post-synaptic membrane of neurons. It is associated with genetic vulnerability in autism and schizophrenia. Here we report the case of an 18 year-old male patient who displayed psychiatric features of bipolar affective disorder associated with early setting of dementia. This mental status is related to sporadic occurrence of *SHANK3* gene complex multiple deletions. A low beta amyloid protein rate (479 mg/L) found in cerebrospinal fluid suggests a possible link between *SHANK3* deletion syndrome-associated regression and dementia of Alzheimer's type. In addition, we propose an overview of the phenotype related to *SHANK3* deletion.

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### 1. Introduction

The *SHANK3* protein is a scaffold protein implicated in the stabilization and post-synaptic membrane expression of the metabotropic glutamate receptor 5 [1]. More precise pathway of this protein remains poorly understood. *SHANK3* is related to various cognitive impairments and was described as candidate-gene for autism [2,3] and schizophrenia vulnerability [4]. A neurobehavioral phenotype in children with 22q13 deletion syndrome (Phelan-McDermid syndrome) that includes *SHANK3* locus was described as distinct of autism even though the response to the environment seems to be poor in these patients [5].

Most studies focused on description of genotype/phenotype correlation in patients with *SHANK3* deletion [6]. Recently, an atypical bipolar disorder was reported in two adult brothers with Phelan-McDermid syndrome [7]. Nevertheless, the psychiatric features in childhood and adolescence, their course and prognosis

were rarely detailed previously. We report here a case of an 18 year-old male patient carrying a de novo deletion of *SHANK3* with late-onset psychiatric features not previously reported in the condition. In addition, our biological findings suggest a possible link between *SHANK3* deletion syndrome-associated regression and dementia of Alzheimer's type.

### 2. Clinical report

The patient was born after full-term pregnancy without complication. Because of advanced maternal age, a prenatal karyotype was performed that revealed a balanced robertsonian translocation between chromosomes 13 and 14: rob(13; 14)(q10; q10), inherited from the mother. His elder brother had the same translocation with no clinical consequences. A recurrent depressive disorder in his father is reported in psychiatric family history.

Growth parameters at birth were within normal range (weight 3.15 kg and length 52 cm). By the age of 9 height was 1.21 m (−2SD), weight was 24.6 kg (−1SD) and OFC 51.5 cm(M). The patient achieved 1.68 m by the age of 18. He twice underwent surgery for severe gastro-esophageal reflux during early childhood. Post operative course was simple.

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The patient had no hypotonia in early childhood. He walked at eighteen months. There were no difficulties in non verbal communication and social integration skills in early childhood. Daily bladder control was acquired by the age of four and night primary enuresis persisted until adulthood. The patient displayed average body temperature around 36 °C and decreased response to pain. A mild facial dysmorphism was observed since early childhood (Fig. 1).

The mental status around the age of three associated a persistent pattern of inattention, hyperactive and impulsive behavior with severe expressive speech and receptive language delay.

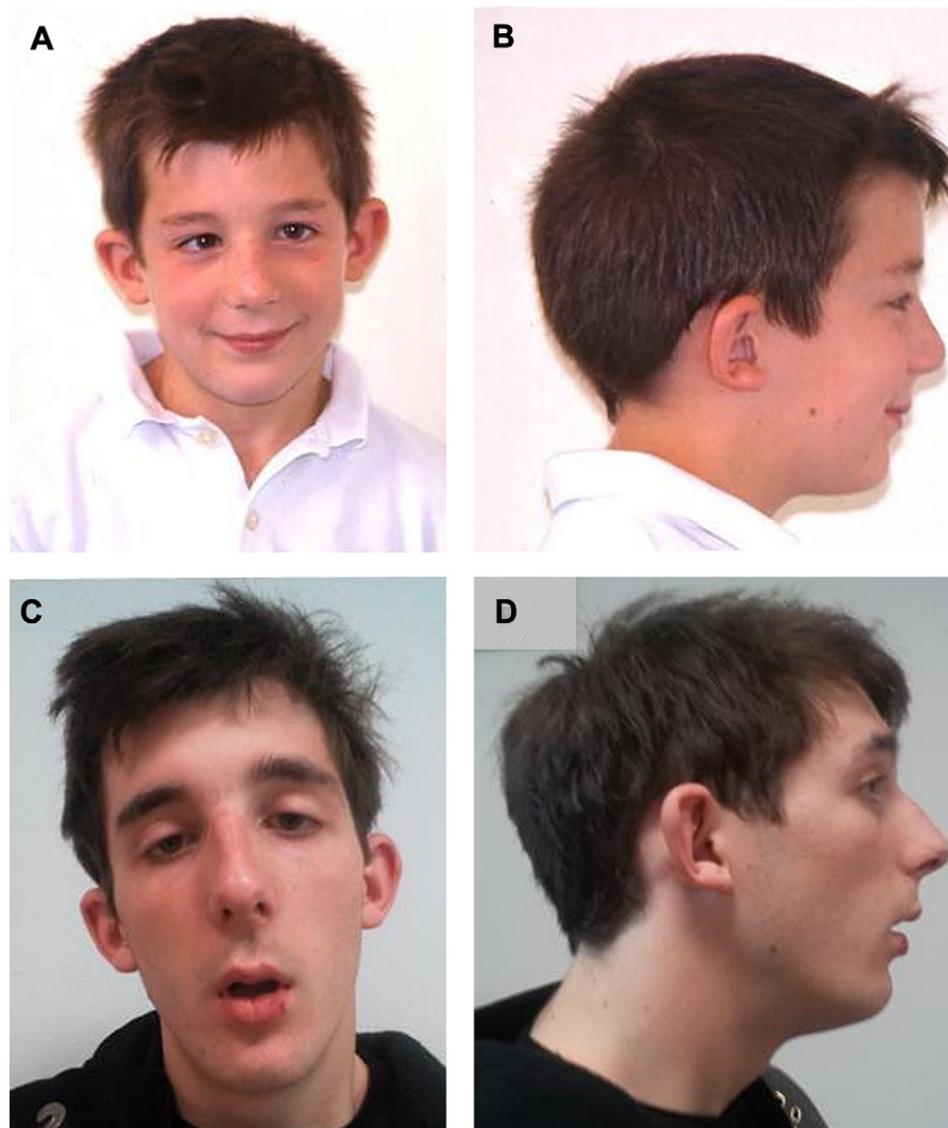
By the age of six, a diagnosis of severe intellectual deficiency was made after measure of adaptive functioning that indicated behavioral profile of 3 year-old child. A standardized intellectual assessment by Weschler Intelligence Scale for Children (WISC) was not realized because the language development was too poor. A Childhood Autism Rating Scale (C.A.R.S) scored 28 that rated the patient as “non autistic”. The evolution was marked by poor language development and non specific sleep disorder that associated successive hypersomnia and insomnia periods. Thus, the

neurobehavioral phenotype in childhood is consistent with intellectual deficiency without autistic features, already described as associated to *SHANK3* deletions [5].

At the age of ten the parents described a transitory episode of psychomotor agitation associated to insomnia during three days.

Around the age of sixteen the patient displayed depressive mood and social isolation that motivated antidepressant outpatient medication management (Table 1). The second episode of psychomotor agitation and insomnia with impulsiveness and aggressiveness occurred two months later. Inpatient psychiatric management was required. Initial psychiatric assessment found euphoric mood, total insomnia with psychomotor agitation, anorexia with weight loss, poor attention span and difficulties to concentrate. There was no stereotyped behavior. Blood tests on psychotropic drugs and illicit substances were negative.

During the inpatient evolution we observed disinhibited behavior with compulsive masturbations and urinations in public, affective instability, expensive mood with rapid depressive shifts and decreased need to sleep, motor hyperactivity and often erratic run away. The magnetic resonance brain imaging was performed in



**Fig. 1.** Pictures of the patient at the age of 6 (A and B) and at the age of 18 (C and D) years showing mild facial dysmorphism: high and narrow forehead, down slanted palpebral fissures, high and broad nose, microstomia, asymmetric face, protruding ears and ptosis.

**Table 1**  
Psychopharmacological treatment in order of chronological introduction from 16 to 18 years.

| Medication      | Dosage (mg/day) | Targeted symptoms     | Efficiency | Side effects                          | Medication use duration |
|-----------------|-----------------|-----------------------|------------|---------------------------------------|-------------------------|
| Risperidone     | 1–2             | Hyperactivity         | No         | Hypersialorrhea                       | 1 month, stopped        |
| Sertraline      | 50              | Depressive mood       | No         | Irritability                          | 1 month, stopped        |
| Amitriptyline   | 50              | Depressive mood       | No         | Switch to euphoric mood and agitation | 1 month, stopped        |
| Pipamperone     | 15              | Impulsiveness         | Yes        | Late dystonia                         | 8 months, stopped       |
| Carbamazepine   | 400–800         | Impulsiveness         | Yes        | Liver cytolysis                       | 2 years, stopped        |
|                 |                 | Mood instability      | No         |                                       |                         |
| Diazepam        | 20              | Anxiety               | No         | Sedation                              | 1 month, stopped        |
|                 |                 |                       |            | Euphoric mood exacerbation            |                         |
| Cyamemazine     | 150             | Psychomotor agitation | No         | Acute dystonia                        | 10 days, stopped        |
| Loxapine        | 50              | Psychomotor agitation | No         | Acute dystonia                        | 10 days, stopped        |
| Zopiclone       | 7,5             | Insomnia              | Partial    | None                                  | 2 years                 |
| Alimemazine     | 30              | Insomnia              | Partial    | None                                  | 2 years, stopped        |
| Hydroxyzine     | 50–100          | Anxiety               | Partial    | None                                  | 2 years, stopped        |
| Buspirone       | 20              | Anxiety               | Partial    | None                                  | 2 years, stopped        |
| Methylphenidate | 20              | Hyperactivity         | No         | Hyperactivity exacerbation            | 10 days, stopped        |
| Aripiprazole    | 30              | Hyperactivity         | Yes        | None                                  | 18 months               |
|                 |                 | Mood instability      | Yes        |                                       |                         |

order to rule out organic cause of mood disorder and it did not show any abnormality.

According to Diagnostic and Statistical Manual of Mental Disorders IV-TR the patient was diagnosed affective bipolar disorder not otherwise specified because of the rapid shifts between manic and depressive symptoms that do not meet criteria for any of the defined bipolar disorder subtypes.

In addition, we hypothesized early dementia onset because the patient displayed a stereotyped behavior with regression of expressive speech (“yes/no” response to any question) and lost his ability of bladder control at the age of 17. In order to assess this hypothesis, we performed a lumbar puncture with dosage of cerebrospinal fluid (CSF) proteins used as biomarkers in dementia of Alzheimer's type. Thus we found: low amyloid beta (479 mg/L, normal: above 500 mg/L), low total tau (82 ng/L, normal: 100–300 ng/L) and normal phosphorylated tau (24 mg/L) protein.

An optimal pharmacological treatment was difficult to find (Table 1). Association of carbamazepine and aripiprazole stabilized mood changes and permitted improvement in attention and concentration. Nevertheless, a residual motor hyperactivity persisted.

### 3. Molecular analyses

#### 3.1. Karyotype

Conventional cytogenetic analyses were performed on peripheral blood lymphocytes using 550 band and/or 850 band level including GTG and RHG banding for the members of the family.

#### 3.2. Array-CGH

DNA was extracted from peripheral blood using standard procedures. Blood genomic DNAs samples were extracted using the QIAamp DNA Blood Midi kit (Qiagen®, Valencia, CA). Array Comparative Genomic Hybridization (Array-CGH) was performed using Array-CGH ISCA (Bluegenome®, UK) slide. Random priming labeling and hybridization were carried out with sex-matched reference DNA according to the manufacturer's recommendations. Pictures were acquired using an Axon scanner. Data were processed with Genepix® 6.0 (Axon, US), BlueFuse® (BlueGnome®, UK).

Array-CGH showed an uncommon complex rearrangement with three small microdeletions of *SHANK3* gene region (22q13.33) (Fig. 2A) associated with a 748 kb duplication in 14q32.33 region, and CNV known to be polymorphic. Karyotype: 45,XY,rob(13; 14)(q10;

q10),der(22)t(14; 22)(q32.33q13.33), and 2009 ISCN nomenclature GRCh build 37 (hg19): arr 14q32.33(106,513,022x2,106,539,707-107,287,505x3), 22q13.33(51,066,503x2, 51,080,647-51,099,280x1, 51,107,409-51,113,580x2, 51,116,107-51,137,385x1, 51,141,268-51,167,619x2, 51,170,164-51,219,009x1).

#### 3.3. Q-PCR

Quantitative Polymerase Chain Reaction (Q-PCR) was performed on the child and parental DNA to confirm the deletions and the breakpoints. Primers a–h were designed in deleted and not deleted segments in the 22q13.33 region. They were tested using classical procedures (Eurogentec®, Belgium) on a LightCycler® 480 Real-Time PCR System (Roche Diagnostics®, US).

Q-PCR confirmed the results of array-CGH for the 8 primers tested (Fig. 2B). In the Child, primers a, c, d, g and h were deleted and b, e and f were not deleted. The parental Q-PCR controls for the three 22q13.33 deletions (8 primers) were normal (Fig. 2B).

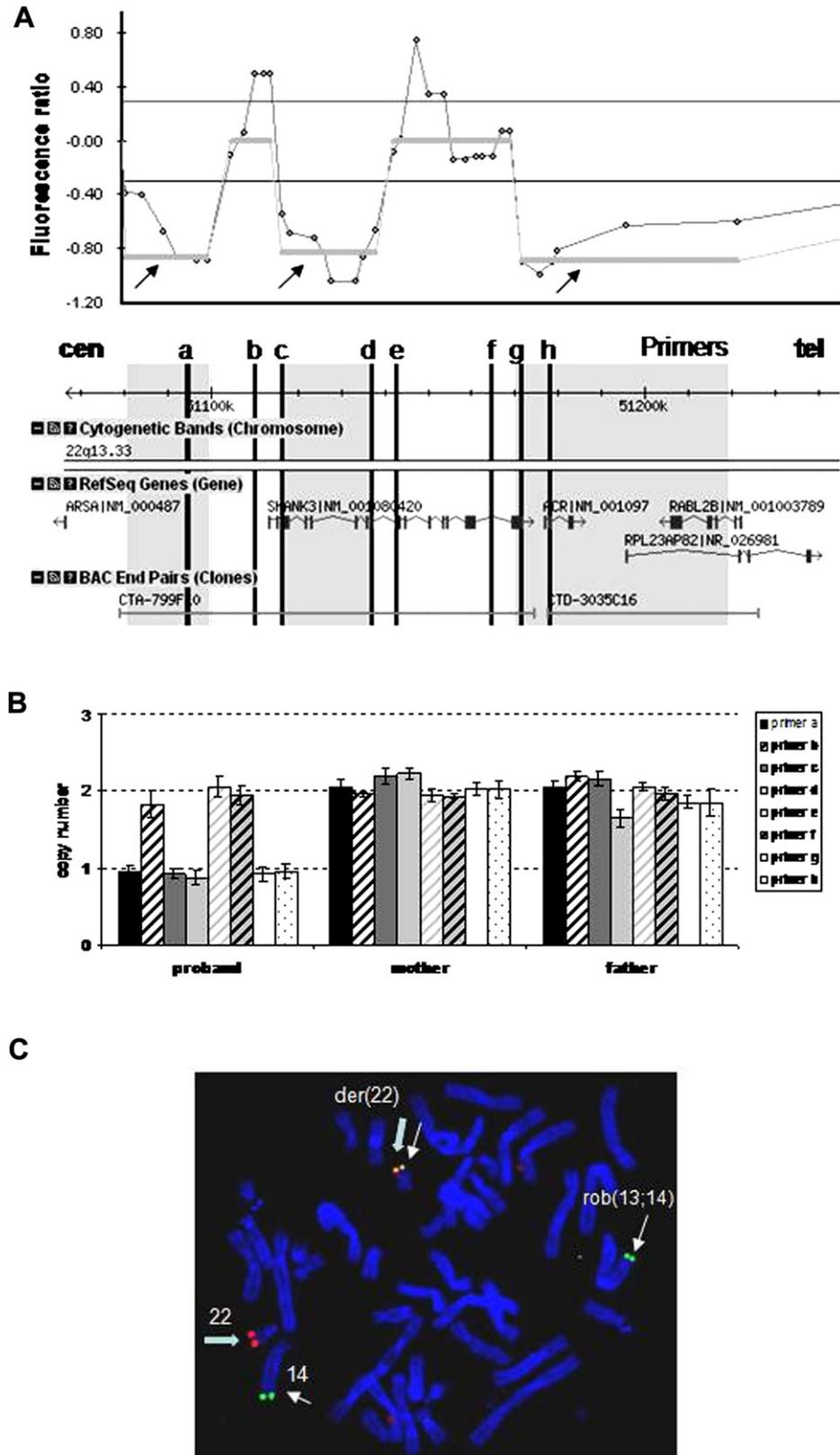
#### 3.4. FISH

Academic and commercial probes were used. DNAs from academic probes were extracted from academic BACs and PACs colonies (S. Knight and J. Carter, Sanger institute, UK), amplified with the illustra TempliPhi amplification kit (GE Healthcare, Piscataway, NJ) and labeled with Cyanine3-dCTP or Biotin-dNTP using a nick translation method (BioNick™ DNA Labeling System, Invitrogen, Carlsbad, CA). Commercial subtelomeric probes hybridizations were performed according to the manufacturer's recommendations.

The FISH analysis showed the presence of a derivative chromosome der(22)t(14; 22)(q32.33; q13.33) displaying the colocalization of both probes CTA-799F10 (22q13.33) and the CTC-820M16 (14q32.33) (Fig. 2C). The probe CTA-799F10 had a diminished intensity on the der(22)t(14; 22) compatible with the deletion of this region diagnosed by array-CGH. Thus, a supernumerary subtelomeric 14q region was translocated to the subtelomeric 22q region. FISH analysis showed normal hybridization in the father and a signal for the CTC-820M16 probe on the rob(13; 14)(q10; q10) chromosome in a mother transmitted to the child.

### 4. Discussion

We report a young adult with complex multiple deletions in *SHANK3* region not reported previously [6,8]. Psychiatric features



**Fig. 2.** A. Array-CGH (ISCA Bluegenome) result and 22q13.33 cytogenetic map. Upper part: In gray, the deleted regions (arrows), two are interstitial and one is terminal. One interstitial deletion encompasses at least 6 *SHANK3* exons. The distal deletion concerns the last *SHANK3* exon and three genes *ACR*, *RABL2B*, *RPL23AP82* not known as related to bipolar affective disorder, autism or schizophrenia. Lower part: a–h: quantitative PCR primers and their genomic position. B. Graphic representation of the genome map and quantitative PCR results. C. FISH analysis in the patient with probes CTA-799F10 (22q13.33)(red, large arrow) and CTC-820M16 (14qter)(green, thin arrow).

displayed by the patient strongly suggest the diagnosis of bipolar spectrum disorder, comforted by partial remission after mood stabilizers introduction. The most plausible diagnosis is bipolar VI disorder described as comorbidity in about 50% of patients with dementia onset [9]. Moreover, SHANK3 pathway abnormalities are found in two other chronic psychiatric conditions as autism and schizophrenia, known to share a part of vulnerability genes with bipolar disorder. Additional genetic vulnerability to bipolar affective disorder is possibly transmitted to the patient by his father who displayed the symptoms of recurrent depressive disorder. Nevertheless, the occurrence of bipolar disorder spectrum involves complex interaction between genes and environment [9]. Moreover, an atypical bipolar disorder was recently described as psychopathological phenotype in case report of two brothers with 22q13 deletion [7], suggesting that this psychiatric disorder is probably related to SHANK3 deletion in the patient.

In addition, the patient displayed severe disturbance of sleep regulation. The unspecified sleep disorder is described in 22q13 deletion syndrome [10], known to implicate partial or complete SHANK3 deletion [11]. There is a growing evidence of learning and memory tasks consolidation [12] as well as synaptic plasticity facilitation [13] during sleep. These functions could be impaired in the patient. Moreover, the succession of hypersomnia and insomnia periods observed since the early childhood suggests that SHANK3 could be implicated in sleep-wakefulness rhythm regulation.

SHANK3 protein is a member of SHANK scaffold family proteins involved in spine morphology and synaptic stability of glutamatergic neurons [14]. In vitro studies of SHANK3 knock-down hippocampal neurons showed dysfunctional dendritic spine synapses rescued by external SHANK adjunction [15]. Protein SHANK3 assembles metabotropic glutamate receptor 5 (mGluR5) with its intracellular signaling proteins and cytoskeleton at post-synaptic density [1]. Interestingly, SHANK3 does not seem to interact with ionic glutamate receptor NMDA. In vitro use of allosteric agonist of mGluR5 receptor permitted its stabilization in post-synaptic density of SHANK3 knock-down neurons [1], suggesting that it could be an interesting pharmacological agent. Phenotype of SHANK3 mutant mice associates autistic-like behaviors as repetitive grooming and deficit in social interaction with abnormalities in striatal circuitry development [16].

The variability in learning and speech improvement acquisitions associated to SHANK3 deletion in the patient could be explained by the synaptic instability related to SHANK3 protein dysfunction. Nevertheless, we hypothesized early neurodegenerative process onset to explain patient's language regression, secondary enuresis development and recent development of stereotyped behavior. Low amyloid beta ( $A\beta$ ) protein with increased total tau and phosphorylated tau in CSF was described in early stages of Alzheimer's disease [17]. We found low  $A\beta$  protein in patient's CSF suggesting that  $A\beta$  plaques could mediate early dementia process. Moreover, severe neurological deterioration with cognitive decline was described in patients over forty with SHANK3 haploinsufficiency [6]. In addition, zinc sequestration by  $A\beta$  induces deregulation in SHANK3 pathway [18], suggesting the possible link between these two proteins in Alzheimer's disease pathogenesis. In order to characterize the link between SHANK3,  $A\beta$  and tau protein in patients with SHANK3 deletion, CSF analyses of these biomarkers should be realized in the cohorts of patients.

## 5. Conclusion

In this case report we suggest not previously described link between SHANK3 deletion, early dementia of Alzheimer's type onset and bipolar affective disorder comorbidity in a male patient. We advice mood stabilizers use from the first episode of mood instability with behavioral symptoms of affective disorder in the patients with SHANK3 deletion.

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