



## Original article

# Disparities in visuo-spatial constructive abilities in Williams syndrome patients with typical deletion on chromosome 7q11.23

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## Abstract

**Background:** Williams syndrome (WS) is known for its uneven cognitive abilities, especially the difficulty in visuo-spatial cognition, though there are some inter-individual phenotypic differences. It has been proposed that the difficulty in visuo-spatial cognition of WS patients can be attributed to a haploinsufficiency of some genes located on the deleted region in 7q11.23, based on an examination of atypical deletions identified in WS patients with atypical cognitive deficits. According to this hypothesis, the inter-individual differences in visuo-spatial cognitive ability arise from variations in deletion.

**Methods:** We investigated whether there were inter-individual differences in the visuo-spatial constructive abilities of five unrelated WS patients with the typical deletion on chromosome 7q11.23 that includes the candidate genes contributing visuo-spatial difficulty in WS patients. We used tests with three-dimensional factors such as Benton's three-dimensional block construction test, which are considered to be more sensitive than those with only two-dimensional factors.

**Results:** There were diverse inter-individual differences in the visuo-spatial constructive abilities among the present participants who shared the same typical genomic deletion of WS. One of the participants showed almost equivalent performances to typically developing adults in those tests.

**Conclusion:** In the present study, we found a wide range of cognitive abilities in visuo-spatial construction even among the patients with a common deletion pattern of WS. The findings suggest that attributing differences in the phenotypes entirely to genetic factors such as an atypical deletion may not be always correct.

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**Keywords:** Williams syndrome; Visuo-spatial construction; Inter-individual differences

## 1. Introduction

Williams syndrome (WS) is a contiguous gene deletion syndrome resulting from a hemizygous deletion on chromosome 7q11.23 [1,2] (OMIM number 194050). In most cases a patient with WS has a deletion of approximately 1.55 megabases (Mb) encoding 26–28

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genes in the WS critical region (WSCR) [3–5], or a slightly larger deletion of 1.84 Mb that occurs less often (approximately 5% of cases [3]). In addition, rare atypical deletions of patients who were diagnosed as having WS have been reported (for example: [6–8]).

Genetic syndromes including WS often show distinctive cognitive, behavioral, and psychiatric patterns [9]. WS is known for its uneven cognitive abilities in addition to cardiovascular symptoms and distinctive facial appearance. In particular, the visuo-spatial difficulties and “so called” hyper-sociality are characteristic of this syndrome [10,11]. The difficulty in visuo-spatial construction, which is considered to be one of the abilities in visuo-spatial cognition, is regarded as the hallmark difficulty in patients with WS [12,13].

Vigorous attempts have been made to explain the atypical cognitive symptoms of WS by atypical deletions in the WSCR. In some of those studies it was argued that *CYLN2*, *GTF2IRD1* or *GTF2I* genes are associated with WS-specific cognitive deficits, especially the difficulty in visuo-spatial cognition [4,14–16]. These findings on candidate genes for visuo-spatial difficulty are interesting but not completely consistent [17]. Many of these studies ascribed the deviations in symptoms to differences in the deleted regions, which we questioned and was the motivation for this study.

At the same time, inter-individual differences in the phenotypes of patients with WS have been demonstrated [12,18,19], though the genetic backgrounds of the participants in these reports were not precisely evaluated. Therefore, patients with the typical deletion, which consists of the majority of WS patients, may show symptomatic deviations similar to those of patients with an atypical deletion. Accordingly, whether there is a direct association between the deviations in the symptoms and differences in the deleted genes may need to be reconsidered.

We therefore compared the ability of visuo-spatial construction of five patients with the same typical WS deletions, including *CYLN2*, *GTF2IRD1* and *GTF2I* genes and examined the phenotypic variations at one point. We focused on the visuo-spatial construction because it is the hallmark difficulty in patients with WS and has been investigated actively.

In addition, we used tasks with three-dimensional factors in evaluating the visuo-spatial constructive abilities. Generally speaking, for the purpose of evaluating visuo-spatial constructive abilities, tests that require examinees to reproduce block figures by mimicking design models are often used. However, many of these tests on deficits in visuo-spatial construction, even those using blocks, have focused only on constructional tasks involving two, rather than three, spatial dimensions [20,21]. Capruso et al. [21] investigated the constructional ability in patients with cerebrovascular lesions and found that “three-dimensional block construction

is a much purer test of spatial ability than two-dimensional mosaic block designs, despite the two-dimensional mosaic block design’s vastly more frequent use in both clinical and experimental neuropsychology”. In line with this, we used Benton’s three-dimensional block construction tests [22] in addition to the two- and three-dimensional line copying tests we used in the previous report [19].

In short, the present study has two salient features. The first is that we investigated whether cross-sectional individual differences in visuo-spatial constructive abilities can be observed even among patients with the same typical deletion in the WSCR. The second is that we used tasks involving three spatial dimensions, which are considered to be more sensitive for detecting deficits in visuo-spatial construction.

## 2. Subjects

Five Japanese males with WS (age 16–24 years) who have been followed at the Institute for Developmental Research, Aichi Human Service Center participated in this study. All of them were confirmed when younger to have the *ELN* deletion by fluorescence in situ hybridization (FISH) in addition to the clinical symptoms typical of WS such as characteristic faces, cardiovascular abnormalities or intellectual disability with visuo-spatial difficulties. Additionally, a comparative genomic hybridization analysis with 60 k oligonucleotide arrays ranging from 70.0 to 77.4 Mb (Agilent Technologies, Santa Clara, CA) detected the typical hemizyosity of the WS genomes containing the *CYLN2*, *GTF2IRD1* and *GTF2I* genes at the telomeric end of the WSCR in all the patients with WS (Supplement Fig. 1). The cognitive profiles of the participants are shown in Table 1.

As is seen in Table 1, the mental ages of the participants with WS at the time of the present investigation were about 7 or 8 adjusted by their data of performance IQ. Fifteen mentally age-matched (7 or 8 years old) typically developing children (TD) were asked to join the study and performed test 2 listed below.

All research tests were carried out with the consent of the participants and their families according to a research protocol approved by the ethics committee in the Institute for Developmental Research, Aichi Human Service Center.

## 3. Methods

The following tests were done in order to evaluate the abilities of visuo-spatial construction (test 1 and 2). Test 3 was added to assess the three-dimensional visuo-spatial ability without the factor of visuo-spatial construction.

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