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# Major clinical improvement in a boy with developmental disabilities and a PTPN4 mutation with intensive re-education and an enriched environment in a day care hospital: a case report

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# Major clinical improvement in a boy with developmental disabilities and a PTPN4 mutation by intensive reeducations and enriched environment in a day care hospital: a case report

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## Abbreviations

ADHD Attention-Deficit/Hyperactivity Disorder

ASD Autism Spectrum Disorder

CNV Copy Number Variation

EEG Electroencephalogram

MRI Magnetic Resonance Imaging

NDDs Neurodevelopmental Disorders

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NMDA N-Methyl-D-Aspartate

PTPN4 Protein Tyrosine Phosphatase, Non-Receptor Type 4

SD Standard Deviation

WISC-V Wechsler Intelligence Scale for Children® Fifth Edition

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**Abstract**

**Background:** The Protein Tyrosine Phosphatase, Non-Receptor Type 4 (PTPN4) is a gene involved in glutamate downstream signaling contributing to cerebral maturation. Loss-of-function of this gene has been reported in patients showing various neurodevelopmental disorders, although PTPN4 gene is not clearly considered a disease causing gene in OMIM catalogue.

**Case presentation:** Here, we report the case of a 7-year-old white boy with a homogeneous, heterozygous, 170 kb chromosomal deletion encompassing several exons of the PTPN4 gene. The mutation was transmitted by his father, who had an undiagnosed communication disorder. The patient was referred to a daycare unit for complex neurodevelopmental disorders and a suspicion of autism spectrum disorder (ASD). He had a severe communication disorder associated with sensory integration issues, anxiety, and elimination disorder. During his 4 years in the daycare hospital, he received educational, creative, and academic group activities and specific reeducations. Group activities help generalize the newly acquired developmental skills by providing social reinforcers and opportunities for positive peer interactions. In turn, achieving social activities positively influences the patient's self-esteem, emotional insight, and motivation to make new progress.

**Conclusions:** Despite severe communication disorder associated with sensory integration issues, anxiety, and elimination disorder, ASD diagnosis was ruled out, and remarkable progress was observed, which allowed our patient to attend same-age mainstream schools with personalized support at discharge. This case illustrates the effect of dimensional interventions to limit developmental impairments in a context of PTPN4 mutation and the benefit of

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providing an enriched environment in combination with individual reeducation to improve developmental outcomes.

**Keywords:** PTPN4 gene; neurodevelopmental disorders; communication disorder; language disorder; speech therapy; integrated care; daycare hospital

## 1. BACKGROUND

This case report details the clinical outcome of a 7 to 11-year-old white boy with complex neurodevelopmental disorders (NDDs) carrying a homogeneous, heterozygous deletion encompassing exons 2-15 (/27) of the *PTPN4* (Protein Tyrosine Phosphatase, Non-Receptor Type 4) gene, encoding for PTPMEG/PTPN4 (1). *PTPN4* has a very high probability of loss-of-function intolerance in case of genomic sequence variation (pLi=0.95 in gnomAD v4.1.0) (2,3). It has been identified as one of 261 genes likely responsible for human-specific cortical development (4). PTPN4 interacts with glutamate receptor delta 2 (NMDA) and its epsilon subunits during glutamate downstream signaling.

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Glutamate transmission, specifically NMDA receptors, plays a key role in memory formation and learning processes (5). Monoallelic loss-of-function variants of *PTPN4* have been implicated in various psychiatric and neurodevelopmental disabilities including severe to moderate intellectual disability, speech and motor developmental delays, attention deficit disorder, motor tics, autism spectrum disorder (ASD), astigmatism, growth abnormalities, seizures, and mildly diminished cerebral white matter volume (6,7). In addition, two monozygotic twins with *de novo PTPN4* deletion were reported and showed a Rett syndrome-

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like phenotype with motor and cognitive development, limited speech, seizure, and important growth delay (8).

So far, no report has been published to determine to what extent environmental interventions could moderate the impairments associated with variants of the *PTPN4* gene. Here, we report the case of a white boy from seven to 11 years old with a *PTPN4* deletion with a remarkably positive evolution thought to be attributable to intensive and individualized treatment in a daycare hospital using an integrative approach.

## 2. CASE PRESENTATION

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A 7-year-old white boy was referred to the daycare hospital for a severe language disorder, food selectivity, school refusal, intolerance to change, sleep impairments, and suspected ASD. He attended 2$^{nd}$ grade school with a dedicated specialized assistant. He failed to learn to read (even to recognize and pronounce letters) and could not perform simple algebraic equations. He had no friends and presented great difficulty participating in group activities.

### 2.1.History

The patient was born full-term with an emergency cesarean for a risk of fetal distress. The pregnancy was marked by tobacco exposure during the first month and Intrauterine Growth Restriction. No neonatal hypotonia was observed. The patient grew up with both parents in the family home in a suburban area. His father works in the construction industry, specializing in interior renovation, and his mother is a spa manager, often working from home. He has a half-brother from his mother's first marriage, who lives with them one week in two and has no

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medical history. He grew up seeing his maternal grandparents regularly, who reported having no personal psychiatric history. He moved to a house built by his father at the age of 6. Food diversification after 4 months of breastfeeding was initially simple. Severe food selectivity suddenly appeared at 18 months, mainly based on sensory characteristics such as texture, color, or smell. The first words appeared around one and a half years, but the first sentences only occurred at five years. Daytime and nighttime cleanliness was acquired at three years old, with secondary encopresis at 5 years in the context of house moving. The patient was described as clumsy with a walking age of 13 months. Sleep difficulties were always noted. A language examination at age 4 confirmed a language disorder with severe impairments in phonology and syntax. First-degree relatives had no known history of psychiatric or NDDs.

Clinical and paramedical assessments found mild dysmorphic features, such as hypertelorism, low-lying hair, broad neck, slightly thick ears not low-lying, eyebrows not sparse, and bilateral clinodactyly. The weight and size growths were regular on -1 SD with a sharp decline in size at -2 SD at six years. He had recurrent ear infections. Paramedical assessments showed: growth hormone peak (GH peak 27.67 mUI/L) despite low IgF1 (56 ng/mL, -2.5 DS); negative IgA and IgG anti-trans-glutaminase and anti-gliadin; normal cerebral MRI centered on the pituitary; normal karyotype was normal (46 XY) and negative search for SHOX variant or variant in genes responsible for Noonan syndrome. Chromosomal microarray analysis identified a homogeneous, heterozygous 170 kb deletion encompassing exons 2-15 exons of the *PTPN4* gene. This copy number variation (CNV) was confirmed by whole-genome sequencing (genomic coordinates chr2(GRCh38):g.(119772338_119942031)del), which did not show any other candidate variant. This deletion was inherited from the father, who presented a very likely oral language disorder (considering a delay in speech acquisition with the first sentences only at 5, through no formal assessments are available). Sampling of paternal grandparents is ongoing. This deletion is known to affect several functional domains of the PTPN4 protein:

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FERM domain C-lobe (found in proteins providing a link between the membrane and cytoskeleton or involved in signal transduction pathways) (9), structural domains (such as band 4.1 and FERM adjacent domains) which play a regulatory role in assembly and stabilization of plasma-membrane domains (10), as well as other putative phosphoinositide and peptide binding sites (for chemical and polypeptide binding respectively).

### 2.2.Neurodevelopmental and psychiatric assessment

Psychiatric assessment at admission showed emotional dysregulation, mental rigidity, inflexible adherence to routines, ritualized patterns, difficulties in maintaining relationships, and persistent negative emotionality (anxiety, depression) frequently related to academic-related stress. Persistent irritability and difficulty tolerating frustration were observed since the early childhood and progressively increased with ages. Retention encopresis was associated with multiple somatizations. He only ate chicken nuggets and mayonnaise. The diagnosis of ASD was ruled out because the deficits in social interaction and restricted behaviors appeared related to contextual psychopathology. In fact, they disappeared when anxiety was monitored and communication improved. The retained DSM-5 diagnoses were communication disorder (oral language), specific learning disorder (written language acquisition of reading and writing), avoidant/restrictive food intake disorder (ARFID), elimination disorder, and anxiety disorder. Table 1 summarizes multidimensional assessments at ages 7 and 11 years.

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### 2.3.Treatment plan

During the daycare hospital, the patient received three types of intervention: i) individualized reeducation targeting several developmental domains, ii) group creative, recreational, or academic activities, and iii) psychotherapeutic and medical interventions.

Individual intensive speech therapy was provided three sessions/week, focusing during the first year on phonological awareness and then written language acquisition. An individual motor

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therapy was provided, focusing on fine motor competence and then participation in group motor therapy. An oral sensory-based program to address food aversion based on sensory habituation was planned every week.

During the day, educators organized several group recreational activities. These activities aim to promote the patient's symbolic expression through age-adapted creative activities (e.g., the co-writing of an illustrated story with a professional illustrator or constructing a space shuttle model). Progressively specialized teaching was provided in the hospital-related school.

The principles of dimensional interventions were explained to the parents (based on psychoeducation, parental guidance, and reward system) to target sleep and elimination difficulties. Dietary consultations were planned with a prescription of a calcium supplement (500mg) and vitamin D.

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### 2.4.Evolution

The high functional impairments observed for the patient in family, school, and relational domains progressively decreased. While food selectivity was initially severe, he was positively reinforced for trying new foods at home after reintroduction during the oral sensory-based program. All meals in the daycare hospital were an opportunity to continue the habituation process initiated in the program. In addition, improved emotional communication was concomitant with expressing his sadness and frustrations related to his communication difficulties, especially in forming close relationships. A decline in behavioral problems was progressively observed, with improvement in self-affirmation. Relations with peers were more reciprocal, with less rigid or coercive behaviors. He developed new non-invasive age-appropriate interests (e.g., Harry Potter) to share with peers. He was progressively more open to social interaction (e.g., managing to make new friends at the park).

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The reluctance to attend reeducation or school activities progressively declines with improved oral language skills. He accepted school adaptations such as a computer with vocal dictation, which appeared key in providing him a sense of autonomy. Parental guidance and educational video games, such as Dynamilis(11) were also offered to continue the rehabilitation work at home after the day care hospital's activities. Dynamilis provides a series of serious games designed to train different writing features: static features, kinematic features, pressure features, and tilt features. Static features include the purely geometric characteristics of a written text, kinematic features designate the dynamics of the handwriting path, pressure features designate characteristics of the pressure recorded between the pen tip and the tablet surface, and tilt features include the characteristics of the pen tilt (11,12).

Creative artistic activities were well invested in and provided an excellent opportunity to consolidate the reeducation. For example, he enjoyed pottery workshops and was congratulated for his creativity and newly acquired skills. For example, co-creating a comic with a professional artist was key to significant improvements in self-esteem and speech progress (from sentences to story construction).

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The parents observed an improvement in the patient's level of understanding and autonomy. He started to sleep in his own bed. For encopresis, guidance was provided for behavioral routine for elimination (going to the toilet 15 minutes several times a day, even if he does not feel the need initially). Improvement of these symptoms coincides with accepting the orientation to a new school. Regressive and anxiety-related behaviors were sometimes reported, but remained limited in times, and environmental stressors were also identified by the patient and his parents. Food intake also improved at home with increased quantities and diversity, with no need for specific meals when he left the structure. A food selectivity score was used to track the change in food competence. The score includes items from forms,

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textures, temperatures, oral praxis, and flavors. The answers are 0 for refusal, 1 for almost acquired, and 2 for fully acquired. The total score changed from 70 (out of 156) at 8 years to 153 at 11 years.

As shown in Table 1, all dimensional assessments improved. Most WISC-V subscores were in the normal ranges. The patient frequently asks with curiosity what the words he doesn't know mean while exhibiting a fragile capacity for verbal conceptualization, a lack of words, and imprecise language. Improvements in motor acquisitions, such as integration of body schema and writing, are presented in Figure 2.

On discharge, when the patient was 11, he could attend mainstream schools, without any age difference, with personalized support in an adapted educational facility. Although he still needs teacher guidance, speech therapy, and occupational therapy, he shows a desire to progress, follow a conventional diet, and demonstrate the ability to manage subtle social interactions. One-year following hospital discharge he still maintains his clinical and functional improvement. The latest information provided by the family at age 12 indicates that the patient is continuing to make progress at school, with increasing periods of inclusion in mainstream classes.

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## 3. DISCUSSION AND CONCLUSIONS

### 3.1.Comparing the current case with previous cases

*PTPN4* encodes a protein tyrosine phosphatase, which interacts with glutamate receptor delta 2 and its epsilon subunits for tyrosine dephosphorylation during glutamate downstream signaling. The role of glutamate is well-established in synaptic transmission, plasticity, and overall development. Furthermore, consistent data across species (such as fish, birds, monkeys, and humans) shows that NMDA receptors are crucial in memory formation and the learning

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process (5). *PTPN4* pathogenic variants have been reported in human cases showing ADHD, autism-like features, speech and motor impairment, among other abnormalities (Table 2). This is consistent with animal studies that showed that the loss of expression of *PTPN4* resulted in defective neuronal development in brain regions involved in olfactory learning, memory, sensory integration, and motor coordination (13–15), in motor learning (16). Growth anomalies were previously reported in patients with *PTPN4* variants (6) and were observed in this case. It may be explained by the implication of the phosphatase activity of PTPN4 in the regulation of cytoskeletal events (17). PTPN4 also dephosphorylates the NMDA receptor subunit GRIN2A (18), which variants may cause epilepsy and intellectual disability (19). Among patients with *PTPN4* pathogenic variants, epilepsy, cognitive and developmental delays were common, but one reported case, like ours, had borderline intelligence (with an IQ of 71) (6). Such variants have also been identified as a possible candidates for ASD (6,20). Our patient was initially referred to us with a suspicion of ASD. This diagnosis was eventually ruled out, but the suspicion may be due to complex NDDs. Indeed, youths with co-occurring NDDs generally also exhibit persistent emotional dysregulation with a significant impact on social skills and sometimes pseudo-autistic presentations (21,22).

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However, some of the variations previously reported as likely or possibly pathogenic in Chmielewska *et al*. have been added to the Genome Aggregation Database (gnomAD v.4.1.0)(23) of control individuals. Therefore, the pathogenicity of the *PTPN4* gene variation can be questioned and must not be taken for granted. In the current case, the CNV has not been reported yet and is also present in the father, who had oral language impairments. Therefore, the pathogenicity of the CNV reported here was categorized as of unknown significance. Taken together, these data do not provide sufficient evidence to support a clear causal link between the PTPN4 gene and the clinical phenotype observed in this family. Consequently, the association between the CNV and the symptoms reported is unclear and

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should not be taken for granted. While the whole-genome sequencing performed here did not found other candidate variant, further in-depth explorations would be required to provide evidence for PTPN4 pathogenicity. [Insert Table 2 about here]

### 3.2.Dimensional tailored intervention and evolution

The pathophysiology of NDDs remains unclear and is probably linked to a complex interaction between genetic and environmental vulnerability factors. Environmental enrichment is the fundamental rationale of early/tailored developmental interventions, which aim to strengthen the environment to mitigate developmental deficits(24). By fostering a more stimulating and adapted environment and offering all interventions in a single setting, the daycare hospital can help to restart interaction and reinforcement loops, maximizing the chances of progress and social adaptation (25). It also favors the interplay between acquisitions in different development areas. This interdependence explains why improvement in a specific skill can often have positive repercussions on other areas of development. For example, progress in motor skills can promote social interaction by enabling better imitation of peers (26). Improvement in language skills can contribute to better emotional regulation, notably by supporting more adaptive regulation strategies (27).

In this case, persistent emotional dysregulation observed could have been underpinned by difficulties with mentalization and inner language. The inability to formulate accurate hypotheses about the mental states of others to adapt to their intentions and emotions can lead to conflict, oppositional behavior, or social avoidance. Mentalization relies on essential prerequisites for self-construction, such as a sense of agency and representational and symbolic skills. These skills are closely linked to motor, language, and sensory-motor skills (27). Progress in self-regulation and mentalization could have contributed to the patient’s enhanced sense of autonomy, facilitating the expression of feelings in distress situations.

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### 3.3.The case for early integrated dimensional care

Here, we made the case for complex severe NDD that integrative day care hospitals can provide dimensional comprehensive assessments of patients, tailored treatment recommendations, and school readaptations (Figure 1, Figure 3). Multi-disciplinarity helps to improve, extend, and consolidate the gains made during remediation by recruiting newly acquired abilities in a more natural and ecological setting, facilitating their transfer to everyday life. Furthermore, individual remediations are continued and optimized by participation in group sessions, reinforcing newly acquired skills and social integration. Achieving positive interaction with peers boosts the patient's self-esteem, which in turn leads to a more positive attitude toward care and learning activities. This approach aligns with recent guidelines for intervention for children with ASD (25). Furthermore, a recent meta-analysis showed no increase effect with increasing the amount of intervention, suggesting that quality is more important than quantity in child care (28).

This is the first report of a longitudinal follow-up of a patient with PTPN4 mutation. The case reported here showed a positive evolution, almost normalizing IQ test and speech impairment and significantly decreasing socio-emotional difficulties. This allowed the patient to attend mainstream schools with personalized support in an adapted educational facility on discharge. The fact that school-adapted and creative group activities played a crucial role in the patient's evolution supports the importance of an integrative and multidimensional approach in the management of complex NDDs.

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**Figure 1.** Timeline of patient's course of symptoms and provided cares

**Figure 2.** Body scheme (a) and cursive writing (b) at 7 and 11 years old.

Note. 1a illustrates the delayed integration of body schema at 7 years that normalizes at 11 years. In 1b the BHK test is impossible to complete at age 7 years. It improves dramatically at age of 11 years. (Translation of the sentences he copied: "*It is sunny*"; "*I am fine*"; "*I see water but I do not know where it goes*")

**Figure 3.** Principle of integrative care provided for the patient in the daycare hospital

*Note.* The scheme, create by the authors, illustrates hypothetic links between neurodevelopmental impairments ("Dev impairments" in red stars) and difficulties of emerging socio-emotional domains in childhood. The yellow box on the right summarizes the main interventions provided in the daycare hospital, with numbers for the priority levels. Black arrows between each "module" express the interdependences of developmental and cognitive competencies and how, during the care, we hoped to ultimately improve high-order cognitive ability (such as emotional regulation).

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## DECLARATIONS

### Ethics approval and consent to participate

Written informed consent was obtained from the patient to publish any potentially identifiable images or data in this article. This manuscript follows the CARE guideline for publishing case reports, with the completed CARE 2013 checklist attached as Supplementary Materials. Ethical committees / Internal Review Boards: not applicable

### Consent for publication

Written informed consent was obtained from the patient's legal guardians for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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**Competing interests:** The authors declare that they have no competing interests.

**Availability of data and materials**

Data sharing does not apply to this article as no datasets were generated during the current study. Genomic databases were used to analyze the case reported. Perez, G. *et al.* The UCSC Genome Browser database: 2025 update. *Nucleic Acids Res.* **53**, D1243–D1249 (2025). https://doi.org/10.1093/nar/gkae974. Firth, H. V. *et al.* DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. *Am. J. Hum. Genet.* **84**, 524–533 (2009). doi: 10.1016/j.ajhg.2009.03.010

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**Authors' contributions**

CT, DC, and XB conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. CT, AO, CG, SO, IZ, OG, and JM followed the patient and contributed to data acquisition. CM analyzed and interpreted genetic data and critically reviewed the manuscript.

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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**Table 1.** Summary of test results

| | 7 years | 11 years | Comments |
|---|---|---|---|
| ***General intelligence*** | | | |
| | **WISC-V** | **WISC-V** | |
| **Verbal Comprehension** | **NC** | **81** | An assessment of Verbal comprehension abilities could not be assessed at admission. But with improvement, they became within the normal range at age 11 despite a below-average vocabulary. |
| Similarities | Impossible | 8 | |
| Vocabulary | Impossible | 5 | |
| **Visual Spatial** | **NC** | **114** | Similarly, improvement in behavior allowed for proper assessment of visual-spatial abilities, which were in the normal range at the age of 11. |
| Block Design | 11 | 13 | |
| Visual Puzzles | Impossible | 12 | |
| **Fluid Reasoning** | **103** | **nan** | Fluid reasoning was around the average, with heterogeneity of indices at age 11. |
| Matrix Reasoning | 11 | 9 | |
| Figure Weights | 10 | 13 | |
| **Working Memory** | **NC** | **79** | Working memory performance was not calculated due to difficulties in understanding the instructions during the initial test. At 11, performance is at the limit for its age group. |
| Digit span | 3 | 7 | |
| Picture span | 4 | 6 | |
| **Processing Speed** | **92** | **72** | At 11, performance worsened to reach weakness. We hypothesized a lack of ease in visual scanning and graphomotor gestures. |
| Coding | 8 | 5 | |
| Symbol Search | 9 | 5 | |
| ***Motor skills*** | | | |
| **Total coordination** M-ABC 2 | 37% | Not assessed as normal previously | Global coordination at age 7 was in the normal range |
| **Manual dexterity** M-ABC 2 | 50% | | |
| **Aiming and catching** M-ABC 2 | 25% | | |
| **Balance** M-ABC 2 | 50% | | |
| **Hand imitation of gestures coordination** EMG | 5.5/10 (-4.23 SD) | | Hand imitation and coordination showed deficits as human body drawing at age 7. Human body drawing improved at age 11. |
| **Finger imitation of gestures** EMG | 10/16 (-0.66 SD) | | |
| **Human body drawing** Goodenough | 25% (5y9m) | 50% (10y6m) | |
| **Left/right knowledge** Piaget Head | Acquired | Acquired | |
| **Basic space-time concepts** Piaget Head | Partially acquired | Acquired | The integration of time concepts related to social activities remained difficult at age 11 |
| **Reproduction of rhythmic structures** Stambak | Impossible | | |
| **Qualitative writing test** BHK-F | Impossible | + 0.5 SD | Initially, writing in in cursive is impossible, spontaneously mixing script and block capitals. At 10y-o, he wrote 23 words per minute, results similar to 5th-grade level, but quality was impaired |
| **Speed writing test** BHK-F | Impossible | -2.3 SD | |
| ***Food Selectivity*** | | | |
| **Food selectivity score** | 70/156 (45%) | 153/156 (98%) | A score based on textures, temperatures, flavors and oral-lingual-facial praxis. Higher score indicates willingness to eat. |
| ***Visual spatial skills*** | | | |
| **Visuo-perception total score** Frostig, DTPV-2 | 102 (50%) | 105 (63%) | Visual spatial abilities seemed OK, but visual motor precision was slow and cognitively costly. Together with processing speed scores, this suggested a sluggish cognitive tempo. |
| **Visual-motor integration** DTPV-2 | | 93 (32%) | |
| **Cubes test** NEPSY-II | | 11 (+0.3 SD) | |
| **Comprehension of instruction** NEPSY-II | | 5 (-1.7 SD) | |
| **Tapping test** NEPSY-II | | 10 (0 SD) | |

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|---|---|---|---|
| **Visual-motor precision test** NEPSY-II | | Time: 14<br>Errors: 26-50%<br>Pencil lift: >75% | |
| ***Oral language***[1] | | | |
| **Word repetition** ELO | 7/32 (-6.2 SD) | 19/32 (-2.7 SD) | Severe phonological disorder: presence of interdental sigmatism; assimilations (e.g., *Tr → Cr*, *Dr → Gr*), substitutions (e.g., vowels: *o/on/an*, *k/g*, *ch/j*, *p/b*, *s/z*) and errors in syllabic structuring processes such as simplifications of consonant clusters, omission of letters in cases of double consonants, omission of final consonants (e.g., *car → ca*), regular omission of */r/*. |
| **Monosyllabic words repetition A** N-EEL | -3.5 SD | Not done | |
| **Monosyllabic words repetition B** N-EEL | 6/28 (-8.5 SD) | 22/28 (-1.3 SD) | |
| **Plurisyllabic words repetition** N-EEL | 20/50 (-7.2 SD) | 48/50 (+0.3 SD) | |
| **Receptive lexicon** ELO | 11/20 (-2.0 SD) | 14/20 (-0.6 SD) | The lexical stock in reception and production were deficient |
| **Productive lexicon** ELO | 16/30 (-4.5 SD) | 30/42 (+0.2 SD) | |
| **Immediate understanding of statements** ELO | 4/21 (-1.0 SD) | 17/21 (+1.3 SD) | Deficient syntactic comprehension and syntactic encoding. The plural forms of nouns and adjectives had not been acquired, nor have the plural forms of verbs. The gender of nouns and adjectives were also challenging as determiners were confused. Difficulties in understanding and expressing the future, past, negation, and passive voice. Understanding instructions was very challenging. Sentence structure was not yet established. |
| **General understanding of statements** ELO | 10/21 (-5.4 SD) | 20/21 (+0.5 SD) | |
| **Statement production** ELO | 3/16 (-3.3 SD) | 8/16 (-2 SD) | |
| ***Reading*** Fiche de Bicêtre | | | |
| **Graphem** | Impossible | 20/26 (-0.3 SD) | Reading remains very challenging. Given the difficulty he was assessed at 11 years with very basic tests that we usually use for first grade. |
| **Simple syllables** | | 22/24 (+0.9 SD) | |
| **Complex syllables** | | 5/10 (NC) | |
| **Digraphs in isolation** | | 9/10 (NC) | |

***SD** = standard deviation. **NC** = not calculable. **1=** At the age of 11, speech impairment scores were assessed using the same test as at intake to ensure intra-individual comparability. Therefore, the normative age-group comparison does not correspond to the child's current age.*

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**Table 2.** Review of published cases with PTPN4 mutation (adapted and completed from Chmielewska et al., 2021)

| Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | CR |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age** | 11y | 23m | 20m | 19y | 15y | 17y | Birth | 5y | 17y | 17y | 11y |
| **Gender** | M | M | M | M | F | M | F | M | F | F | M |
| **Mutation type** | Substitution | | | | | | | | Deletion | | |
| **Transmission** | de novo | | | | N/A | Maternal[6H] | de novo | | | | Paternal |
| **Height**<br>**Weight**<br>**OPC** | >99th<br>>99th<br>>99th | 5%<br>2%<br>79% | <1%<br>2%<br>20% | 65%<br>71%<br>>99% | 61%<br>30%<br>7% | >99th<br>2%<br>98% | 2%<br><1%<br><1% | 50%<br>50%<br>25% | 50%<br>>10%<br>50% | >10%<br>50%<br>>10% | <3%<br><3%<br>>99% |
| **Growth** | Overgrowth | | OFC >99% at 16m | Homogenous | | | | At 3y-o : Height >75%, Weight 25%, OFC 50% | Delay | | |
| **Development** | DD Averbal | DD | DD | Moderate ID | BIF | Mild ID | N/A | ID | ID | ID | Normal [LB1] |
| **Behavioral** | ADHD Autism | None | None | ADHD Autism | ADHD | ADHD | N/A | Rigidity, ritualized behaviors | Stereotypic behaviors | Rett syndrome-like | ADHD Rigidity & Ritualized behaviors |
| **Speech impairement** | Yes | Yes | Not reported | | | | | Yes | Yes | Yes | Yes |
| **Neurological signs** | Tight harmstrings | Hypotonia; distal extremity tremor | Congenital torticollis | Normal tone, Motor Delays | Tic disorder | None | Increased tone in all extremities | Sensory deficit | None | | Motor delays |
| **Musculo-skeletal** | None | | Radial deficiency and vertebral anomalies[3M] | Joint laxity, pes planus | Butterfly vertebrae | None | | | | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| **Other** | Tapering fingers, crouch gait, café-au-lait macules | Tapering fingers, Café-au-lait macules, other anomalies[2O] | Meets criteria for VACTERL association | Tapering fingers. Joint laxity, motor unsteadiness astigmatism, hyperacusis | Visual processing deficit | None | Hypoplastic Left Heart Syndrome | None | | | Hypertelorism low-lying hair, broad neck, slightly thick ear not low-lying, eyebrow not sparse. |
| **Seizures & EEG** | No seizures N/A | No seizures Negative | No seizures N/A | No seizures N/A | Absences seizures Abortive generalized spike wave discharges | Abnormal | No seizures Not done | No seizures N/A | Seizures; spike and wave generalised paroxysmal discharges | Generalized seizures | No seizures Negative |
| **MRI** | Normal non-contrast MRI | Large perivascular space/neuroglial cyst | Diminished white matter volume[3I] | Diminished white matter volume and other anomalies[4I] | Nomal non-contrast MRI | Normal | Anatomical anomalies[7I] | Normal non-contrast MRI | N/A | N/A | Normal non-contrast MRI |
| **Reference** | Chmielewska et al | | | | | | | Szczałuba et al. | Christodolou et al. | | This study |

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**N/A=** Not available ; **ADHD =** Attention Deficit Hyperactivity Disorder : **DD =** Developmental Delay ; **ID =** Intellectual Disability ; **BIF =** Borderline intellectual function ; **LB1 =** normal intelligence with discrepancy between indexes ; **2O :** Wide distal phalanges; strawberry hemangioma x 1; wide-based gait ; **6H :** from mosaic mother ; **3M :** Radial deficiency with oligodactyly talipes equinovarus and vertebral anomalies (thoracic region block vertebrae with rib fusions and lumbosacral hemivertebra : **3I :** Mildly diminished cerebral white matter volume; Prominence of the ventricles and supratentorial extra-axial spaces may reflect white matter loss and or impaired cerebrospinal fluid resorption ; **4I :** large cavum septum pellucidum, slight reduction in white matter around posterior horns, thin corpus callosum; **7I :** semilobar holoprosencephaly and microcephaly, small 3rd ventricle, formed but thin splenium of corpus callosum, partial thalamic fusion, complete basal ganglia fusion , dorsal interhemispheric fissural cyst

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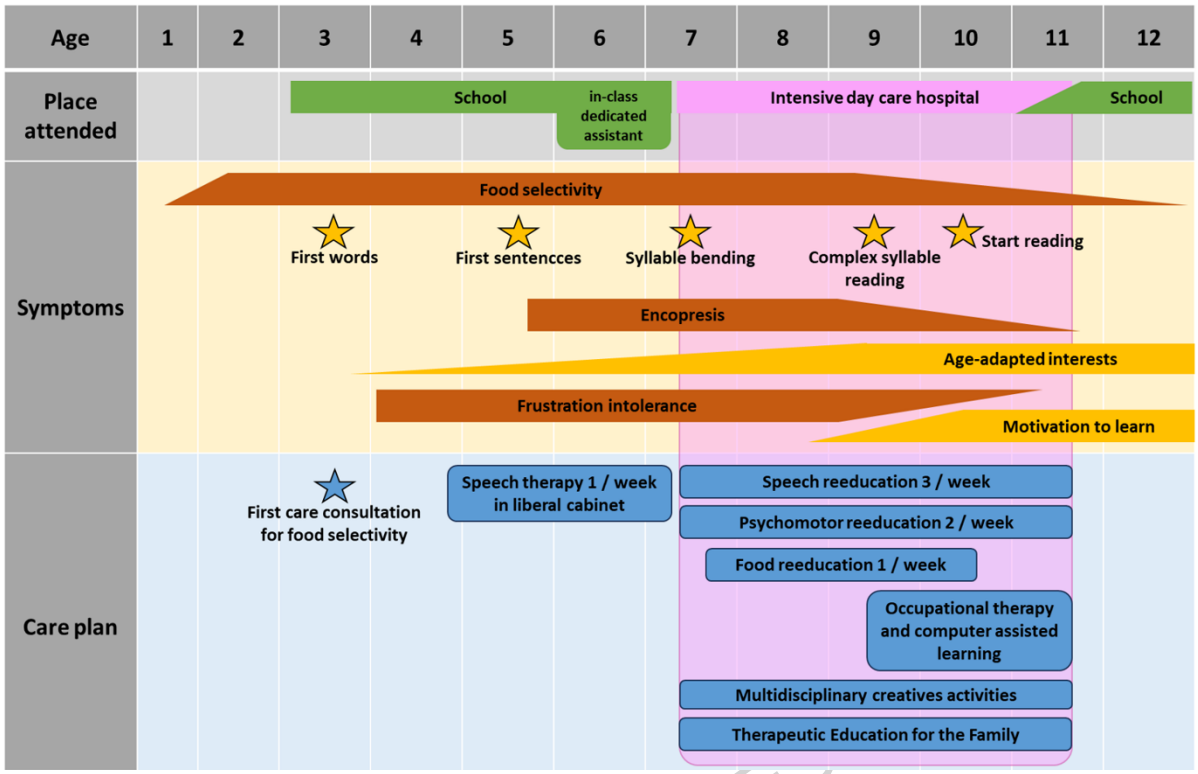


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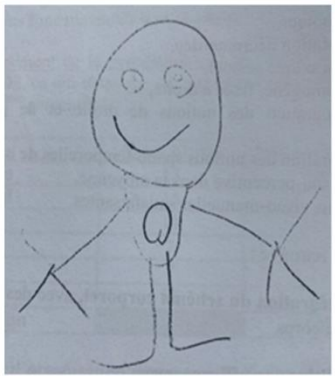
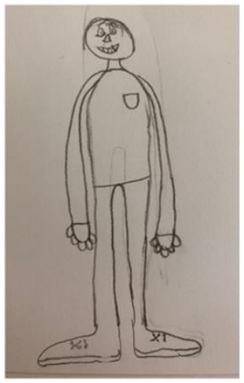
**1a**

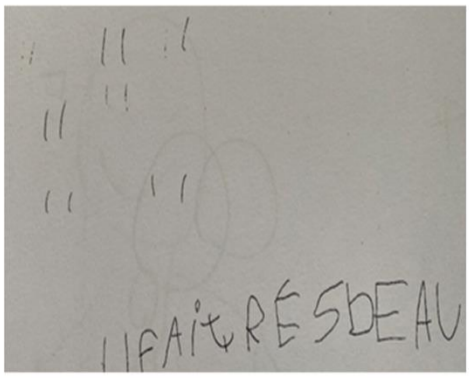
***7 years***

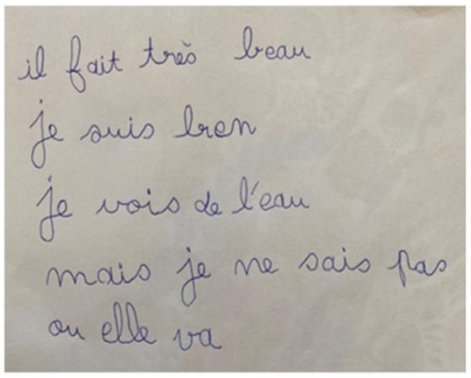


***11 years***



**1b**

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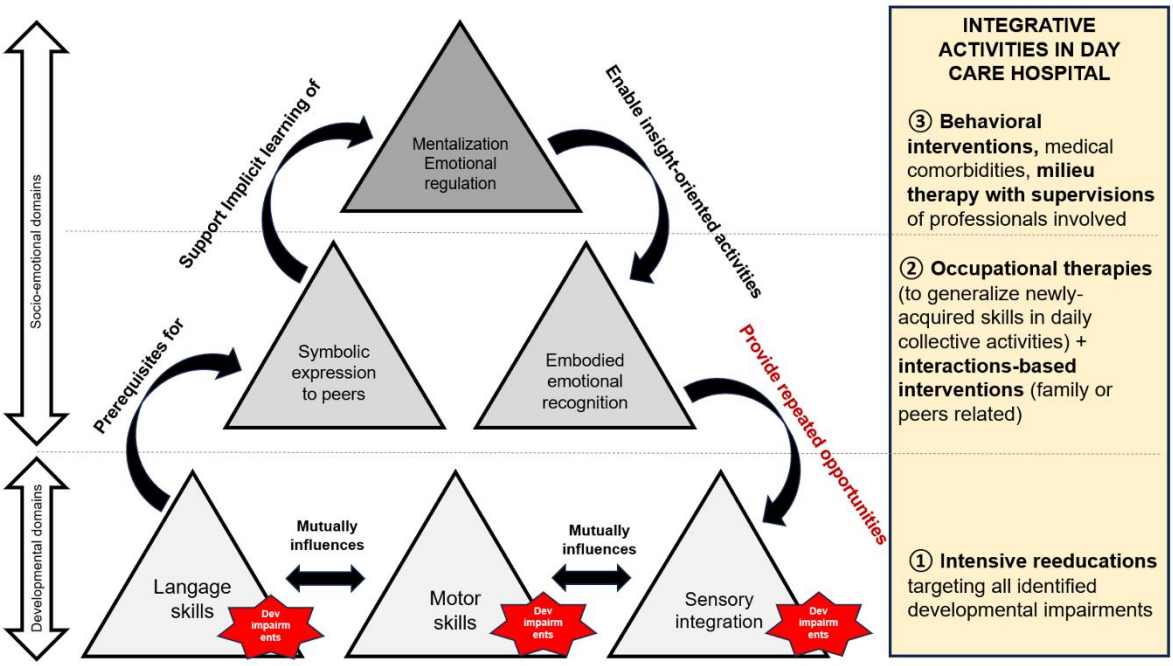


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