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REVIEW

Neuropsychological Genotype–Phenotype in Patients with Williams Syndrome with Atypical Deletions: A Systematic Review

Carlos Alberto Serrano-Juárez[1] · Belén Prieto-Corona[1] · Mario Rodríguez-Camacho[1] · Lucero Sandoval-Lira[1] · Ángel Fernando Villalva-Sánchez[1] · Ma. Guillermina Yáñez-Téllez[1] · María Fernanda Rangel López[2]

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Abstract
Williams syndrome (WS) is a neurodevelopmental disorder caused by a microdeletion in the q11.23 region of chromosome 7. Recent case series reports and clinical case studies have suggested that the cognitive, behavioral, emotional, and social profile in WS could depend on the genes involved in the deletion. The objective of this systematic review was to analyze and synthesize the variability of the cognitive and behavioral profile of WS with atypical deletion and its probable relationship with the affected genes. The medical subject headings searched were "Williams syndrome," "genotype," "phenotype," "cognitive profile," and "atypical deletion." The studies included were in English or Spanish, with children and adults, and published between January 2000 and October 2022. Twenty-three studies are reported. The characteristics of the participants, the genes involved, the neuropsychological domains and instruments, and the prevalence of the WS cognitive profile criteria were used for the genotype–phenotype analysis. The genes with a major impact on the cognitive profile of WS were (a) *LIMK1* and those belonging to the *GTF2I* family, the former with a greater influence on visuospatial abilities; (b) *GTF2IRD1* and *GTF2I*, which have an impact on intellectual capacity as well as on visuospatial and social skills; (c) *FZD9*, *BAZ1B*, *STX1A*, and *CLIP2*, which influence the cognitive profile if other genes are also effected; and (d) *GTF2IRD2*, which is related to the severity of the effect on visuospatial and social skills, producing a behavioral phenotype like that of the autism spectrum. The review revealed four neuropsychological phenotypes, depending on the genes involved, and established the need for more comprehensive study of the neuropsychological profile of these patients. Based on the results found, we propose a model for the investigation of and clinical approach to the WS neuropsychological phenotype.

Keywords Williams syndrome · Genes · Genotype · Neuropsychological phenotype · Cognition

Introduction

Williams syndrome (WS) is a genetic neurodevelopmental disorder caused by a hemizygous deletion of 1.5–1.8 Mb in the q11.23 region of chromosome 7. The prevalence of WS is one in 7,000 to one in 25,000 births (Antonell et al., 2006; Miezah et al., 2021). 95% of people with WS have heterozygous deletion of 1.5 Mb (the typical deletion) that spans 24 genes (*TRIM50* to *GTF2I*). Another 4% have a 1.8 Mb deletion that spans two additional genes (*NCF1* and *GTF2IRD2*), and 1% have larger or smaller deletions and usually present phenotypes different from those commonly reported (Domínguez-García et al., 2022; Porter et al., 2012; Serrano-Juárez et al., 2018). Among the clinical manifestations of WS are (a) supravalvular aortic stenosis, (b) facial characteristics, and (c) a cognitive phenotype characterized by intellectual disability and visuospatial deficiencies, but a better development of verbal skills (Antonell et al., 2006; Bellugi et al., 1999). Nikitina et al. (2014) report that the cognitive alteration of people with WS is based on a triad of signs including severe deficiencies in visuospatial skills, verbal skills with better development, and hypersociability.

✉ Belén Prieto-Corona
bemapado@gmail.com

[1] Neuroscience Group. Laboratorio de Neurometría, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Av. De los Barrios #1, Col. Los Reyes Iztacala, Tlalnepantla, Estado de México CP 54090, México

[2] Universidad Autónoma del Estado de México, Tlalnepantla, Estado de México, México

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In WS, the altered genes code for transcription factors of proteins involved in synaptic transmission, as well as in neuronal structure and migration, myelinization, and neuronal maturation (Antonell et al., 2006; Osborne & Mervis, 2021), and reorganization of the cellular cytoskeleton, all of which are essential for proper neuroanatomic, neurofunctional, and neuropsychological development (Barak et al., 2019; Chailangkarn et al., 2018). Although the deletion spans 24 to 28 genes, reports with animal models, as well as neurobiological and neuropsychological studies (Antonell et al., 2006; Osborne, 2010; Osborne & Mervis, 2021), have identified that the genes most likely related to cognitive and behavioral disorders (the neuropsychological phenotype of WS) are *FZD9*, *BAZ1B*, *STX1A*, *LIMK1*, *CLIP2*, *GTF2I*, *GTF2IRD1*, *GTF2IRD2*, and *HIP1* (Campbell et al., 2009; Jackowski et al., 2009; Martens et al., 2008; Sampaio et al., 2013). These genes have a major expression in regions of the brain, including the parietal and prefrontal cortices, as well as in the cerebellum, basal ganglia, and limbic system, including the amygdala and hippocampus (Ferrero et al., 2010; Karmiloff-Smith et al., 2003; Morris et al., 2003; Tassabehji et al., 1999; Van Hagen et al., 2007).

Mervis et al. (2000) proposed the operationalization of the cognitive phenotype of WS based on the Differential Ability Scales (DAS), and specified four criteria for the Williams Syndrome Cognitive Profile (WSCP), including (a) *T* scores above the 1st percentile on verbal tests (Similarities, Vocabulary or Denomination, or Digit Recall), (b) *T* scores below the 20th percentile on visuoconstructive tasks, (c) *T* scores below the mean on visuoconstructive tasks, and (d) a lower *T* score on visuoconstructive tasks than on Digit Recall. Although use of this approach would improve characterization of the phenotypes and their relationship with the deleted genes, only a few clinical case reports have done so. The Mervis et al. (2000) approach considers cognitive variables but not behavioral disturbances or social manifestations, which also seem to vary depending on which genes are missing. The ability to identify WSCP and social skills with the size of the deletion could thus provide a better understanding of the impact of genes on the neuropsychological phenotype.

In recent years, cases have been reported of atypical deletions in persons with WS who do not seem to meet all the criteria for the cognitive profile. Although these findings have contributed to our understanding of the relationship of genes, the brain, cognition, and behavior in WS, they are isolated cases that are difficult to generalize.

The objective of this systematic review was to analyze and synthesize the variability of the cognitive and behavioral profile of atypical WS reports and any probable relationship with the affected genes. This systematic review could help to provide a better understanding of which genes influence the characteristics of the neuropsychological phenotype in WS.

Method

Selection of Studies and Inclusion Requirements

This systematic review was based on the PRISMA model (Moher et al., 2009), using the databases PubMed, ScienceDirect, and Springer Link. The medical subject headings used were "Williams syndrome," "genotype," "phenotype," "cognitive profile," and “atypical deletion.” The search included studies in English or Spanish, initially for the previous 10 years (CASJ). However, given the low prevalence of WS and the atypical cases reports, we expanded the search to the period 2000 to 2022. A total of 345 articles were obtained from this search, but 10 duplicates were eliminated.

As seen in Fig. 1, the abstracts of 345 articles were evaluated by two of the authors (CASJ and LSL), who are neuropsychologists, to select articles that met the following inclusion criteria: (a) patients with WS aged 5–60 years, (b) evaluation of neuropsychological variables (emotion, cognition, and behavior), (c) case series or clinical cases, (d) reporting the deletion range, and (e) reporting the neuropsychological genotype–phenotype relationship. The exclusion criteria were: (a) theoretical articles, systematic reviews, and book chapters, (b) animal studies, and (c) reports of other genetic variations (inversions and duplications, among others). The age range chosen was 5–60 years because development scales are generally used with children under 5 years, which makes it difficult to categorize neuropsychological variables. After 60 years of age there is significant cognitive decline, so it would be difficult to assess whether the cognitive profile is a result of the loss of genes or aging. The review was limited to cases with deletions since neuropsychological differences have been found in duplications that could be associated with the type of chromosomopathy and not with the missing genes (Mervis et al., 2015; Morris et al., 2015; Osborne & Mervis, 2021). Abstracts were classified as eligible, probably eligible, or ineligible, and there was 92% agreement between the two reviewers. Where there was disagreement, the abstracts were sent to a third reviewer, who is also neuropsychologist (AFVS). Abstracts were kept where at least two reviewers agreed. There were 23 studies that met all these criteria.

To evaluate the validity of the evidence reported in the case articles, we used the scale of Murad et al. (2018) created for systematic reviews that assesses the methodological quality of the reports and case series based on the domains of selection, ascertainment, causality, and reporting. The scale is composed of eight items divided into four categories including (a) selection (one item, "1. Does the patient(s) represent(s) the whole experience of

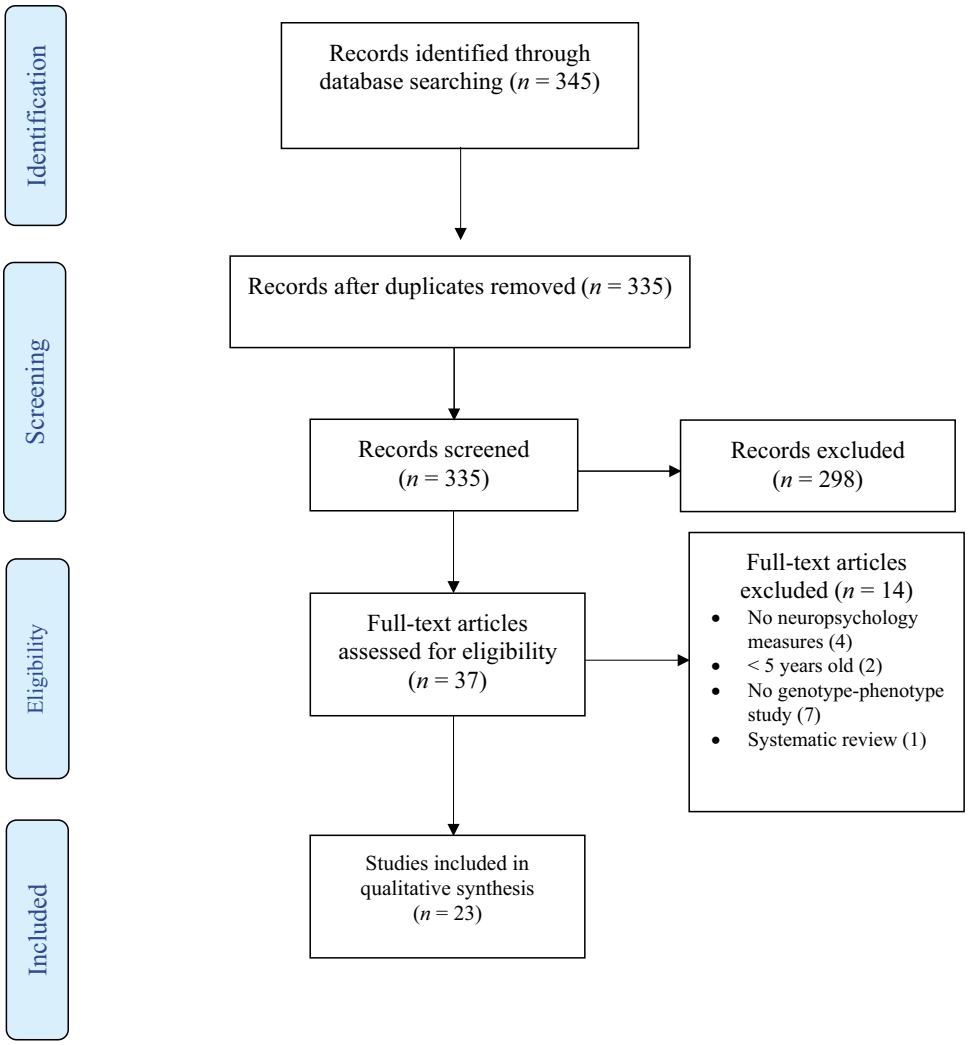


Fig. 1 PRISMA flow diagram

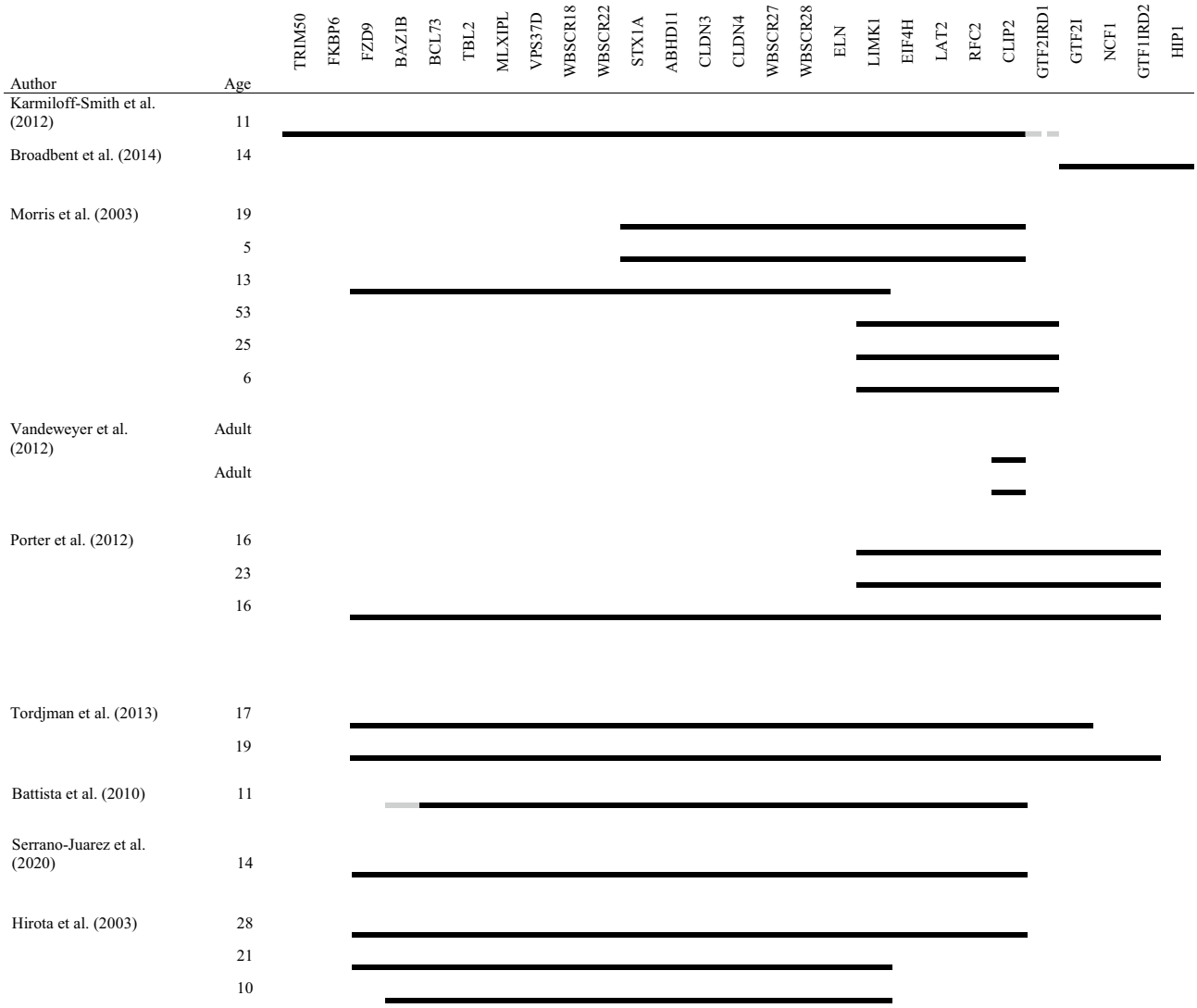
the investigator (centre) or is the selection method unclear to the extent that other patients with the similar presentation may not have been reported?"), (b) ascertainment (two items, "2. Was the exposure adequately ascertained?" and "3. Was the outcome adequately ascertained?"), (c) causality (four items, three of which assess the adverse effects of drugs or other medical treatments, but since the purpose of this systematic review was to evaluate the effect of the genes on behavior, not the effects of treatment, these three were omitted. The item used was "4. Were other alternative causes that may explain the observation ruled out?"), and (d) reporting (one item, "5. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?"). A score of 1 was assigned if the criterion was met and zero if not. The minimum score was zero and the maximum 5. The analysis is shown in Table S1, Supplementary Material.

Analysis and Synthesis of Articles

Table 1 shows lines that represent individual deletions in studies reviewed. Table 2 shows the deletion or preservation of the genes related to cognitive and behavioral alterations in WS (*FZD9*, *BAZ1B*, *STX1A*, *LIMK1*, *CLIP2*, *GTF2IRD1*, *GTF2I*, *GTF2IRD2*, *HIP1*). These were encoded with symbols ("+" if they were preserved, "±" if they were partially preserved, and "-" if they were missing).

The data from each of the articles were extracted into an Excel table for analysis. The demographic and control variables obtained were age, sex, missing genes, neuropsychological domains, neuropsychological instruments used, and WSCP criteria. These data are shown in Table 3. Analysis of the neuropsychological phenotype considered the scores obtained in tests of full intellectual quotient (FIQ), attention, memory, language, visuospatial ability, visuoconstructive praxis and motor skills, executive functions, social

Table 1 Individual deletion of genes in the studies reviewed



cognition, and neuropsychiatric traits. Given the variability of the tests applied and the descriptions of the findings, these test scores were coded into categories of average (average standard scores), low average (standard scores between 1 SD and 1.5 SD below average), borderline (standard scores more than 1.5 SD but less than 2 SD below average) or alteration (standard scores more than 2 SD below average). This procedure allowed an objective summary of the neuropsychological findings.

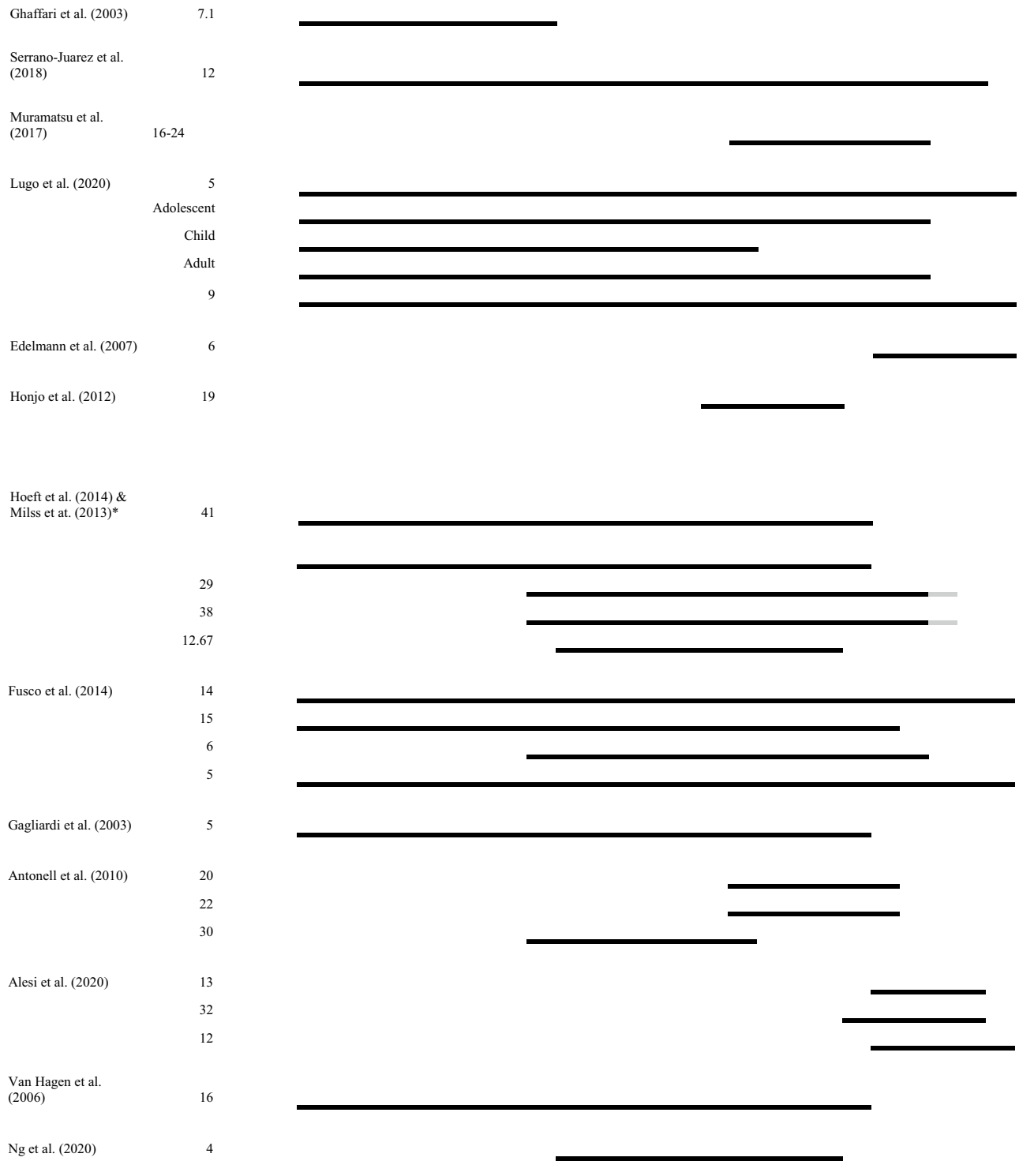
Results

The evaluation of the studies using the scale of Murad et al. (2018) yielded high scores ($M = 4.56$; $SD = 0.66$). These results showed adequate quality and allowed the validation of the reported evidence of cases and case series for the systematic review. The articles showed favorable scores in selection (100%), ascertainment (82%), causality (88%), and reporting (100%), reflecting adequate levels of reliability for data extraction.

Of the articles reviewed, 70% were about unique cases and 30% discussed case series and families. A total of 78 cases with atypical deletions were found including 41 (55%) with loss of *FZD9*, 43 (58%) of *BAZ1B*, 48 (65%) of *STX1A*, 61 (78%) of *LIMK1*, 49 (66%) of *CLIP2*, 41 (55%) of *GTF2IRD1*, 33 (45%) of *GTF2I*, and 26 (35%) of *GTF2IRD2*. The sex distribution of participants was 38 (51%) female, 31 (40%) male, and six (8%) not reported, with an age range of 5–53 years. Only 30 (40%) of participants met the four criteria of the WSCP proposed by Mervis et al. (2000).

The main cognitive variables evaluated in the cases were intellectual capacity (76 of 78 cases, 97%),

Table 1 (continued)



Ghaffari et al. (2003)	7.1
Serrano-Juarez et al. (2018)	12
Muramatsu et al. (2017)	16-24
Lugo et al. (2020)	5
	Adolescent
	Child
	Adult
	9
Edelmann et al. (2007)	6
Honjo et al. (2012)	19
Hoeft et al. (2014) & Milss et at. (2013)*	41
	29
	38
	12.67
Fusco et al. (2014)	14
	15
	6
	5
Gagliardi et al. (2003)	5
Antonell et al. (2010)	20
	22
	30
Alesi et al. (2020)	13
	32
	12
Van Hagen et al. (2006)	16
Ng et al. (2020)	4

Note: ----Deleted; ------ Partially conserved

Genes belonging to the Williams Syndrome region are shown at the top of the table. Lines represent the individual deletion in each case.

visuospatial abilities (61 cases, 78%), visuoconstructive praxis (59 cases, 75%), verbal abilities (55 cases, 70%), and social cognition (55 cases, 70%). Cognitive and behavioral processes assessed less often were attention (32 of 78 cases, 41%), memory (29 cases, 37%), executive functions (29 cases, 37%), and neuropsychiatric traits

Table 2 Genes Related to Cognition and Behavior Reported in the Studies Reviewed

Author (Year)	Age	Gender	*FZD9*	*BAZ1B*	*STX1A*	*LIMK1*	*CLIP2*	*GTF2IRD1*	*GTF2I*	*GTF2IRD2*	*HIP1*
Karmiloff-Smith et al. (2012)	11	Female	-	-	-	-	-	-	+	+	+
Broadbent et al. (2014)*	14	Male	+	+	+	+	+	+	-	-	-
Morris et al. (2003)	19	NM	+	+	-	-	-	+	+	+	+
	5	NM	+	+	-	-	-	+	+	+	+
	13	NM	-	-	-	-	+	+	+	+	+
	53	NM	+	+	+	-	-	-	+	+	+
	25	NM	+	+	+	-	-	-	+	+	+
	6	NM	+	+	+	-	-	-	+	+	+
Vandeweyer et al. (2012)	Adult	Female	+	+	+	+	-	+	+	+	+
	Adult	Male	+	+	+	+	-	+	+	+	+
Porter et al. (2012)	16	Female	+	+	+	-	-	-	-	-	+
	23	Female	+	+	+	-	-	-	-	-	+
	16.41	6F:3 M	-	-	-	-	-	-	-	-	+
Tordjman et al. (2013)	17	Male	-	-	-	-	-	-	-	+	+
	19	Male	-	-	-	-	-	-	-	-	+
Battista Ferrero et al. (2010)	11	Male	+	±	-	-	-	+	+	+	+
Serrano-Juarez et al. (2021)	14	Male	-	-	-	-	-	+	+	+	+
Hirota et al. (2003)	28	Female	-	-	-	-	-	+	+	+	+
	21	Female	-	-	-	-	+	+	+	+	+
	10	Female	+	-	-	-	+	+	+	+	+
Ghaffari et al. (2018)	7.1	4 M: 6F	-	-	-	+	+	+	+	+	+
Serrano-Juarez et al. (2018)	12	2 M:2F	-	-	-	-	-	-	-	-	+
Muramatsu et al. (2017)	16–24	5 M	+	+	+	-	-	-	-	+	+
Lugo et al. (2020)	5	Female	-	-	-	-	-	-	-	-	-
	Adolescent	Male	-	-	-	-	-	-	-	+	+
	Child	Male	-	-	-	-	+	+	+	+	+
	Adult	Female	-	-	-	-	-	-	-	+	+
	9	Female	-	-	-	-	-	-	-	-	-
Edelmann et al. (2007)	6	Female	+	+	+	+	+	-	-	-	-
Honjo et al. (2012)	19	Male	+	+	+	-	+	+	+	+	+
Hoeft et al. (2014) & Mills et al. (2013)*	41	Male	-	-	-	-	-	+	+	+	+
	29	Male	+	+	-	-	-	-	-	+	+
	38	Male	+	+	+	-	+	+	+	+	+
	12.67 (2.66)	12.67 (2.66)	+	+	+	-	+	+	+	+	+

Table 2 (continued)

Author (Year)	Age	Gender	*FZD9*	*BAZ1B*	*STX1A*	*LIMK1*	*CLIP2*	*GTF2IRD1*	*GTF2I*	*GTF2IRD2*	*HIP1*
Fusco et al. (2014)	14	Female	-	-	-	-	-	-	-	-	-
	15	Female	-	-	-	-	-	-	+	+	+
	6	Male	+	+	-	-	-	-	-	+	+
	5	Female	-	-	-	-	-	-	-	-	-
Gagliardi et al. (2003)	5	Male	-	-	-	-	-	+	+	+	+
Antonell et al. (2010)	20	Female	+	+	+	-	-	-	+	+	+
	22	Female	+	+	+	-	-	-	+	+	+
	30	Female	+	+	-	-	+	+	+	+	+
Alesi et al. (2020)	13	Female	+	+	+	+	-	-	-	-	+
	32	Female	+	+	+	+	-	-	-	-	+
	12	Female	+	+	+	+	+	-	-	-	-
van Hagen et al. (2006)	16	Male	-	-	-	-	-	+	+	+	+
Ng et al. (2020)	17.04 (2.03)	1 M: 3 M	+	+	+	-	+	+	+	+	+

Not Mentioned (NM), Female (F), Male (M), preserved (+), deleted (-), partially preserved (±), Same clinic cases (*), Genes related to cognition and behavior are underlined (+)

*TRIM50 FKBP6 FZD9 BAZ1B BCL73 TBL2 MLXIPL VPS37D WBSCR18 WBSCR22 STX1A ABHD11 CLDN3 CLDN4 WBSCR27 WBSCR28 ELN LIMK1 EIF4H LAT2 RFC2 CLIP2 GTF2IRD1 GTF2I NCF1 GTF2IRD2 HIP1

Table 3 Genotype, Neuropsychological Phenotype, and WSCP Criteria in Clinical Cases and Case Series of People with Williams Syndrome Included in the Studies Reviewed

Author (year)	Age	Gender	Missing Gene	Neuropsychological Instruments	FIQ	Attention	Memory	Language	Visuospatial	Praxia & Motor Skills	Executive Functions	Social Cognition	Neuropsychiatry	WSCP Criteria				
														1	2	3	4	Total
Karmiloff-Smith et al. (2012) & Broadbent et al. (2014)*	11	Female	*FZD9,BAZ1B,STX1A, LIMK1, CLIP2, GTF2IRD1*	BAS-II; RCPM; Social Attribution Task; Strange Stories Task; Smarties Task and Where-Will-She-Look; Social and psychiatric inventories	Average	NE	NE	Border	Border	NE	NE	ToM & Social Judgment Average	Anxiety	+	+	+	+	4
	14	Male	*GTF2I-GTF2IRD2*		Alteration	NE	NE	Alteration	Alteration	NE	NE	Alteration	Autism behavior	-	+	+	+	3
Morris et al. (2003)	19	NM	*STX1A, LIMK1,CLIP2*	K-BIT; PPVT-R	Average	Low Average	Average	Average	Low Average	Low Average	NE	NE	NE	+	-	+	+	3
	5	NM	*STX1A, LIMK1, CLIP2*		Average	Average	Average	Average	Low Average	Low Average	NE	NE	NE	+	-	-	-	1
	13	NM	*FZD9, BAZ1B, STX1A, LIMK1*		Average	Average	Average	Average	Alteration	Alteration	NE	NE	NE	+	+	+	+	4
	53	NM	*LIMK1, CLIP2, GTF2IRD1*		Average	Alteration	Alteration	Average	Alteration	Alteration	NE	NE	NE	+	+	+	-	3
	25	NM	*LIMK1, CLIP2, GTF2IRD1*		Average	Average	Average	Low Average	Alteration	Alteration	NE	NE	NE	+	+	+	+	4
	6	NM	*LIMK1, CLIP2, GTF2IRD1*		Average	Average	Average	Average	Average	Average	NE	NE	NE	+	-	-	+	2
Vandeweyer et al. (2012)	Adult	Female	*CLIP2*	WAIS-III	Average	Average	Average	Average	Average	Average	Average	NE	NE	+	-	-	-	1
	Adult	Male	*CLIP2*		Average	Average	Average	Average	Average	Average	Average	NE	NE	+	-	-	-	1
Porter et al. (2012)	16	Female	*LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2*	WJ-R COG; Diagnostic Analysis of Nonverbal Accuracy; Shape School Test; Social and psychiatric inventories; Benton Face Recognition Test; BJLO; DAS	Border to Alteration	Alteration	Low Average	Border	Alteration	Alteration	Low Average	Alteration	NE	+	+	+	+	4
	23	Female	*LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2*		Alteration	Alteration	Low Average	Border	Alteration	Alteration	Border	Alteration	NE	+	-	-	+	2

Table 3 (continued)

Author (year)	Age	Gender	Missing Gene	Neuropsychological Instruments	FIQ	Attention	Memory	Language	Visuospatial	Praxia & Motor Skills	Executive Functions	Social Cognition	Neuropsychiatry	WSCP Criteria				
														1	2	3	4	Total
	16.41	6F:3 M	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2*	WJ-R COG; Diagnostic Analysis of Nonverbal Accuracy; Shape School Test; Psychiatric inventories	Alteration	Alteration	Border	Border	Alteration	Alteration	Alteration	Alteration	NE	+	+	+	+	4
Tordjman et al. (2013)	17	Male	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I*	ADIR-R; ADOS	Alteration	Alteration	Alteration	Alteration	Alteration	Alteration	Alteration	Withouth social interaction	Autism	-	+	+	-	2
	19	Male	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2*		Alteration	Alteration	Alteration	Alteration	Alteration	Alteration	Alteration	Withouth social interaction	Autism	-	+	+	-	2
Battista Ferrero et al. (2010)	11	Male	*BAZ1B, STX1A, LIMK1, CLIP2*	WPPSI-R; DTVP	Average	Alteration	NE	NE	Border	Average	NE	NE	ADHD	+	-	±	+	2.5
Serrano-Juarez et al. (2021)	14	Male	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2*	WISC-IV; WAIS-IV; Ekman's Faces; Happe's Strange Stories	Alteration	NE	NE	NE	NE	NE	Social Judgement Average	Average ToM	NE	+	+	+	+	4
Hirota et al. (2003)	28	Female	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2*	WAIS-R; Drawing Copy Task	Alteration	NE	NE	Border	Alteration	Alteration	Alteration	Alteration	NE	+	+	±	+	3.5
	21	Female	*FZD9, BAZ1B, STX1A, LIMK1*		Alteration	NE	NE	Border	Alteration	Alteration	Average	Withouth Hypersociability	NE	+	+	+	+	4
	10	Female	*BAZ1B, STX1A, LIMK1*	WISC-III; Drawing Copy Task	Alteration	NE	NE	Border	Alteration	Alteration	Average	Withouth Hypersociability	NE	+	+	+	+	4
Ghaffari et al. (2018)	7.1	4 M; 6F	*FZD9, BAZ1B, STX1A*	WISC	Border to Alteration	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	0
Serrano-Juarez et al. (2018)	12	2 M:2F	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2*	WISC-IV; WAIS-IV; Neuropsi Attention and Memory; ENI-2; DTVP-3; SENA; ABAS-2	Alteration	Alteration	Alteration	Border	Alteration	Alteration	Alteration	Alteration	Isolation	+	+	+	+	4

Table 3 (continued)

Author (year)	Age	Gender	Missing Gene	Neuropsychological Instruments	FIQ	Attention	Memory	Language	Visuospatial	Praxia & Motor Skills	Executive Functions	Social Cognition	Neuropsychiatry	WSCP Criteria				
														1	2	3	4	Total
Muramatsu et al. (2017)	16–24	5 M:0F	*LIMK1, CLIP2, GTF2IRD1, GTF2I*	Benton's Three-Dimensional Block Construction Test; Copying Figures; Yerke Test	Alteration	NE	NE	NE	Alteration	Alteration	NE	ToM first order Average	NE	+	+	+	+	4
Lugo et al. (2020)	5	Female	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2, HIP1*	Social Responsiveness Scale; WPPSI-IV	NE	NE	NE	Alteration	NE	Alteration	NE	Alteration	Autism	NE	NE	NE	NE	0
	Adolescent	Male	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I*	Social Responsiveness Scale	NE	NE	NE	NE	NE	NE	NE	NE	Autism	NE	NE	NE	NE	0
	Child	Male	*FZD9, BAZ1B, STX1A, LIMK1*	Social Responsiveness Scale; WPPSI-IV	Border	NE	NE	Border	Alteration	Alteration	Alteration	Hypersociability	ADHD, Anxiety, ODD	+	+	+	+	4
	Adult	Female	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I*	WAIS-IV; Social Responsiveness Scale	Border	NE	NE	Border	Alteration	Alteration	Alteration	Hypersociability	NE	+	+	+	+	4
	9	Female	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2, HIP1*	WISC-V; Social Responsiveness Scale	Alteration	NE	NE	Alteration	Alteration	Alteration	Alteration	Autism	Phobia, Anxiety, ADHD, Aggression	NE	NE	NE	NE	0
Edelmann et al. (2007)	6	Female	*GTF2IRD1, GTF2I, GTF2IRD2, HIP1*	WPPSI-III	Alteration	NE	NE	Alteration	Alteration	Alteration	NE	Poor empathy & social cognition	Autism, Aggression	-	+	+	-	2
Honjo et al. (2012)	19	Male	*LIMK1*	WAIS-III; ROCF	Low Average	NE	NE	NE	Alteration	Average	NE	WithoutHypersociability	NE	+	+	+	+	4

Table 3 (continued)

Author (year)	Age	Gender	Missing Gene	Neuropsychological Instruments	FIQ	Attention	Memory	Language	Visuospatial	Praxia & Motor Skills	Executive Functions	Social Cognition	Neuropsychiatry	WSCP Criteria				
														1	2	3	4	Total
Hoeft et al. (2014) & Mills et al. (2013)*	41	Male	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2*	WAIS; BJLO; VMI; Approach Test	Low Average	Average	Average	Average	Average	Average	NE	Hypersociability	NE	+	-	-	+	2
	29	Male	*STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I*		Low Average	NE	NE	Low Average	Low Average	Average	NE	Hypersociability	NE	+	-	-	+	2
	38	Male	*LIMK1*		Low Average	NE	NE	Low Average	Average	Average	NE	Hypersociability	NE	+	-	-	+	2
	12.67 (2.66)	1 M:4F	*LIMK1*		Border	NE	NE	Low Average	Low Average	Average	NE	Hypersociability	NE	+	-	-	+	2
Fusco et al. (2014)	14	Female	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2, HIP1*	WISC III; Leiter International Performance Scale-Revised and Griffiths Scales of Mental Development	Alteration	NE	NE	Border	Alteration	Alteration	NE	Alteration	Autism	±	+	+	±	3
	15	Female	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1*		Alteration	NE	NE	Border	Alteration	NE	NE	NE	Anxiety & obsessive, Autism	±	+	+	+	3.5
	6	Male	*STX1,LIMK1, CLIP2, GTF2I, GTF2IRD1*		Alteration	NE	NE	Border	Alteration	Alteration	NE	NE	NE	±	+	+	+	3.5
	5	Female	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2, GTF2IRD1, GTF2I, GTF2IRD2, HIP1*		Alteration	NE	NE	Border	Alteration	Alteration	NE	Alteration	Aggression, self-harm, stereotypes, hyperactivity & social alterations	-	+	+	±	2.5
Gagliardi et al. (2003)	5	Male	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2*	Stanford Binet Development Scale; VMI; ROCF; Digit and Corsi Span	Average to Low Average	Border	Border	Border	Border	Alteration	Border	Without Hypersociability	NE	+	+	+	-	3
Antonell et al. (2010)	20	Female	*LIMK1, CLIP2, GTF2IRD1*	WAIS III; ROCF; Attention, Memory, and Executive Function Test	Border	NE	NE	Alteration	Average	Average	NE	Hypersociability	Anxiety/ ADHD	+	-	-	±	1.5
	22	Female	*LIMK1, CLIP2, GTF2IRD1*		Border	NE	NE	Alteration	Average	Average	NE	Hypersociability	Anxiety/ ADHD	+	-	-	±	1.5
	30	Female	*STX1A, LIMK1*		Border	Average	Average	Border	Average	Average	Average	Hypersociability	Anxiety	+	-	-	±	1.5

Table 3 (continued)

Author (year)	Age	Gender	Missing Gene	Neuropsychological Instruments	FIQ	Attention	Memory	Language	Visuospatial	Praxia & Motor Skills	Executive Functions	Social Cognition	Neuropsychiatry	WSCP Criteria				
														1	2	3	4	Total
Alesi et al. (2020)	13	Female	*CLIP2, GTF2IRD1, GTF2I, GTF2IRD2*	WISC; Visuospatial and Attention Test	Alteration	Border	NE	Border	Alteration	Alteration	NE	Hypersociability/ Emotional dysregulation	ODD	+	+	+	+	4
	32	Female	*CLIP2, GTF2IRD1, GTF2I, GTF2IRD2*	WAIS; Visuospatial and Attention Test	Alteration	NE	NE	Border	Alteration	Alteration	NE	Hypersociability/ Emotional dysregulation	NE	+	+	+	+	4
	12	Female	*GF2IRD1, GTF2I, GTF2IRD2*	Attention, Emotion and Visuomotor Test	Alteration	Border	NE	Border	Alteration	Alteration	NE	Hypersociability/ Emotional dysregulation	Autism/ Anxiety/ OCD traits	+	+	+	+	4
van Hagen et al. (2006)	16	Male	*FZD9, BAZ1B, STX1A, LIMK1, CLIP2*	WISC; PPVT; Boston Naming Test; RCPM; BJLO; Trail Making Test	Low Average	Border	Alteration	Border	Alteration	Alteration	NE	NE	NE	+	-	+	+	3
Ng et al. (2020)	17.04 (2.03)	1 M: 3 M	*LIMK1*	WISC IV; EQ-SQ	Low Average	NE	NE	NE	NE	NE	NE	Empathy Average	NE	+	-	-	-	1

Not mentioned (NM), Not explored (NE), British Ability Scale-II School Age (BAS-II), Raven's Coloured Progressive Matrices (RCPM), Kaufman Brief Intelligence Test (K-BIT), Peabody Picture Vocabulary Test-Revised (PPVT-R), Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III), Woodcock-Johnson Test of Cognitive Ability-Revised (WJ-R COG), Differential Ability Scale (DAS); Benton Judgment of Line Orientation (BJLO), Autism Diagnostic Interview-Revised (ADI-R); Autism Diagnostic Observation Schedule (ADOS); Wechsler Preeschool and Primary Scale Intelligence (WPPSI-R); Development Test of Visual Perception (DTVP); Wechsler Adult Intelligence Scale-Revised (WAIS-R); Wechsler Intelligence Scale for Children 3rd Edition (WISC-III); Wechsler Intelligence Scale for Children (WISC-IV); Wechsler Adult Intelligence Scale (WAIS-IV); Child Neuropsychological Assessment (ENI-2); Development Test of Visual Perception (DTVP-3); Asssessment System for Children and Adolescents (SENA); Adaptive Behavior Assessment System (ABAS-2); Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV); Wechsler Adult Scale of Intelligence 4th Edition (WAIS-IV); Wechsler Intelligence Scale for Children 5th Edition (WISC-V); Wechsler Preeschool and Primary Scale Intelligence 3rd Edition (WPPSI-III); Wechsler Adult Scale of Intelligence (WAIS-III); Rey-Osterreith Complex Figure Test (ROCF); Beery Visuo-Motor Integration (VMI); Theory of Mind (ToM); Empathy Quotient and Systemizing Quotient (EQ-SQ); attention deficit hyperactivity disorder (ADHD); obsessive compulsive disorder (OCD); oppositional defiant disorder (ODD); preserved (+); deleted (-); partially preserved (±); Williams syndrome cognitive profile (WSCP); full intellectual quotient (FIQ); same clinic

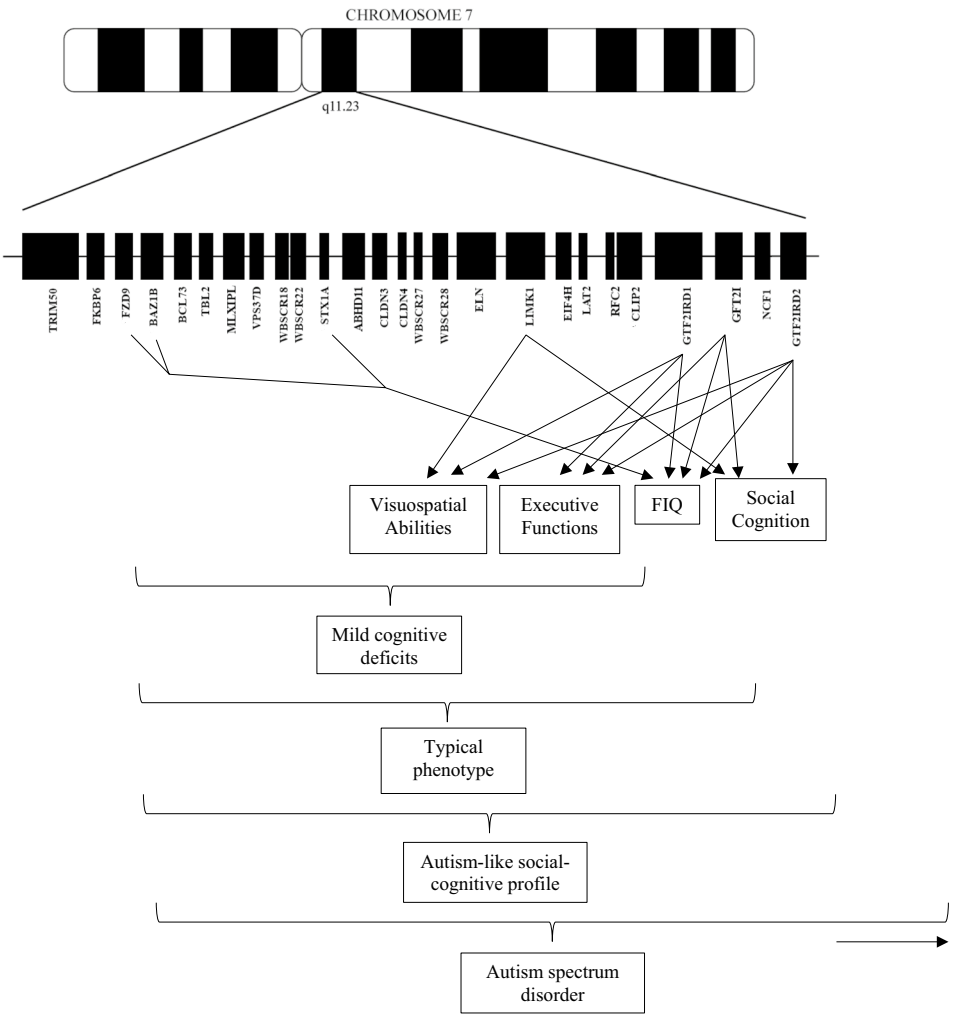


Fig. 2 Relationship between genotypes and neuropsychological phenotypes of Williams syndrome. This figure shows the missing genes for each of the neuropsychological phenotypes

(22 cases, 28%). The instruments most used in the studies were Wechsler intelligence scales (21 of 23 articles, 91%), followed by the Rey-Osterreith Complex Figure Test (ROCF; 3 articles, 13%), the Beery Visuo-Motor Integration Test (VMI; 3 articles, 13%), and the Differential Ability Scale (DAS; 2 articles, 9%). There was thus a high degree of variability in the instruments used to assess the processes of the neuropsychological phenotype. The psychiatric disorders most reported were anxiety (11%), autism spectrum disorder traits (10%), and ADHD (10%). Half of the articles provided a description of social skills or social cognition domains, however, many of these articles mentioned only the presence or absence of hypersociability, and only four examined aspects of social cognition.

Cognitive-behavioral alterations related to gene loss. No case was found missing the *FZD9, BAZ1B,* and *STX1A* genes in isolation. However, 10 cases missing these three genes were identified that showed borderline to mildly affected intellectual ability where it was not possible to determine whether they met the WSCP criteria. In the cases that presented a deletion from *FZD9* to *LIMK1*, 66% presented hypersocial behavior, 100% reported alterations in visuospatial abilities and visuoconstructive praxis, none presented intellectual disability or alterations in attention and memory, and 80% met the WSCP criteria. In those that presented isolated loss of *LIMK1*, no alterations in intellectual capacity, attention, language, memory, or executive functions were reported. However, 14% presented alterations in visuospatial abilities, 100% presented hypersociability, and 13% met WSCP criteria. Of the patients missing *FZD9* to *CLIP2*, 13% met WSCP criteria, 25% had alterations in intellectual capacity, visuospatial ability, visuoconstructive praxis, and hypersociability, while those missing only *CLIP2* presented no alterations and did not meet the WSCP criteria. In the cases with loss of *GTF2IRD1*, 25% presented intellectual deficits, 13% met WSCP criteria, and 25% presented alterations in visuospatial ability, visuoconstructive praxis, and hypersociability. Of the patients missing *GTF2I*, 66% had

impaired intellectual capacity, 77% impaired visuospatial ability and visuoconstructive praxis, 88% hypersociability, and 67% met WSCP criteria. Of those missing *GTF2IRD2*, 95% presented impaired intellectual capacity, attention, language, visuospatial ability, praxis, and executive functions, 84% met WSCP criteria but with a predominance of autistic traits and significant alterations in social cognition. Finally, of the patients missing *HIP1*, 100% had intellectual disability and significant alterations in attention, memory, language, visuospatial ability, and visuoconstructive praxis, while 83% had autism spectrum disorder and only 16% met the WSCP criteria.

Discussion

The objective of this systematic review was to analyze and synthesize the variability of the cognitive and behavioral profile of WS patients with atypical deletions and the relationship with the affected genes.

Most patients presented mild to moderate intellectual disability, superior verbal development with severe visuospatial alterations, and hypersociability, the profile of patients with WS as reported by Nikitina et al. (2014).

Categorization of the findings was complicated by the different instruments used and the variability of the deletions. Analysis and synthesis of the findings of the atypical deletion case reports can be summarized in four different neuropsychological phenotypes by considering the missing genes that have the greatest effect on cognitive and behavioral alterations. Although a small group of patients shared the same missing genes, their cognitive and behavioral profile was not identical, which may be the result of different environmental influences (Boyce et al., 2020; Plomin, 1989).

The results revealed a relationship between the number of affected genes and the neuropsychological profile. Specifically, greater cognitive impairment was found when the deletion encompassed genes located towards the telomere, such as those of the *GTF2I* gene family (*GTF2IRD1* and *GTF2IRD2*). It was also found that the *FZD9*, *BAZ1B*, and *STX1A* genes influence intellectual capacity without causing intellectual disability or meeting the WSCP criteria. *LIMK1* appears to influence visuospatial ability and hypersociability and met WSCP criteria. *GTF2IRD1* and *GTF2I* appear to contribute to intellectual disability and executive dysfunction, causing the typical neuropsychological phenotype and meeting the WSCP criteria. Loss of *GTF2IRD2* influences intellectual ability, major neuropsychological alterations, and autism-like social-cognitive phenotype, and loss of *HIP1* is associated with the prevalence of autism spectrum disorder (Crespi & Hurd, 2014). Figure 2 summarizes the four neuropsychological phenotypes according to genotype, which include a mild cognitive deficit without intellectual disability spans genes from *FKBP6* to *CLIP2*, the typical phenotype spans *FKBP6* to *GTF2I*, an autism-like social phenotype spans *FKBP6* to *GTF2IRD2*, and an autism spectrum disorder phenotype spans *FKBP6* to the telomere genes. Figure 2 also highlights the genes with a major involvement in FIQ, visuospatial abilities, executive function, and social cognition. These results are not confirmation of the relationship of these neuropsychological phenotypes to the genotypes. Additional studies are necessary for verification. However, the results do demonstrate a prevalence of certain cognitive-behavioral profiles in the presence of specific deletions. In the following section, we describe how the genes could influence these phenotypes through neurobiological mechanisms that have been reported in other studies.

Neuropsychological Genotype and Phenotype Relationship

Every individual is the result of a genotype (Lisker et al., 2013). From the first moments of development, living beings are the product of a series of chemical and metabolic processes chronologically and spatially regulated by genes. These sequences of processes are carried out through the activation and inactivation of genes and proteins that influence the formation of organs and systems that can in turn be modified by the environment (Boyce et al., 2020; Lezcano, 2001; Plomin, 1989).

Of all the reported cases in our review, 77% referred to a loss of the *LIMK1* gene, which is relevant to the cognitive and clinical profiles of patients with WS. Only 9% of the cases presented a single deletion of this gene, with a cognitive profile characterized by average intellectual capacity and adequate attention, memory, language, and executive function skills. There were partial alterations in both visuospatial ability and visuoconstructive abilities. All of these cases presented hypersociability and only one met the WSCP criteria.

Another 7% of cases were found to have a deletion of other genes from the centromere to *LIMK1*. These cases presented low average intellectual capacity, adequate attention and executive functions, but also visuospatial and visuoconstructive alterations, hypersociability, and anxiety traits, and a high percentage met the WSCP criteria. There is a high probability that the loss of the *LIMK1* gene affects visuospatial abilities, but that with the deletion of other genes towards the centromere there is a greater effect on other processes. This gene, widely expressed in the cerebral cortex, is involved in the regulation of axonal generation (Gray et al., 2006) through a protein kinase that is found mainly in parietal and frontal areas, in the cerebellum, and in the fifth cranial nerve (Frangiskakis et al., 1996). The deletion of *LIMK1* is associated with alterations of visuomotor integration, visuospatial construction,

and global cognitive deficit (Del Campo Casanelles & Pérez Jurado, 2010). It has also been found to be associated with structural and connectivity alterations of the intraparietal sulcus, which is related to visuospatial, arithmetic, and social skills (Gregory et al., 2019). In animal models, visuospatial alterations are expressed only when both copies of the gene are missing (Osborne, 2010). In experimental mice with a single copy (a model that simulates WS in humans), these alterations are not evident. It is thus believed that the alteration of other genes is necessary for the cognitive alterations associated with the *LIMK1* gene to manifest themselves (Li et al., 2009; Osborne, 2010). Most of the cases in which *LIMK1* is affected are characterized by a profile without intellectual disability (average FIQ) and without hypersociability, but with visuospatial alterations (Frangiskakis et al., 1996; Hoeft et al., 2014; Honjo et al., 2012; Tassabehji et al., 1999). These patients meet criteria one and four of Mervis et al. (2000), but only partially meet criteria two and three, because their visuospatial scores are lower than the mean but not below the 20th percentile. Therefore, it seems that this gene has greater involvement in visuospatial alterations, but not in intellectual and social capacities.

The deletion of the genes belonging to the *GTF2I* family (*GTF2IRD1*, *GTF2I*, and *GTF2IRD2*) was found in 52% of the cases. These genes code for the BEN and TFII-I proteins (Li et al., 2015). In mice, their haploinsufficiency has multiple manifestations, including embryonic death, cerebral hemorrhage, and neural tube defects (Enkhmandakh et al., 2009). Differences in the neuropsychological phenotype were identified as a function of the number of genes deleted from this family. In 10% of these cases, deletions were reported up to the *GTF2IRD1* gene and were characterized by borderline to low average intellectual capacity, and partial alterations in attention, language, visuospatial skills, visuoconstructive abilities, and social cognition. Half of the cases presented anxiety traits, three had ADHD, and all had hypersociability. Only one of the cases met the four criteria proposed by Mervis et al. (2000). The other cases fulfilled the criterion of better developed linguistic abilities, although they presented visuospatial alterations below the mean but not the 20th percentile. Of those with deletions up to *GTF2I*, 11% presented intellectual capacity in the low to limited range, and alterations in attention, memory, visuospatial ability, visuoconstructive praxis, and social cognition. Two reported autistic characteristics, and 66% of them met all the WSCP criteria. Crespi and Hurd (2014) report that the *GTF2I* gene has implications for the autistic characteristics of people with WS. In addition to contributing to cognitive deficits in general, *GTF2I* could be involved in social approach and hypersociability behaviors.

Within this same gene family, Palmer et al. (2012) found that the *GTF2IRD2* gene regulates the activity of the *GTF2IRD1* gene and TFII-I proteins. Of the cases reviewed, 23% had a deletion up to *GTF2IRD2*, showing low intellectual capacity and alterations in attention, memory, visuospatial ability, visuoconstructive praxis, executive functions, and social cognition, with two presenting autism and obsessive traits. No cases of hypersociability were reported, but four presented data showing social isolation (Serrano-Juárez et al., 2018). Both the *GTF2I* and the *GTF2IRD1* genes are expressed in the dorsolateral prefrontal cortex, as well as in the cerebellum, hippocampus (Chailangkarn et al., 2018; Frangiskakis et al., 1996; Hoeft et al., 2014; Morris et al., 2003), and intraparietal sulcus (Hoeft et al., 2014), and their deletion has been linked to problems with identifying emotions such as fear and aggression (Young et al., 2008), as well as alterations in visuomotor integration and visuospatial processing (Hirota et al., 2003; Hoeft et al., 2014; Mills et al., 2013), intellectual disability (Morris et al., 2003), and hypersociability (Chailangkarn et al., 2018; Young et al., 2008). Patients with deletions up to *GTF2IRD1* (Antonell et al., 2009; Fusco et al., 2014; Morris et al., 2003) presented a less severe profile. Only two of eight patients in these studies presented low FIQ, and most did not meet the WSCP criteria. *GTF2I* is among the genes that are lost in 1.5 Mb deletions. Patients missing this gene presented greater intellectual alterations when there was also loss of genes towards the telomere (Antonell et al., 2009; Fusco et al., 2014; Morris et al., 2003). This gene is likely involved in intellectual abilities, executive functions, and visuospatial ability (Muramatsu et al., 2017).

Deletion of *GTF2I* is probably also important to the WSCP criteria, since a high percentage of such cases met all four, however, the interaction with other genes would influence the severity of the neuropsychological profile. The 84% of patients with deletions that included *GTF2IRD2* met all the criteria (Alesi et al., 2021; Edelmann et al., 2007; Fusco et al., 2014; Lugo et al., 2020; Porter et al., 2012; Serrano-Juárez et al., 2018, 2021; Tordjman et al., 2013), while the remaining 16% presented severe verbal, visuospatial, and social deficiencies (Karmiloff-Smith et al., 2012; Serrano-Juárez et al., 2021). Broadbent et al. (2014), Porter et al. (2012), and Serrano-Juárez et al., (2018, 2021) reported greater alterations in visuospatial skills, social cognition, and social behaviors characteristic of autism in patients missing *GTF2IRD2*. Of the cases with deletion of this gene, 54% had characteristics compatible with autism spectrum disorder, such as isolation behaviors and difficulties in social interaction, so it could be related to alterations in social behavior and greater effects on the cognitive function profile of this syndrome. In six cases, deletion of the genes of the *GTF2I* family was reported, together with loss of *HIP1*, as associated with characteristics of low intellectual capacity and alterations in attention, language, visuospatial ability, visuoconstructive abilities, and social cognition.

All six cases presented obsessive and aggressive traits and four presented characteristics of autism. Only one patient met the WSCP criteria, as the others had severe language impairment.

A deletion up to the *CLIP2* gene was reported in 13% of the patients, who presented intellectual capacity in the limit to average range, and partial alteration of attention, memory, visuospatial ability, executive functions, and social cognition. Half of these patients presented hypersociability, and only two cases met the criteria of the WSCP. The *CLIP2* gene may be involved in global growth retardation, abnormal hippocampal function, and impaired learning (Honjo et al., 2012). Studies of animal models have reported that when there is only one copy of this gene, growth and behavioral problems occur, and structural alterations are seen in the posterior fibers of the cortex (Osborne, 2010; Vandeweyer et al., 2012). Honjo et al. (2012) reports the case of a 19-year-old patient with a deletion that affected the *ELN*, *LIMK1*, and a portion of the *CLIP2* genes. This patient had a low normal FIQ score and severe visuospatial alterations. Vandeweyer et al. (2012) reported the case of two brothers with the unique loss of *CLIP2* who did not present the characteristic cognitive profile of WS and had an average FIQ and adequate verbal and visuospatial skills, which could indicate that the unique haploinsufficiency of *CLIP2* is not enough to generate the clinical manifestations of WS, and that it would have to interact with the loss of other genes for the characteristic cognitive profile of WS to appear.

None of the cases evaluated presented unique deletions of the *FZD9*, *BAZ1B*, or *STX1A* genes. Four patients were found with a loss of *FZD9*, *BAZ1B*, *STX1A*, and *LIMK1*. Their phenotype was characterized by borderline to average intellectual capacity, adequate attention, memory, and language, partial alterations in executive functions, and alterations in visuospatial and visuoconstructive abilities, and 75% met the WSCP criteria. One patient had a deletion of the *BAZ1B*, *STX1A*, and *LIMK1* genes, resulting in a phenotype with low intellectual capacity, alterations in visuospatial abilities and visuoconstructive abilities, and met the WSCP criteria. Another, identified with deletion of the *STX1A* and *LIMK1* genes (Antonell et al., 2009), showed borderline intellectual capacity, attention, memory, language, visuospatial ability, and visuoconstructive abilities, but also showed adequate executive functions and did not meet the WSCP criteria. The *FZD9*, *BAZ1B*, and *STX1A* genes are located towards the centromere and appear to influence the cognitive profile only when there is a deletion of other genes that are located towards the telomere. In mice, Zhao et al. (2005) blocked the *FZD9* gene and found structural alterations in the hippocampus and alterations in apoptosis. Chailangkarn et al. (2016) found that blocking of this gene is accompanied by apoptosis of neural progenitor cells. This alteration is also accompanied by atypical cell death, mainly in the dentate gyrus of the hippocampus, affecting visuospatial memory (Zhao et al., 2005). The *BAZ1B* gene has been associated with the nucleus accumbens, which influences the reward circuit and inhibitory control (Lalli et al., 2016; Sun et al., 2016). The *STX1A* gene has been related to intellectual capacity and explains 15% of the variation in people with WS (Gao et al., 2010). However, Botta et al. (1999) have reported two cases in which the exclusive loss of this gene was not enough to explain the characteristic cognitive profile.

In summary, our systematic review found that the genes that most influence the neuropsychological phenotype of WS are *LIMK1* and the *GTF2I* gene family. *LIMK1* is related to visuospatial skills but its haploinsufficiency is not enough to present intellectual disability, while *GTF2I* could influence intellectual capacity, executive functions, and social behaviors. The *FZD9*, *BAZ1B*, *STX1A*, and *CLIP2* genes require the haploinsufficiency of other genes to influence the cognitive profile of WS. Our systematic review thus detected an important variation in the cognitive profile of WS that could be associated with the genes affected in the deletion size.

Future Directions

Our review found that the processes most affected in WS are visuospatial as well as FIQ, however, social skills are also affected in these patients depending on the genes involved. When the deletion involves a greater number of genes towards the telomere, such as *GTF2IRD2* and *HIP1*, characteristics of autism appear instead of the commonly reported hypersociability. When the genes of the *GTF2I* family are preserved, patients show better performance in tasks associated with the domains of social cognition. Järvinen et al. (2013) report a social profile for patients with typical deletions characterized by alterations in various domains of social cognition, including social judgment, emotional processing, theory of mind, disinhibition, and approach to strangers. This profile has been associated with alterations of the amygdala, fusiform gyrus, and orbitofrontal and parietal cortices. Alterations in social cognition also affect the quality of life of the patient, so we believe it is important that this area be explored in study of the cognitive profile of WS. Studies are also needed that examine other atypical deletion case reports, case series, and group studies to confirm the relationship of neuropsychological phenotypes with genotypes. These studies should use neuropsychological instruments to assess visuospatial abilities, language, memory, executive functions, and social cognition.

Towards a Model for the Clinical and Applied Study of WS

One way to explain the relationship between genes and behavior is through different neurodevelopmental disorders that have their etiology in genetic alterations. Taking into account the findings in WS genotypes and the models proposed by Morton and Frith (1995) and Bishop and Snowling (2004), we propose a model to help with clinical follow-up and neuropsychological research on patients with WS (Fig. 3). At the first level are the generalist genes that have been studied in WS, both in animal and human models, that could affect the morphological and physiological neuronal processes of different brain areas through pleiotropy. The second level includes the brain areas where structural and physiological alterations have been found in WS (Jackowski et al., 2009; Martens et al., 2008; Sampaio et al., 2013). At this level, recent reports of neural networks that could be involved in different cognitive processes must be considered. The third level includes the cognitive processes commonly altered in the WS phenotype, which are associated with the cortical structures of the second level (Jackowski et al., 2009). On a fourth level, behaviors affected by cognitive damage are indicated. Finally, the environment in which the patient develops must also be considered, since education, culture, educational level of parents, stimulation, and other variables influence neuroplasticity and the cognitive profile of these patients (Bishop, 2009; Johnston & Edwards, 2002; Kaminski et al., 2018). These variables are marked in Fig. 3 to indicate environmental feedback, where the genotype, phenotype, and environment all interact to produce the cognitive and behavioral profile.

Limitations

Our systematic review allowed us to establish a relationship between specific genes and the neuropsychological phenotype of patients with WS. However, the small number of studies, as well as the variability of neuropsychological instruments and cognitive processes studied, makes it difficult to generalize the specific influence of genes on cognition and behavior. The use of a percentile scale could help to facilitate the comparison of studies independent of the neuropsychological tests involved. The low prevalence of WS makes it difficult to compile a uniform study group. Our

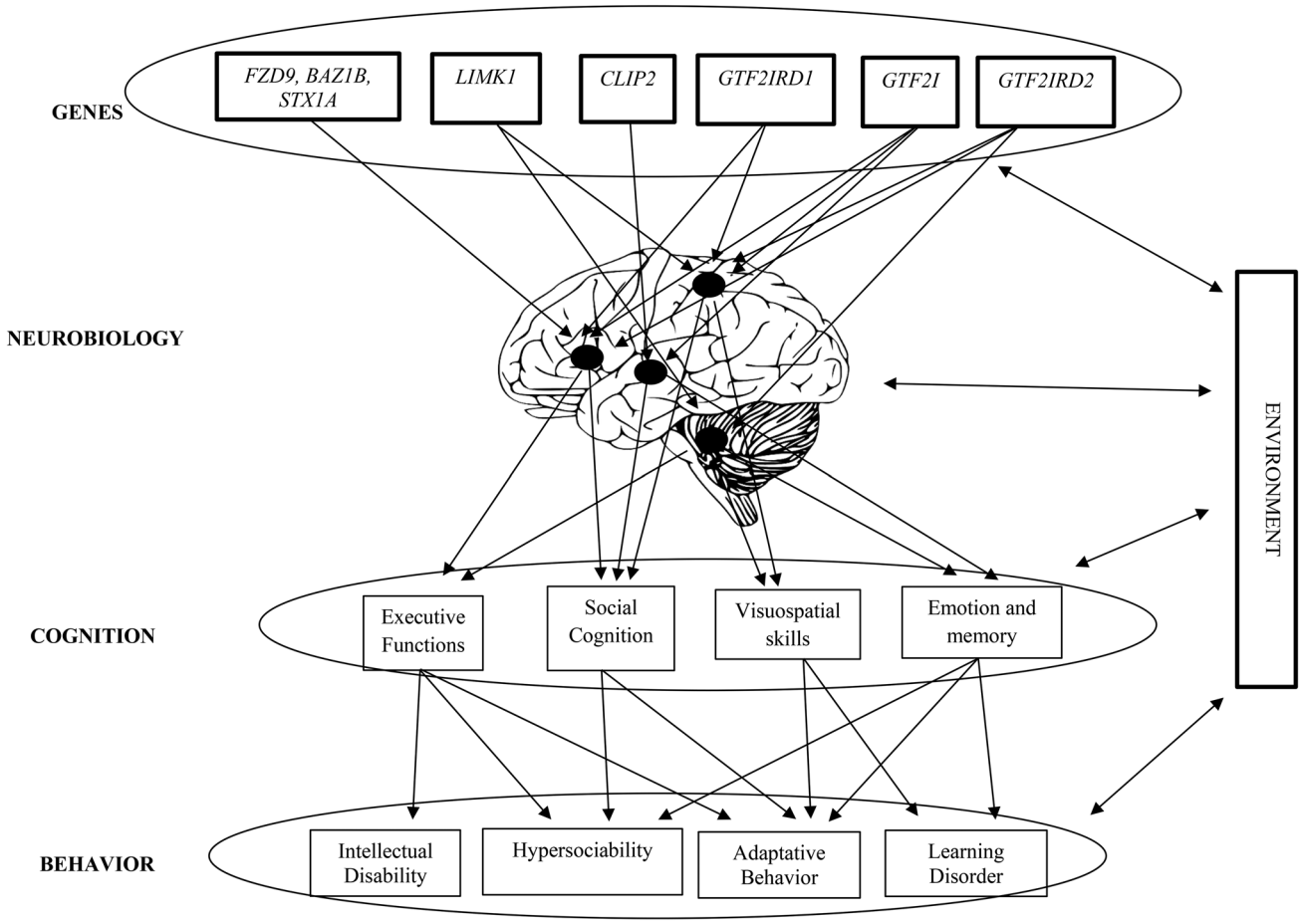


Fig. 3 Model for the clinical approach and investigation of the relationship between genotypes and neuropsychological phenotype of WS

search found patients with similar deletions, but in but different countries and evaluated with different neuropsychological tests, which makes it difficult to generalize the findings.

Another limitation is that few studies evaluate social cognition in WS. To our knowledge, there are not many instruments which evaluate these processes that are standardized for different populations.

Conclusions

Our study is the first systematic review of the neuropsychological genotype and phenotype relationship in Williams syndrome (WS) atypical deletions that considers both cognitive and behavioral variables. Genetic alterations in WS occur with the deletion of 24 to 26 genes, which causes various alterations in the cerebral cortex and results in a neuropsychological phenotype that depends on the genes affected. This information is important to improving the quality of life of patients with WS.

Neuropsychological assessment is important for the diagnosis of genetic diseases. However, in developing countries, access to genetic tests for the confirmation of chromosomal pathologies is usually costly. The establishment of phenotypes associated with certain genotypes would be of major importance to neuropsychological evaluation and could provide an idea of the size of the deletion. Cognitive-behavioral follow-up and neuropsychological intervention would also have to consider the genotype. Although improvement is possible regardless of the size of the deletion, it is also variable (Domínguez-García et al., 2022). Improved knowledge regarding different neuropsychological phenotypes could also allow for better diagnosis of neurodevelopmental disorders, avoiding inaccurate assessments of ASD in WS.

Research on the cognitive and behavioral processes in patients with WS with different degrees of deletion allows us to better interpret how genes influence neuropsychological variables. More studies are needed to improve our understanding of the gene-brain-cognition-behavior relationship. The model proposed here relies on a comprehensive understanding of these patients, considering both the genotype and the environment in which the individual develops, since both factors influence the cognitive-behavioral phenotype.

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