# Severe Expressive-Language Delay Related to Duplication of the Williams–Beuren Locus

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## SUMMARY

The Williams–Beuren syndrome (WBS) locus, at 7q11.23, is prone to recurrent chromosomal rearrangements, including the microdeletion that causes WBS, a multisystem condition with characteristic cardiovascular, cognitive, and behavioral features. It is hypothesized that reciprocal duplications of the WBS interval should also occur, and here we present such a case description. The most striking phenotype was a severe delay in expressive speech, in contrast to the normal articulation and fluent expressive language observed in persons with WBS. Our results suggest that specific genes at 7q11.23 are exquisitely sensitive to dosage alterations that can influence human language and visuospatial capabilities.

The underlying genetic bases for the majority of cases of language impairment have been postulated to be complex, involving several loci that interact with one another and the environment to produce an overall susceptibility to disease onset.[1] Clues to the discovery of which genes potentially influence language ability may be found in mendelian disorders that have distinctive language components to their clinical phenotype. The Williams–Beuren syndrome (WBS) is one such neurodevelopmental disorder, in which persons show considerable strength in expressive language relative to their overall level of intellectual ability.[2] WBS is also associated with a recognizable facies, supravalvular aortic stenosis, hypersensitivity to sound, visual impairment, dental problems, growth deficiency, infantile hypercalcemia, musculoskeletal abnormalities, and a hoarse voice.[3] The syndrome is caused

by the recurrent deletion of a specific set of genes, so it provides a unique opportunity to identify genes that are directly involved in language ability.[4]

The chromosomal locus that is deleted in WBS (on chromosome 7, band q11.23) is prone to deletion because it is flanked by blocks of DNA that have a very high degree of similarity to one another (called low copy repeats [LCRs]).[4] The deletions, which almost invariably span a common interval, are caused by nonallelic homologous recombination within the LCRs of either the same chromosome 7 (i.e., intrachromosomal) or different chromosome 7s (i.e., interchromosomal). In each case, the chromosomes are envisaged to form loops, thereby allowing the alignment of the two LCRs, the occurrence of recombination, and the excision of the DNA contained within the intervening loop.[4] The syndrome occurs at a frequency of approximately 1 in 7500 live births, with approximately two thirds of the deletion events being interchromosomal.[5] Other microdeletion disorders — including the velocardiofacial syndrome, the Smith–Magenis syndrome, the Prader–Willi and Angelman syndromes, and hereditary neuropathy with liability to pressure palsies — are also mediated by nonallelic homologous recombination.[6] For each of these microdeletions, a reciprocal duplication disorder has also been identified: dup22q11.2, dup17p11.2, dup15q11-q13, and Charcot–Marie–Tooth type 1A, respectively.[6]

Theoretically, duplications of the WBS region should occur at the same frequency as deletions occurring through interchromosomal nonallelic homologous recombination[6] (i.e., at a frequency of 1 in 13,500). However, such duplication has not yet been described, even though there has been ample opportunity for the observation of such rearrangements in studies of patients with WBS-like clinical features but no deletion.[4,7,8] That duplications have not been found in these patients suggests that the effect of duplication of the WBS locus is either lethal or has no observable consequence. Alternatively, the duplication could result in a clinical presentation that does not overlap with that of WBS and is therefore not represented in this study population. The patient we describe here, who has an exact duplication of the WBS region, has a phenotype that includes a severe delay in expressive language —a characteristic that is distinct from any of the typical clinical features seen in WBS.

## CASE REPORT

The proband (Patient 1) was born after a full-term pregnancy complicated by maternal Crohn's disease and poor weight gain. (Patient 1's mother died when he was four years three months old.) His birth weight was 2520 g (below the 5th percentile), his length was 44.5 cm (below the 5th percentile), and his head circumference was 33 cm (at the 10th percentile). He initially required gavage feeding and was evaluated for failure to thrive and hypotonia at 13 months. According to a parental report, he sat at one year and walked at two years. He was evaluated by a speech pathologist and given diagnoses of moderate-to-severe language delay at the age of two years and severe delay in receptive and expressive language at the age of three years two months. When he was four years two months of age, attention deficit–hyperactivity disorder (ADHD), an overall developmental delay, an unspecified sleep disorder, and a severe delay in speech and language and in fine motor skills were diagnosed. Results of behavioral audiometry and otoacoustic emissions were consistent with the

presence of normal hearing. At the age of eight years, Patient 1 was again evaluated by a speech pathologist, and childhood apraxia of speech was diagnosed. Additional clinical, biochemical, and genetic analyses did not reveal any abnormalities (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Patient 1's sister (Patient 2) was also given a diagnosis of ADHD, and both were receiving 5 mg of dextroamphetamine sulfate (Dexedrine) twice daily. The history revealed that both parents had also had attention and academic difficulties but that Patient 1 was the only member of the family who had difficulty with language acquisition.

Written informed consent was obtained from the guardians of the patients for genetic and psychological studies, which were approved by institutional ethics review boards. At the time of our assessment, Patient 1 was 8 years 10 months old, and Patient 2 was 11 years 1 month old.

## MILD PHYSICAL MANIFESTATIONS

Patient 1 had growth retardation and mild dysmorphism. His physical examination showed height, weight, and head circumference at the 2nd, 5th, and 30th percentiles, respectively. Dysmorphic features included dolichocephaly, a high and narrow forehead, long eyelashes, a high and broad nose, a short philtrum, a high-arched palate, dental malocclusion (specifically, an anterior open bite), retrognathia, and asymmetric crying face (Fig. 1 and Table 1). Patient 1 did not have any of the facial features of WBS.[3] He had bilateral simian creases, and the left hand was smaller than the right. On neurologic examination, he was noted to have very mild dysmetria and mild difficulty with tandem gait and unipedal stance.

## SEVERE DELAY IN EXPRESSIVE LANGUAGE

Patient 1's difficulties with expressive language were immediately apparent. He was able to pronounce only a very small number of words correctly; most words were approximations composed of the first consonant (or a related consonant) and the first vowel (or a related or neutral vowel) of the target word. The results of the intellectual and vocabulary assessments are summarized in Table 2. Patient 1's performance on the Differential Ability Scales[9] differed from his sister's only on the verbal cluster, in which verbal responses, manual signs, gestures, pantomime, and drawing were all considered acceptable responses from him. If only verbal responses had been accepted, his verbal-cluster standard score would have been considerably lower.

To provide a direct comparison of Patient 1's receptive and expressive language abilities, the Pea-body Picture Vocabulary Test,[10] which measures receptive vocabulary, and the Expressive Vocabulary Test[11] were administered (Table 2). Patient 1's standard score on receptive vocabulary was in the low-average range (age equivalent, 6 years 10 months). In contrast, his standard score on expressive vocabulary was in the severe-impairment range (age equivalent, two years three months), even though both word approximations and manual signs were considered acceptable responses. Similar results were obtained with the Clinical Evaluation of Language Fundamentals test[12] (see the Supplementary Appendix).

Although Patient 1's standard scores on the non-verbal reasoning and spatial clusters of the Differential Ability Scales were in the range of mild mental deficiency, his performance was very similar to his sister's and was consistent with the type of difficulties his mother was also reported to have had, indicating that the duplication was not the primary basis for these difficulties. Both children's scores on the Conners' scales[13] (found in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed.) were consistent with their previous diagnosis of ADHD.

## METHODS AND RESULTS

### DUPLICATION OF THE 1.5-Mb WBS REGION

Patient 1 was initially referred for testing for the velocardiofacial syndrome and was screened with the use of a real-time method on the basis of a polymerase-chain-reaction (PCR) assay, which detected the duplication of markers within the WBS critical region.[14] Fluorescence in situ hybridization (FISH) with probes from 7q11.23[7] showed that the in-tandem duplication was limited to the region commonly deleted in WBS (Fig. 2A). Probes from within the WBS common deletion (CTA-208H19 and RP5-1186P10) gave three signals on interphase FISH, whereas probes flanking the deletion region (RP11-815K3 and CTB-139P11) gave only two signals (Fig. 2A; some data not shown). Cosmid LL07NCO1-207g3, which lies between the medial and telomeric LCRs, also gave only two signals, indicating that the duplication was restricted to the region spanning the centromeric and medial LCRs, which corresponds to the region commonly deleted in WBS. No duplication was present in Patient 1's father or sister or in more than 250 other controls with or without WBS who were also examined.

Analysis of single-copy microsatellite markers from within the WBS region revealed that Patient 1 carried three distinct alleles at loci *D7S2476, D7S3194,* and *D7S1870* (Table 1 of the Supplementary Appendix). In each case, only one of the alleles was present in the father, indicating that Patient 1 had inherited two different copies of the WBS region from his mother. Analysis of the maternal grandparents revealed that the duplicated chromosome in the proband contained segments of chromosome 7 that were inherited independently from each maternal grandparent (Table 1 and Fig. 1 of the Supplementary Appendix). These analyses indicate that the meiotic interchromosomal recombination that led to the duplication took place in the mother's germ cells, making it a new rearrangement.

### RECIPROCAL OF THE WBS DELETION

Further narrowing of the duplication breakpoints could not be accomplished with FISH or microsatellite analysis, owing to the high sequence identity of the LCRs. We used site-specific nucleotide (SSN) dosage analysis to define the relative number of B block–type copies (centromeric, medial, or telomeric) at each position analyzed, an approach that enabled us to infer the position where the recombination had occurred.[4] Analysis of seven SSNs showed that in Patient 1 the transition between blocks $B_m$ and $B_c$ occurred between SSN 4 and SSN 6, within the *NCF1* gene (Fig. 2B). The majority of WBS deletion breakpoints (>90 percent) also occur within the B block,[4] indicating that the duplication is the exact reciprocal of the common WBS deletion.

## ALTERED EXPRESSION OF GENES WITHIN THE DUPLICATION

Gene-expression analysis in lymphoblastoid cell lines by real-time PCR demonstrated that five of six genes that were examined within the duplicated region (*GTF2I, LIMK1, WBSCR1, RFC2,* and *BAZ1B*) showed increased expression in Patient 1 and reduced expression in persons with WBS (Table 2 of the Supplementary Appendix). The exception was *WBSCR5,* which showed reduced expression in persons with WBS but levels in Patient 1 that were consistent with levels in controls. *WBSCR16,* located just outside the telomeric deletion or duplication, did not show altered expression in either Patient 1 or in persons with WBS, indicating that the rearrangement breakpoints do not affect its transcription. The nearest gene outside the centromeric breakpoint, the gene encoding calneuron 1, was not expressed in lymphoblasts, but it is at least 300 kb from the proximal B block[4] and is separated from the breakpoint by the complex and actively transcribed LCRs; hence, its expression unlikely to be affected.

# DISCUSSION

We describe a syndrome that is associated with a reciprocal duplication of the WBS microdeletion region. Patient 1 has intellectual strengths and weaknesses that are in direct contrast to those of children with WBS. Expressive language, especially syntax and phonology, is the area of greatest weakness for Patient 1, whereas for children with WBS, expressive language is a relative strength.[2] When Patient 1 had difficulty making himself understood, he often successfully resorted to drawing what he was trying to express. Visuospatial construction (including drawing) is the area of greatest weakness for children with WBS, and most children with WBS who are Patient 1's age are able to draw only a few recognizable objects.[15]

Previous descriptions of persons with larger duplications of the region (supernumerary ring chromosome 7) have noted delay in expressive language or impairment accompanied by articulation problems, but none of these reports contain standardized assessment results or comparative data on expressive and receptive language.[16] Karyotypes were derived from G-banding, not from molecular analysis, so the extent of each duplication remains unknown. Our findings specify the expressive-language phenotype associated with dup7q11.23 and define the precise region of chromosome 7 contributing to it as the 1.5-Mb interval commonly deleted in WBS.

There appears to be a subtle but recognizable facial phenotype that is shared by both Patient 1 and previously described persons with supernumerary ring chromosome 7, one that consists of a high and broad nose, posteriorly rotated ears, a high-arched palate, and a short philtrum.[16–18] When accompanied by delay in expressive language, this gestalt warrants testing for duplication of the WBS critical region.

Although there is a strong genetic component to language impairment, so far only the transcription factor FOXP2 has been implicated as a cause of the problem, and only in a few cases.[19] Disruption of FOXP2 results in reduced functional dosage and leads to deficits in both expressive and receptive language, in addition to orofacial dyspraxia that impairs the coordination of complex fine-motor movements of the lower face.[19,20] The remaining cases

of language impairment were predicted to involve complex causes.[1] The identification of a second locus associated with language impairment is therefore unexpected and opens up the possibility of linking the expressive-language phenotype to a specific gene or genes from within the WBS region.

The contrast between phenotypes associated with deletion and those associated with duplication of the WBS region, as well as the accompanying changes in gene expression, suggests that genes within this region are dosage sensitive. These observations also suggests that perturbation can have a dramatic, negative effect on both language development and visuospatial construction ability.

The duplication or deletion encompasses 26 to 27 genes, many of which can be ruled out as important contributors to the WBS phenotype on the basis of the correlation of genotype with phenotype in persons with atypical deletions.[21–24] The minimal critical interval that must be deleted in classic WBS spans the region between the gene encoding elastin and the common distal breakpoint and encompasses just nine genes. Included within the WBS minimal critical interval are three general transcription factor 2 I (*GTF2I*) genes, encoding a family of proteins that are predicted to possess some functional redundancy.[25] In a simple or more complex model, alteration of expression of a single gene — or in the case of the *GTF2I* family, possibly a combination of genes — might lead to a distinctive language-impairment phenotype that overlaps with that observed in Patient 1. Our discovery of the WBS duplication provides both the long-sought-after reference case for ascertainment of other patients and an entry point toward the discovery of new genes required for the normal acquisition and expression of language. The association between expressive-language delay and duplication of the WBS region also has implications for the molecular diagnosis of language delay.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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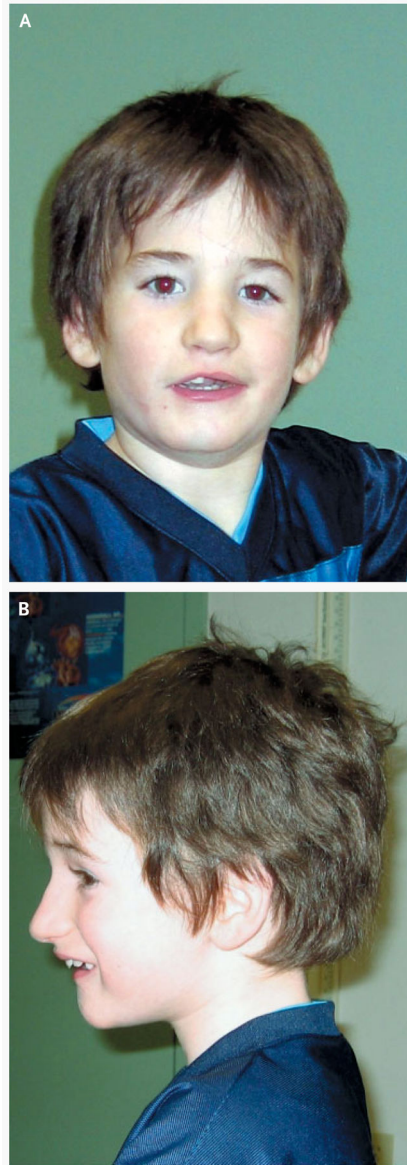
**Figure 1. Photographs of Patient 1 at the Age of Eight Years**
Patient 1 has a high and narrow forehead, a high and broad nose, a short philtrum, and facial asymmetry (Panel A). In Panel B, long eyelashes and retrognathia can be clearly seen.
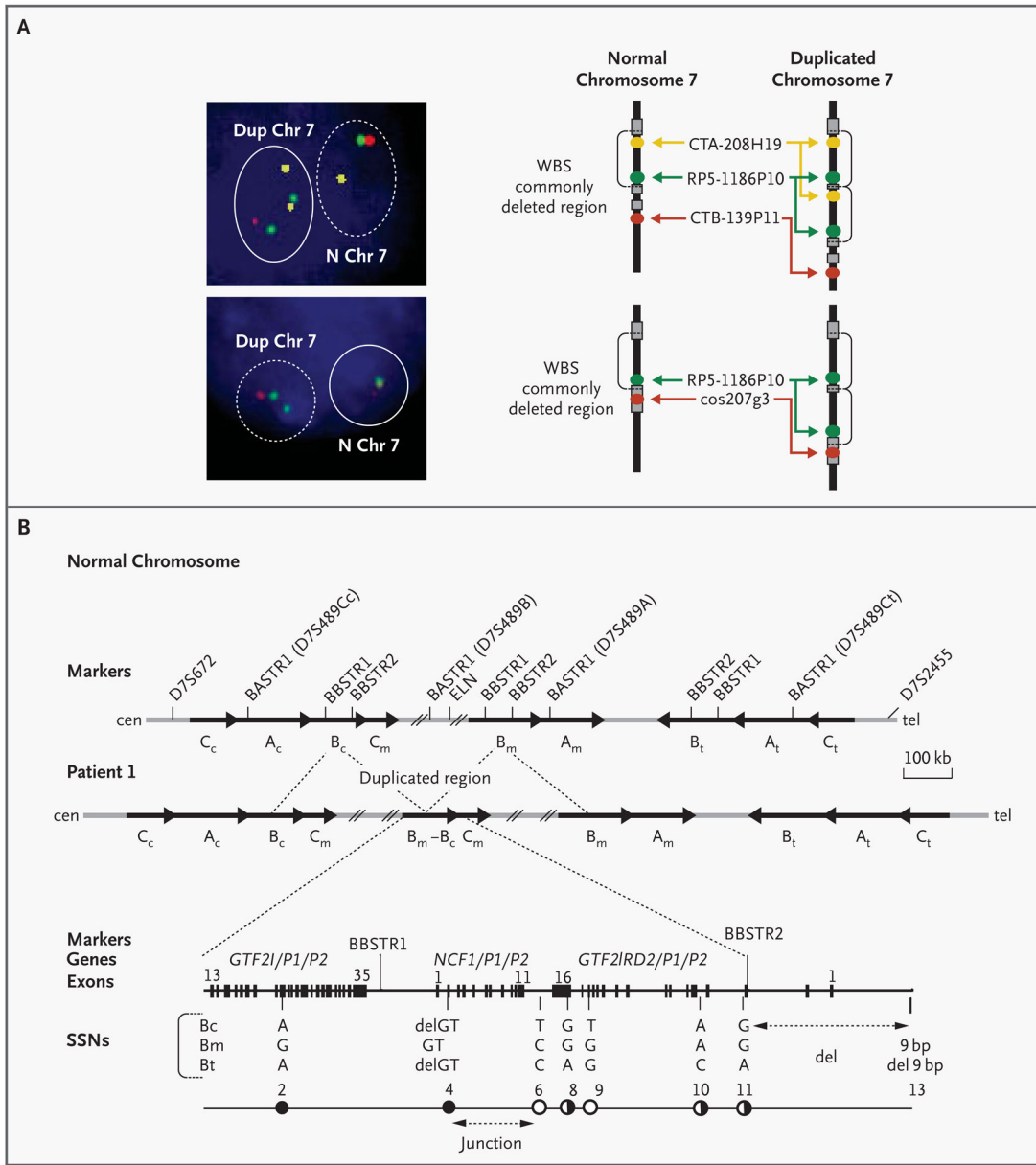
**Figure 2. Schematic Representation of the 7q11.23 Duplication**
In Panel A, analysis by fluorescence in situ hybridization (FISH) was performed on interphase and metaphase spreads prepared from both fresh lymphocytes and lymphoblastoid cell lines, as described previously,[7] and in all cases the results were the same. Shown is FISH analysis of Patient 1 with clones from within the region (CTA-208H19 and RP5-1186P10) that is commonly deleted in the Williams–Beuren syndrome (WBS) and from an area flanking that region (CTB-139P11 and cos207g3). Fluorescent signals are grouped into those from the normal chromosome 7 (N Chr 7) and from the duplicated chromosome 7 (Dup Chr 7). A schematic representation of the location of the probes on each chromosome is also shown. The chromosomes are oriented with the centromere at the top, and the low copy repeats (LCRs) are depicted as gray boxes. The probes are depicted in

colors corresponding to the FISH image. The 1.5-Mb region of chromosome 7q11.23 that is commonly deleted in WBS is indicated. Panel B shows a map of the region of exchange in block B leading to duplication of the common 1.5-Mb WBS deletion region. Polymorphic microsatellite markers and genes from the WBS region are shown on the top. The unique sequence is depicted by gray lines, and the repetitive blocks that constitute the LCRs are depicted as black arrows, indicating their orientation on the chromosome. A detailed schematic representation of the entire 143-kb length of block B is also shown. The dotted arrow on the right shows that the last 38 kb is absent in the centromeric B block ($B_c$). The genomic structure of genes within the region is also shown. The genes are those encoding general transcription factor 2 I (*GTF2I*), neutrophil cytosolic factor 1 (*NCF1*), and *GTF2I* repeat domain containing protein 2 (*GTF2IRD2*). Functional copies of these genes are present in block $B_m$, and corresponding pseudogenes (P1 or P2) are present in blocks $B_c$ and $B_t$, except for the $B_t$ copy of *GTF2IRD2* that appears to be a functional gene as well. Exons are depicted as black boxes, and the numbers indicate the first and last exons within the block. Numerical identification, location, and sequence difference of each site-specific nucleotide (SSN) that was used in this study are indicated and have been described previously.[4] All dosage-analysis calculations were performed with regard to Patient 1, who carried one normal chromosome 7, and his father, who carried two normal chromosomes 7. The inferred recombinant block B in the duplicated chromosome is shown at the bottom. The predicted genotypes at each position are depicted as circles: white circles denote $B_c$-type, black circles $B_m$-type; and black-and-white circles either $B_c$-type or $B_m$-type. The region of exchange occurred somewhere between SSN 4 and SSN 6 within the *NCF1* gene and one of its pseudogenes.

**Table 1**

Clinical and Neurobehavioral Differences between Williams–Beuren Syndrome (WBS) and WBS Region Duplication.

| Feature | WBS | WBS Region Duplication |
|---|---|---|
| Cognitive abilities | Developmental delay or mental retardation | Developmental delay or mental retardation [*] |
| | Weakness in spatial skills | Relative strength in spatial skills |
| | Relative strength in expressive language | Severe speech and language delay [*] |
| Behavior | Excessively social | Normal social interaction |
| | Attention deficit–hyperactivity disorder | Attention deficit–hyperactivity disorder [†] |
| | Hypersensitivity to sound | Normal hearing [*] |
| | Specific phobia of loud noises | Normal response to loud noises |
| Facies | Broad forehead | Somewhat narrow forehead |
| | Bitemporal narrowing | Normal bitemporal area |
| | Low nasal root and bulbous nasal tip | High, broad nose [*] |
| | Prominent earlobes | Posteriorly rotated ears [*] |
| | Periorbital fullness | Normal periorbital area |
| | Ocular problems | No ocular problems reported |
| | Stellate iris | Normal iris |
| | Malar flattening but full cheeks | Normal malar area |
| | Long philtrum | Short philtrum [*] |
| | Full lips and wide mouth | Thin lips [*] |
| | Small jaw | Small jaw |
| | Small, widely spaced teeth | Generous-sized teeth [*] |
| | Normal palate | High palate [*†] |
| Other features | Low birth weight | Low birth weight |
| | Growth retardation | Growth retardation [†] |
| | Kidney and bladder abnormalities | Normal kidney and bladder |
| | Musculoskeletal problems | No musculoskeletal problems reported |
| | Hypercalcemia | Hypercalcemia not tested |

| Feature | WBS | WBS Region Duplication |
|---|---|---|
| | Cardiovascular problems | Normal cardiovascular system |

*
This characteristic is present in other persons with duplication of this region.

†
This characteristic is common to other family members.

**Table 2**

Standard Scores on Intellectual and Vocabulary Assessments.[*]

| Assessment | Patient 1 | Patient 2 |
|---|---|---|
| Differential Ability Scales | | |
| Verbal [†] | 65 | 93 |
| Nonverbal reasoning | 65 | 70 |
| Spatial ability | 70 | 68 |
| General conceptual ability | 62 | 73 |
| Special nonverbal composite | 65 | 67 |
| Vocabulary | | |
| PPVT-III | 82 | 106 |
| EVT[‡] | 40 | 104 |

[*] The Differential Ability Scales provide specific information about a child's strengths and weaknesses across a wide range of intellectual activities. The six core subtests for school-aged children are divided into three clusters: verbal and nonverbal reasoning and spatial ability. The general conceptual ability (similar to IQ) score is based on the performance on the six core subtests. The special nonverbal composite is based on the four core subtests included in the nonverbal reasoning and spatial clusters. The third edition of the Peabody Picture Vocabulary Test (PPVT-III) measures receptive vocabulary. The Expressive Vocabulary Test (EVT) measures the ability to label pictures and to produce synonyms for words presented by the examiner in the context of a picture illustrating the word. For each of these assessments, the population average score is 100.

[†] Patient 1 responded with a combination of words, manual signs, gestures, and pantomime; all these modes were acceptable for the Differential Ability Scale verbal cluster, provided his meaning was clear.

[‡] For Patient 1, responses composed of words or word approximations and manual signs (but not gesture or pantomime) were acceptable for the EVT.