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ORIGINAL PAPER

An Exploration of Social Cognition in Children with Different Degrees of Genetic Deletion in Williams Syndrome

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Abstract

An explanation for the social dysfunction observed in Williams syndrome may be deficits in social cognition. This study explored aspects of social cognition in children with Williams syndrome with different genotypes. The 12 participants included one with a 1.1 Mb deletion that retained the *GTF2IRD1*, *GTF2I*, and *GTF2IRD2* genes, seven with a 1.5 Mb deletion that preserved the *GTF2IRD2* gene, and four with a 1.8 Mb deletion with loss of all three genes. The participant retaining all three genes was found to have better performance on social judgment and first-order theory of mind tasks than the group with loss of all three genes. These results may reflect the influence of the *GTF2I* gene family on social cognition in Williams syndrome.

Keywords Williams syndrome · Social cognition · Genotypes · *GTF2I* family · Social phenotype · *GTF2IRD2*

Introduction

Williams syndrome (WS) is a rare genetic disorder with an incidence of one in 7000 live births (Martens et al. 2008; Pober 2010). According to Borg et al. (1995), Porter and Coltheart (2005), and Porter et al. (2008), WS is a heterogeneous disorder in both its phenotypic (physical, cognitive, behavioral, and social) and genotypic characteristics.

Taking into account the genotype, the most common deletion, in about 90% of cases, is ~ 1.5 Mb, followed by ~ 1.8 Mb in about 8% and atypical deletions in the remaining 2% (Ramírez-Velasco and Domínguez-Quezada 2017). The classic cognitive-behavioral phenotype of WS is characterized by mild to moderate intellectual disability (Bellugi et al. 1999; Mervis and Morris 2007; Meyer-Linderberg et al. 2006), severe visuospatial alterations, and an uninhibited social attitude, also called hypersociability (Järvinen et al. 2015), that contributes to social dysfunction. This social dysfunction can be related to alterations in social cognition (van der Fluit et al. 2012).

Social cognition can be defined as a neurobiological, psychological, and social process through which social events are perceived, recognized, and evaluated, which then generates the most appropriate behavior according to the particular circumstance (Adolphs 2001). It is a psychological process that allows for the interpretation of social signs to respond appropriately to the context (Quinn et al. 2006). Adolphs (2009) reports that the main domains of social cognition are the identification of facial emotions, judgment and social reasoning, empathy, theory of mind, and decision making. The domains of social cognition involve various cortical and subcortical structures, including the amygdala, the ventromedial and orbitofrontal prefrontal cortex, the

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insula, and the right somatosensory cortex (Adolphs 2009; Butman 2001).

The social brain hypothesis is based on a neurobiological approach to understanding the social alterations in clinical phenomena like autism and seeks to explain the brain functioning related to the ability to interact socially with peers of the same species (Adolphs 2009). Various studies have assessed the alterations in social cognition of people with WS (Karmiloff-Smith et al. 2012; Porter et al. 2008, 2012; Pavlova et al. 2016) in the domains of emotion recognition (Campos et al. 2014; Gagliardi et al. 2003; Plesa Skwerer et al. 2006) and theory of mind (Campos et al. 2014). Theory of mind is a metacognitive and socio-emotional process that allows people to recognize the intentions, beliefs and emotions of others, as well as their own, allowing for effective human interaction. Tests that include understanding metaphors, jokes, ironies, gaffes, or false beliefs can be used to evaluate theory of mind. There are false beliefs of the first order and second order. First-order false beliefs are related to the intentional attitudes of other people; second-order false beliefs refer to the ability to attribute false beliefs to others (Zegarra-Valdivia and Chino-Vilca 2017). The main theory of mind deficiencies found in people with WS are related to the interpretation of jokes, ironies, or figurative language (Järvinen-Pasley et al. 2008; Karmiloff-Smith et al. 1995; Tager-Flusberg and Baron-Cohen 1998), as well as tasks involving second-order false beliefs (Porter, Coltheart and Langdon 2008). Studies have reported that people with WS have a lesser capacity to recognize fear and sadness on faces than those with typical development, but a greater ability to recognize expressions of happiness and anger than people with Down syndrome of similar mental age (Campos et al. 2014; Järvinen et al. 2015).

Different genes have been identified that influence the social behavior characteristics of people with WS. In a systematic review, Järvinen, Korenberg and Bellugi (2013) report a social profile for people with typical deletions (1.5 Mb) that is characterized by alterations in social judgment, emotional processing, theory of mind, disinhibition, and approach to strangers, and is related to neuroanatomical and neurohistological alterations in the amygdala, fusiform gyrus, and orbitofrontal and parietal cortices. These cortical areas have been associated with the social cognition domains of emotional processing, social judgment, theory of mind, and empathy (Adolphs 2001, 2009), and the *GTF2I* and *GTF2IRD1* genes could be involved in these social traits (Järvinen et al. 2013).

In a review of the functions of the *GTF2I* gene family, Chailangkarn et al. (2018) describe its association with various neuronal metabolic and physiological processes, its high density of expression in the dorsolateral prefrontal cortex, and its association with the activity of the amygdala. Hoef et al. (2014) found that people with WS with *GTF2I* and *GTF2IRD1* (1.5 Mb) deletions have a larger bilateral amygdala volume, while those who preserve these genes have a right amygdala of similar size as those with typical development. *GTF2IRD2* and *GTF2IRD1* belong to the *GTF2I* gene family (Chailangkarn et al. 2018). The *GTF2IRD1* and *GTF2I* genes have been associated with reduced response to stimuli that cause fear (Hoeft et al. 2014; Chailangkarn, Noree and Muotri 2018; Malenfant et al. 2012), and the *GTF2IRD2* gene has a regulatory effect on them (Makeyev et al. 2004; Palmer et al. 2012; Tipney et al. 2004). These genes may also influence the structural and histological neurodevelopment of areas involved in social cognition, such as the right orbitofrontal and parietal cortices (Hoeft et al. 2014; Atlas 2010; Chailangkarn et al. 2018; Makeyev et al. 2004; Palmer et al. 2012; Porter et al. 2012; Uhlén et al. 2015) and amygdala bilateral volume (Hoeft et al. 2014). The *GTF2IDR1* gene has been associated with executive functions of people with WS (Dai et al. 2008), while those in whom the *GTF2I* gene is lost are characterized by reduced social communication and low anxiety (Crespi and Hurd 2014).

Case studies have described some patients without deletions of the *GTF2I* gene family. Hirota et al. (2003) described the behavioral phenotype of a 21-year-old woman with a deletion of *FKBP6* to *CLIP2*, who showed better performance in social judgment. Ferrero et al. (2010) evaluated the case of an 11-year-old boy with a deletion of *BAZ1B* to *CLIP2* without hypersociability characteristics. Karmiloff-Smith et al. (2012) described an 11-year-old patient with a deletion of *FKBP6* to *CLIP2* who did not have many deficiencies in ToM tasks. These cases do not present commonly reported alterations in social cognition in people with WS, so it may be the deletion of the genes of the *GTF2I* family that are involved in the alterations in social cognition. However, it has been reported that patients who lose only some of the genes in this family exhibit heterogeneous social behavior. For example, Dai et al. (2008) described a 7-year-old girl with a deletion of *FKBP6* to *GTF2IRD1* who presented decreased eye contact with strangers and did not have the characteristic social phenotype of WS, and Antonell et al. (2010) reported two people with partial deletions of *GTF2I*, without hypersociability.

The loss of *GTF2IRD2* seems to be related to greater deficiencies in social cognition. Karmiloff-Smith et al. (2012) reported a 14-year-old boy with a deletion from *GTF2I* to *GTF2IRD2* who showed major social cognition deficiencies and autistic mannerisms. Porter et al. (2012) found that people with WS missing the *GTF2IRD2* gene, with a 1.8 Mb deletion, present greater failures in tasks related to theory of mind, and more isolation behaviors. Similar results were found by Serrano-Juárez et al. (2018), who also noted that those with a 1.8 Mb deletion have lesser abilities both in emotional intelligence and adaptive social and

leisure behavior. These findings suggest that the loss of the *GTF2IRD2* gene could be generating a greater alteration of social cognition, and that the genes of the *GTF2I* family influence social behavior to different degrees.

A neuropsychological phenotype has been reported for people with WS that is characterized by better verbal than visuospatial skills and hypersociability (Miezah et al. 2020). Social cognitive failure has also been reported (Fisher and Morin 2017), which could vary according to the deletion of genes (Bellugi et al. 2007; Karmiloff-Smith et al. 2012; Hirota et al. 2003; Dai et al. 2008; Porter et al. 2012). The deficiencies in social cognition seem to be heterogeneous: it appears that genes of the *GTF2I* family may be involved, through their influence on cerebral structures and cognitive processes related to social cognition. The objective of the present study was thus to explore the relationship between genes and social cognition in children with different WS genotypes (1.1 Mb, 1.5 Mb, and 1.8 Mb), to assess whether these are related to possible differences in performance in social cognition tests, with the social brain hypothesis as theoretical framework. Specifically, we analyzed how the genes of the *GTF2I* family influence the tasks of social judgment, theory of mind, and identification of facial emotions. Our hypothesis was that people with WS with deletions of 1.1 Mb, 1.5 Mb, and 1.8 Mb would have differences in social phenotype related to the deletion or preservation of the *GTF2I* gene family, specifically, that those lacking all three genes (*GTF2IR1*, *GTF2I*, and *GTF2IRD2*) would have more alterations than those who conserved them all in tasks of social judgment, theory of mind, and recognition of emotions on faces.

Method

Participants

The sample was composed of 12 Mexican children with Williams syndrome, recruited from two associations for people with the syndrome. Participants had a mean age of 11.73 years (SD ± 3.75 years). Figure 1 shows their deletion sizes, evaluated with chromosomal microarray analysis (CMA): (a) 1.1 Mb ($n = 1$, 14-year-old boy), encompassing the gene *FKBP6* to *CLIP2* and retaining the genes *GTF2IRD1*, *GTF2I*, and *GTF2IRD2*; (b) 1.5 Mb ($n = 7$; $M = 11 \pm 3.55$ years old), encompassing *FKBP6* to *GTF2I* and missing *GTF2IRD1* and *GTF2I*; and (c) 1.8 Mb ($n = 4$; $M = 12 \pm 4.96$ years old), encompassing *FKBP6* to *GTF2IRD2* and missing *GTF2IRD1*, *GTF2I*, and *GTF2IRD2*.

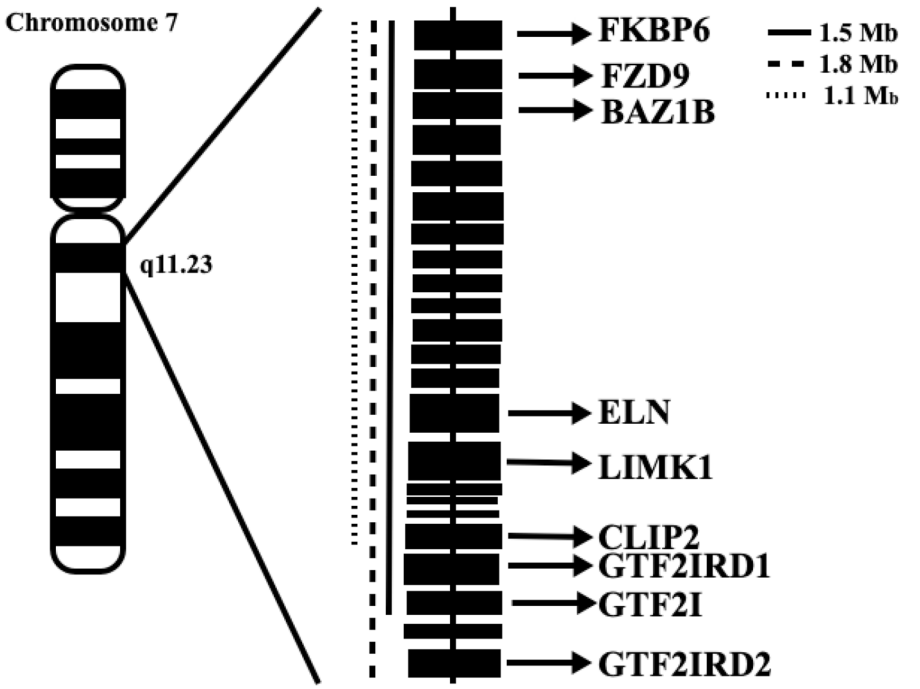

Fig. 1 Scheme of genotypes found in people with WS

Genotype	*GTF2IRD1*	*GTF2I*	*GTF2IRD2*
1.1Mb	+	+	+
1.5Mb	-	-	+
1.8Mb	-	-	-

Note: + = preserved; – = losses

In order to assure that social cognition deficits were not due to intellectual disabilities, participants were matched by gender and full intellectual quotient (FIQ) with a control group of seven Mexican children with Down syndrome (DS) ($M = 12.57 \pm 4.19$ years old). People with DS and WS have similar social approach features, personality traits, and kind, empathic behavior. They have similarities in vocabulary and comprehension, but both have difficulty with pragmatic language (Levy and Eilam 2013). Another control group of seven Mexican children with typical development (TD) ($M = 11.14 \pm 3.67$ years old), matched by chronological age and gender, was used to compare the results of the theory of mind and identification of facial emotion tasks, which do not have Mexican norms.

Table 1 shows the differences in the demographic variables between the participant with the 1.1 Mb deletion and the other groups, and between the groups with 1.5 Mb and 1.8 Mb deletions and the control groups. A Kruskal–Wallis *H* analysis was used to compare demographic variables (chronological age, mental age, years of education, and FIQ). Significant differences were found in the FIQ score and mental age; Dunn's procedure with Bonferroni post-hoc analysis revealed that the group with TD had a higher FIQ score ($M = 108$) and a higher mental age ($M = 11.85$) than the groups with deletions of 1.5 Mb (FIQ $M = 50$; mental age $M = 5.57$) and 1.8 Mb (FIQ $M = 55.25$; mental age $M = 6.75$), and the group with DS (FIQ $M = 45.14$; mental age $M = 5.71$). All of the raw scores for each participant are included in the Supplementary Material.

To compare the demographic variables of the single participant with the 1.1 Mb deletion with the other WS groups (1.5 Mb and 1.8 Mb) and the DS and TD groups, the Student's *t* of Crawford and Howell (1998) was used. A significant difference was found in the FIQ, where the TD group had higher scores than the participant with the 1.1 Mb deletion ($p < 0.05$). No differences were found between the 1.1 Mb, 1.5 Mb, 1.8 Mb, and DS groups.

Table 1 Demographic Statistics of the 1.1 Mb, 1.5 Mb and 1.8 Mb WS, DS, and TD Groups

Variable	1.1 Mb	1.5 Mb		1.8 Mb		DS		TD		X^2	*P*	E^2_R
	Raw Score	Mean (*SD*)	Mean Rank	Mean (*SD*)	Mean Rank	Mean (*SD*)	Mean Rank	Mean (*SD*)	Mean Rank			
Chronological Age	14	11 (3.55)	11.71	12 (4.96)	13.13	12.57 (4.19)	15.07	11.14 (3.67)	12.14	0.87	0.83	0.04
Mental Age	8	5.57 (1.51)	9.43	6.75 (3.59)	11.38	5.71 (2.05)	9.57	11.85 (3.57)	20.93	11.73	**< 0.01**	0.49
FIQ	54	50 (3.69)	10.86	55.25 (13.27)	11.38	45.14 (4.74)	7.07	108 (15.08)*	22	15.87	**0.001**	0.66

They are presented in bold to highlight the variables that were significant

SD Standard deviation, *WS* Williams syndrome, *DS* Down syndrome, *TD* Typical Development, E^2_R Effect size

*1.1 Mb < TD (t (6) = − 3. 35; p = .01)

Instruments

Genetic

- Chromosomal microarray analysis (CMA). This technique is based on the hybridization of nucleic acids and their detection by image analysis of fluorescence. It provides a high-resolution image of the affected area in addition to the rest of the genome, and nominal measurements of the size of the deletion and the preserved genes (Venegas Vega 2012).

Neuropsychological and Behavioral

- Structured interview. The objective was to collect participants' medical history and to assess whether there were alterations not related to the syndrome.
- Wechsler Intelligence Scale for Children and Adolescents (WISC-IV; Wechsler 2007). This test was used to obtain participants' FIQ and to assess their capacity for social judgment, using the comprehension subtest. It was given to participants aged 6 years 0 months to 16 years 11 months. It has Mexican norms.
- Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler 2014). This test was used to obtain participants' FIQ and to assess their capacity for social judgment. It was given to participants aged 16 years 11 months to 18 years. It has Mexican norms.

Social Cognition

The following instruments were used to evaluate social cognition:

- *Social Judgment:* The Comprehension subtest (Wechsler 2007, 2014) was used to evaluate social judgment. This subtest allows for the evaluation of social cognition, defined as the realization of inferences and deductions in social contexts (Hernández Galván and Yáñez-Téllez 2003). Participants are asked to describe the expected behavior in response to different situations and social contexts. Scalar scores were used ($M = 10$, $SD = 3$).
- *Identification of Facial Emotions:* Ekman's faces (Ekman et al. 1976) were used to evaluate identification of facial emotions. This instrument consists of photographs of actors representing different emotional states of varying intensity. Thirty faces with four emotions (joy, anger, fear, and sadness), and also neutral expressions, all previously piloted with Mexican children, were used. The images were randomized and presented on a laptop. Participants were asked to orally identify the emotion of the person in the photograph from a set of emotion labels; raw scores were used. Correct identifications were given a score of 1 and incorrect ones received 0. Before beginning the test, participants were presented with five photographs to familiarize them with the task.
- *Theory of Mind:* Happé's Strange Stories (Happé 1994) were employed to assess intentions of theory of mind (Tirapu-Ustárroz et al. 2007). The Spanish translation by Andrés-Roqueta (2009) was used; it consists of 12 stories of six different intention types, grouped into first-order stories (pretense, lie, and white lie) and second-order stories (irony, joke, and figure of speech); this classification into first and second order is different from that of false beliefs. Each story was told while participants observed an image associated with it. At the end of the story, they were asked "Did X tell the truth …?" to assess their understanding, and then "Why do you think X said …?" to evaluate the first-order, second-order, and total theory of mind scores. Following Andrés-Roqueta (2009), two stories were used to evaluate the understanding of each communicative intention. If participants gave the social intention of the character's response, they were given a score of 2. If they gave a response connected to the context without arriving at a mentalistic idea, they were given a score of 1. If they gave a response without context, they were given a score of 0. Responses were transcribed and scored by two expert evaluators in neuropsychology. Calculation of Cohen's k showed moderate agreement between the experts' judgments: $k = 0.56$ (95% CI: 0.49–0.63), $p < 0.001$. Where there was conflict between the experts' scores, responses were categorized by consensus, following the procedure in Andrés-Roqueta (2009).

Procedure

Children with Williams syndrome and Down syndrome were recruited through invitations distributed through associations for people with those syndromes; children with typical development matched by chronological age were recruited from an institutional database. The first session was informative. Parents were asked to provide written informed consent, and participants gave their assent. The research protocol was approved by the University Research Ethics Committee (CE/FESI/062,017/1177) as being in compliance with the Helsinki Declaration. Participants with WS were sent for clinical evaluation by an expert geneticist and then referred to a laboratory to have a blood sample taken for the CMA. On a separate occasion, they were scheduled to take the social cognition tests, which were completed in a 90-min session. The results of this study were made available to participants after all of them completed the social cognition tasks.

Participants with WS were divided into groups, based on the CMA analysis of the size of their genetic deletion, and their results were compared with those of the DS and TD groups. Two statistical models were used: first, a Student's t, as modified by Crawford and Howell (1998), was used to compare the raw scores of the single participant with the 1.1 Mb deletion with the mean of those with the 1.5 Mb and 1.8 Mb deletions, those with DS, and those with TD. In a second analysis, a non-parametric Kruskal–Wallis H, with Dunn's procedure for pairwise comparisons and Bonferroni post-hoc adjustment (Dunn 1964; Laerd Statistics 2015), was used to analyze the mean rank of the groups with 1.5 Mb and 1.8 Mb deletions and with DS and TD.

Results

Social Judgment

Figure 2 shows that the single participant with a 1.1 Mb deletion had a raw score of 7 on the comprehension test, which was higher than those of the 1.5 Mb group ($M = 1.71$, $SD = 1.88$; $t = 2.63$; $p = 0.04$) the 1.8 Mb group ($M = 1.75$, $SD = 0.95$; $t = 4.94$; $p = 0.02$), and the DS group ($M = 1$, $SD = 0$; $t = 6.23$; $p < 0.001$), and did not show a significant difference with that of the TD group ($M = 9.28$, $SD = 1.71$; $t = -1.33$; $p = 0.23$).

Figure 2 also shows that the comparison of mean rank between the 1.5 Mb, 1.8 Mb, DS, and TD groups in the social judgment task indicated significant differences ($\chi 2\ (3) = 19.63$, $p \leq 0.001$). The post-hoc analysis revealed that the TD group performed better ($M = 9.57$) than the DS group ($M = 1$, $p < 0.001$) and the 1.5 Mb group ($M = 1.71$; $p < 0.01$). There was no statistically significant difference between the 1.5 Mb and the 1.8 Mb groups.

Identification of Facial Emotions

Figure 3 shows that the participant with a 1.1 Mb deletion had a better ability to recognize neutral faces ($p < 0.05$) than the 1.5 Mb, 1.8 Mb, and DS groups, but the 1.8 Mb and TD groups had a better ability to identify fear ($p < 0.05$). The 1.1 Mb participant had a lesser ability to identify anger ($p < 0.05$) than the TD group, but this ability was similar to that of the 1.5 Mb, 1.8 Mb, and DS groups. The 1.1 Mb participant showed no significant differences with the 1.5 Mb, the 1.8 Mb, the DS, or the TD group in identifying faces of joy or sadness. The emotions with significant differences were fear ($\chi^2\ (3) = 15.81$, $p = 0.001$), sadness ($\chi^2\ (3) = 8.69$, $p = 0.03$), and neutral ($\chi^2\ (3) = 15.35$, $p = 0.002$). The post-hoc analysis showed that the TD group performed better in the identification of fear ($M = 5.85$) than the DS group ($M = 2.42$; $p = 0.04$) and the 1.5 Mb group ($M = 3.28$; $p < 0.01$). The 1.5 Mb group performed better ($M = 5.14$) in the identification of sadness than the DS group ($M = 2.42$; $p = 0.03$). The TD group ($M = 5.71$) performed better in the identification of neutral faces than the 1.5 Mb group ($M = 1.28$; $p = 0.01$), the 1.8 Mb group ($M = 0.75$; $p = 0.01$), and the DS group ($M = 1.28$; $p < 0.001$).

Theory of Mind

Figure 4 shows the statistical results of the evaluation with Happé's Strange Stories. The 1.1 Mb participant performed better with first-order ($p < 0.01$) and second-order tasks ($p < 0.01$), as well as total ToM ($p < 0.01$), than the 1.8 Mb and DS groups. That participant also showed a lower level of performance than the TD group ($p < 0.05$) with second-order tasks and total ToM ($p < 0.05$). In the type of story analysis, this participant performed better with joke stories ($p < 0.05$) than those in the 1.5 Mb, 1.8 Mb, and DS groups (see Supplementary Material).

The comparison between first- and second-order stories, shown in Fig. 4, revealed significant differences between

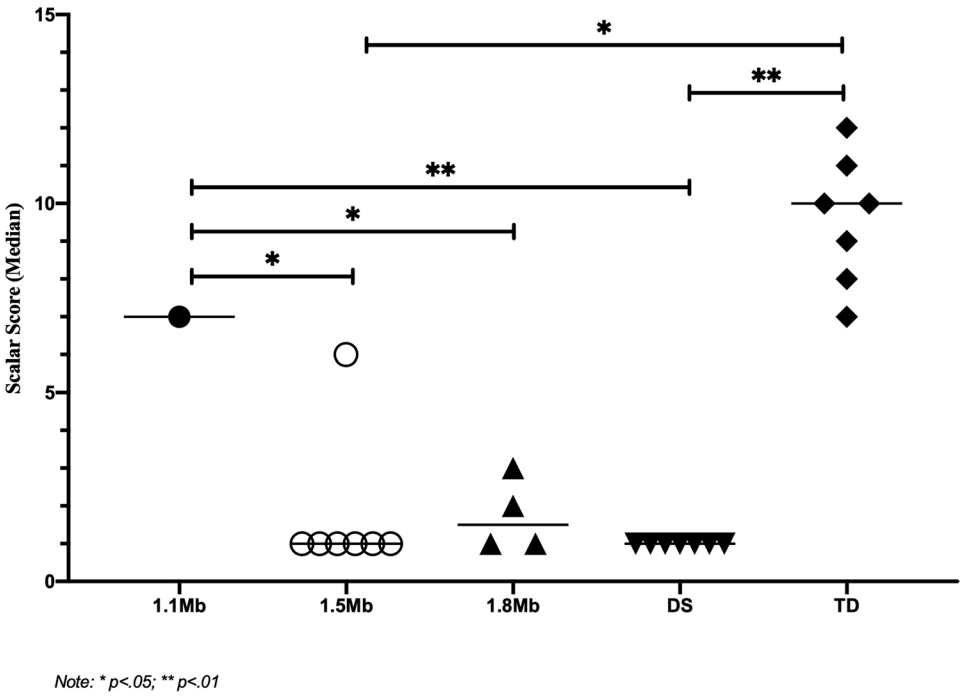

Fig. 2 Scores on comprehension test of 1.1 Mb, 1.5 Mb, 1.8 Mb and the DS and TD groups

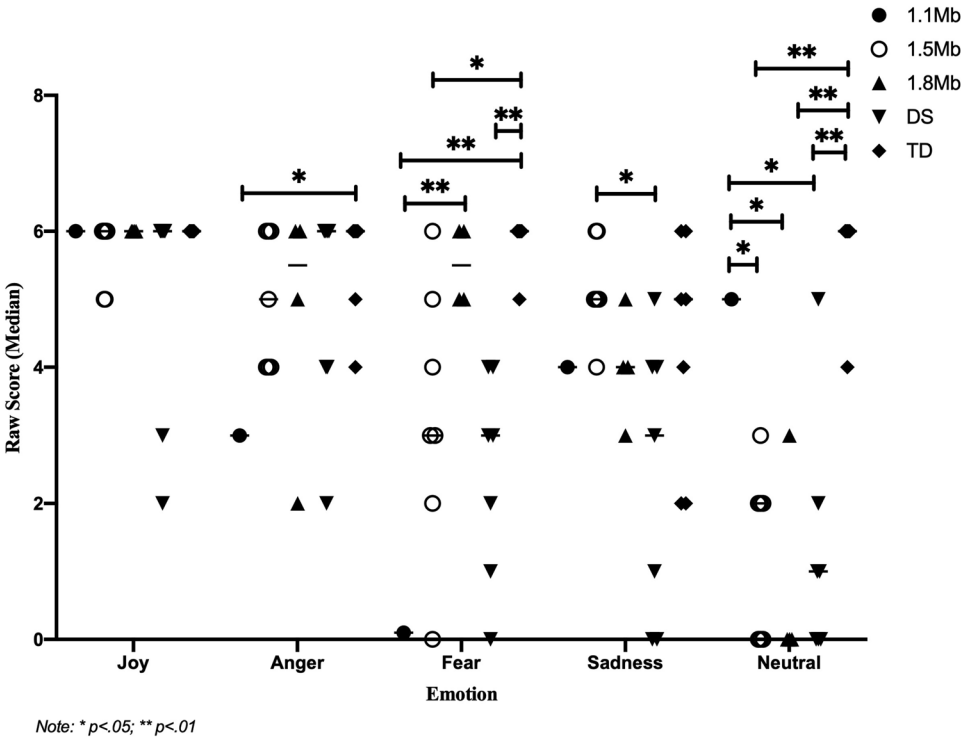

Fig. 3 Identification of facial emotions of 1.1 Mb, 1.5 Mb, 1.8 Mb, and the DS and TD groups

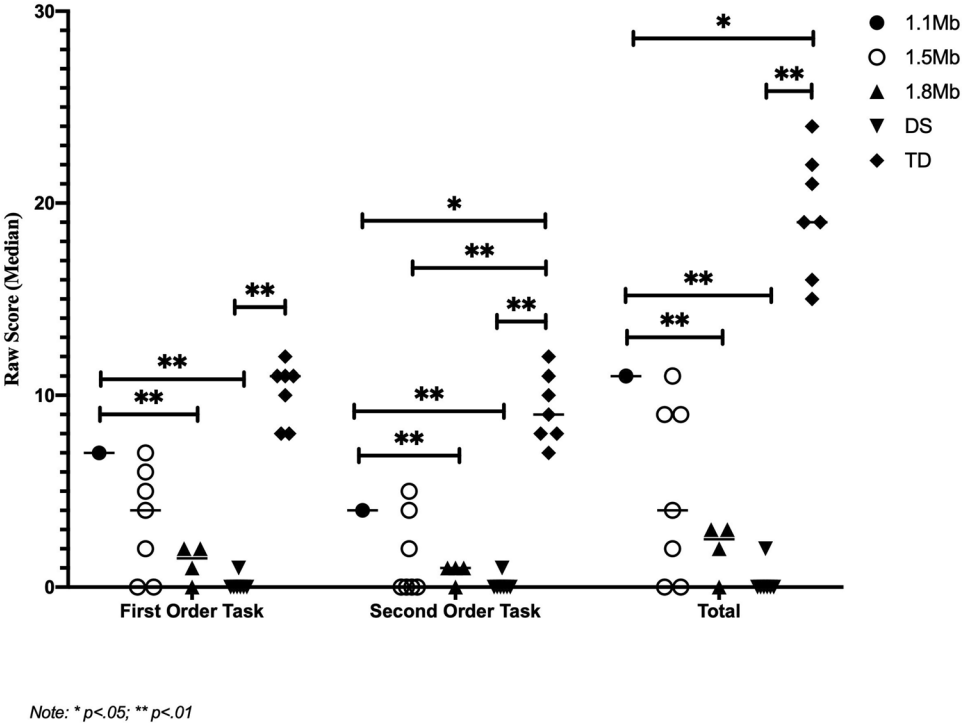

Fig. 4 Identification of Intentions of first and second order tasks, and tools ToM of 1.1 Mb, 1.5 Mb, 1.8 Mb, and the DS and TD groups

groups for both first-order (χ^2 (3) = 18.64, $p < 0.001$) and second-order tasks (χ^2 (3) = 17.36, $p < 0.01$) and total ToM (χ^2 (3) = 18.64, $p < 0.001$). The post-hoc analysis showed that the TD group performed better on first-order tasks than the DS group ($p < 0.001$). This analysis also showed that the TD group performed better on second-order-tasks than the 1.5 Mb group ($p < 0.01$) and the DS group ($p < 0.001$). In the total ToM score, the TD group performed better than the DS group ($p < 0.001$).

Discussion

The objective of this study was to explore social cognition in different WS genotypes (with deletions of 1.1 Mb, 1.5 Mb, and 1.8 Mb) to evaluate how genes of the *GTF2I* family, which the literature suggests may be related to the WS social phenotype, might influence the execution of tasks that evaluate social cognition. The main differences found between WS genotypes were between the participant with a 1.1 Mb deletion and the 1.8 Mb group in the tasks of social judgment and theory of mind, as well as in the identification of neutral faces. These differences suggest that the loss of the three genes (*GTF2IRD1*, *GTF2I*, and *GTF2IRD2*) could influence the severity of social cognition disorders, specifically with respect to social judgment and theory of mind (as evaluated with Happé's pretense, lie, and white lie stories). The participant who retained all three genes performed significantly better on ToM and social judgment tasks than the group missing all three genes. The group with the 1.8 Mb deletion showed major alterations in theory of mind, which could manifest themselves in social isolation and an autistic-like social-cognitive profile, as reported by Karmiloff-Smith et al. (2012), Porter et al. (2012) and Serrano-Juárez et al. (2018).

Our results showed that the loss of the *GTF2IRD1*, *GTF2I*, and *GTF2IRD2* genes could cause greater failures in social judgment and theory of mind in people with WS. These results are consistent with those of Crespi and Hurd (2014), who found that the *GTF2I* gene family is involved in the neurogenetic basis of social skills both in people with WS and in those with typical genomes. The loss of the *GTF2IRD2* gene also could influence the expression of major alterations in theory of mind and an autistic-like social-cognitive profile (Karmiloff-Smith et al. 2012; Porter et al. 2012). It is possible that both *GTF2I* and *GTF2IRD2* might influence the severity of alterations not only in social judgment and theory of mind, but also in other domains of social cognition not evaluated in this study. It is important to note that there may be other genes proximal, to the critical region in WS like *LIMK1* (Hoeft et al. 2014), *BAZ1B* (Lalli et al. 2016), *FZD9* (Chailangkarn et al. 2016) and *CLIP2* (Meyer-Linderberg et al. 2006), that influence the components of the social brain and should also be taken into account, as suggested by Karmiloff-Smith et al. (2012), Kopp et al. (2019), and Hoeft et al. (2014).

The cases with 1.5 Mb deletion previously reported and those of this study show heterogeneous performance in tasks of social cognition; this deletion conserves some of the genes of the *GTF2I* family and seems to affect only certain processes of social cognition (social judgment and recognition of neutral faces). It may be that these are generalist genes with a pleiotropic effect on multiple brain structures and functions (Kovas and Plomin 2006), but that each of these structures supports specific cognitive processes of social cognition.

In this study, the use of a group with DS was methodological; it was not the objective of the study to identify differences in social cognition between those with DS and WS. However, it was found that children with DS present deficiencies in all tasks of social cognition, mainly in theory of mind tasks of the first and second order, as has been reported in the literature (Amadó et al. 2012), possibly due to their problems with pragmatic language (Levy and Eilam 2013).

The only task where there were no consistent differences between the participants with 1.1 Mb and 1.8 Mb deletions was that of identifying emotions on faces, possibly because, as Martínez-Castilla et al. (2015) reported, people with WS have the same pattern of emotional recognition as those with typical development.

The chromosomal microarray analysis and the neuropsychological evaluation allow us to establish a relationship between genes and cognition: participants missing the three genes of the *GTF2I* family showed lesser performance in theory of mind and social judgment than the single participant who retained them. However, the limitations of the study, such as its small sample size and its lack of evaluation of other aspects of social cognition, prevent a more complete characterization of genetic effects. Although there were some variables with no significant differences between the groups with DS, 1.5 Mb, and 1.8 Mb deletions and the TD group, in second-order theory of mind tasks a non-statistically significant trend was observed ($p = 0.058$) of better scores in the TD than in the other groups. A larger sample size could help identify these differences in each deletion. It is also important to remember other variables that affect cognition and behavior, such as neuroplasticity, stimulation, exposure to social relationships, and the educational level of parents, which modify children's phenotypes despite their having similar genotypes. Our study offers an initial exploration of the relationship of genes, cognition, and social behavior in people with WS. Future research on WS genotypes and social cognition should also use neuroimaging and neurophysiology techniques to demonstrate the expression of *GTFIRD2* in the prefrontal, parietal, and cerebellar cortex (Porter et al. 2012; Chailangkarn et al. 2018), as well as the regulation of the genetic functions of the *GTF2I* gene family (Makeyev et al. 2004; Palmer et al. 2012) that influence social cognition.

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References

Adolphs, R. (2001). The neurobiology of social cognition. *Current Opinion in Neurobiology, 11*(2), 231–239. https://doi.org/10.1016/s0959-4388(00)00202-6.

Adolphs, R. (2009). The social brain: neural basis of social knowledge. *Annual Review of Psychology, 60*, 693–716. https://doi.org/10.1146/annurev.psych.60.110707.163514.

Amadó, A., Benejam, B., Mezuca, J., Serrat, E., & Vallès-Majoral, E. (2012). Socio-cognitive abilities in children with Down's syndrome: results of a preliminary study. *Medical Review on Down's Syndrome., 16*(3), 34–39.

Andrés-Roqueta, C. (2009). *Pragmática y Cognición social en niños y niñas con Trastorno específico del lenguaje (TEL).* (Doctorado), Universitat Jaume I de Castelló, Castellón.

Antonell, A., Del Campo, M., Magano, L., Kaufmann, L., Martínez de la Iglesia, J., Gallastegui, F., et al. (2010). Partial 7q11.23 deletions further implicate GTF2I and GTF2IRD1 as the main genes responsible for the Williams-Beuren syndrome neurocognitive profile. *Journal of Medical Genetics, 47*, 312–320. https://doi.org/10.1136/jmg.2009.071712.

Atlas, A. H. B. (2010). Allen Institute for Brain Science. Retrieved from human.brain-map.org

Bellugi, U., Lichtenberger, L., Mills, D., Galaburda, A., & Korenberg, J. (1999). Briding cognition, the brain and molecular genetics: evidence from Williams syndrome. *Trends in Neurosciences, 22*, 197–207.

Bellugi, U., et al. (2007). Affect, social behavior, and the brain in Williams syndrome. *Current directions in psychological science, 16*(2), 99–104.

Borg, I., Delhanty, J. D., & Baraitser, M. (1995). Detection of hemizygosity at the elastin locus by FISH analysis as a diagnostic test in both classical and atypical cases of Williams syndrome. *Journal of medical genetics, 32*(9), 692–696.

Butman, J. (2001). La cognición social y la corteza cerebral. *Revista Neurológica Argentina, 26*, 117–122.

Campos, R., & Martínez-Castilla Sotillo, M. (2014). Cognición social en el síndrome de Williams. *Revista de Psicología Social: International Journal of Social Psychology, 28*(3), 249–360.

Chailangkarn, T., Trujillo, C. A., Freitas, B. C., Hrvoj-Mihic, B., Herai, R. H., Diana, X. Y., et al. (2016). A human neurodevelopmental model for Williams syndrome. *Nature, 536*(7616), 338–343.

Chailangkarn, T., Noree, C., & Muotri, A. R. (2018). The contribution of GTF2I haploinsufficiency to Williams syndrome. *Molecular and cellular probes, 40*, 45–51.

Crawford, J. R., & Howell, D. C. (1998). Comparing an Individual´s Test Score Against Norms Derived from Small Samples. *The Clinical Neuropsychologist, 12*(4), 482–486. https://doi.org/10.1076/clin.12.4.482.7241.

Crespi, B. J., & Hurd, P. L. (2014). Cognitive-behavioral phenotypes of Williams syndrome are associated with genetic variation in the GTF2I gene, in a healthy popoulation. *BMC Neuroscience*. https://doi.org/10.1186/s12868-014-0127-1.

Dai, L., Bellugi, U., Chen, X., Pulst-Korenberg, A. M., Järvinen-Pasley, A., Tirosh-Wagner, T., et al. (2008). Is it Williams Syndrome? GTF2IRD1 Implicated in Visual-Spatial Construction and GTF2I in sociability revealed by high resolution arrays. *American Journal of Medical Genetics, 149A*, 302–314.

Dunn, O. J. (1964). Multiple comparisons using rank sums. *Technometrics, 6*, 241–252.

Ekman, P., Friesen, W., & Press, C. (1976). *Pictures of facial affect* (Vol. 21). Palo Alto CA: Consulting Psychologists Press.

Ferrero, G., Howald, C., Micale, L., Biamino, E., Augello, B., Fusco, C., et al. (2010). An atypical 7q11.23 deletion normal IQ Williams-Beuren syndrome patient. *European Jorunal of Human Genetics, 18*, 33–38.

Fisher, M. H., & Morin, L. (2017). Addressing social skills deficits in adults with Williams syndrome. *Research in developmental disabilities, 71*, 77–87.

Gagliardi, C., Frigerio, E., Burt, M., Cazzaniga, I., Perrett, D., & Borgatti, R. (2003). Facial expression recognition in Williams syndrome. *Neuropsychologia, 41*(6), 733–738. https://doi.org/10.1016/S0028-3932(02)00178-1.

Happé, F. (1994). An advanced test of theory of mind: understanding of story characters´ thoughts and feelings by able autistic, mentally handicapped, and normal children and adults. *Journal of Autism and Developmental Disorders, 24*(2), 129–154.

Hernández Galván, A., & Yáñez-Téllez, M. G. (2003). *Evaluación de la cognición social en adultos mayores: presentación de la batería COGSOC-AM* (pp. 269–278). XXII: Revista Argentina de Clínica Psicológica.

Hirota, H., Matsuoka, R., Chen, X.-N., Salandanan, L., Lincoln, A., Rose, F., et al. (2003). Williams syndrome deficits in visual spatial processing linked to GTF2IRD1 and GTF2I on chromosome 7q1123. *Genet Med, 5*(4), 311–321. https://doi.org/10.1097/01.GIM.0000076975.10224.67.

Hoeft, F., Dai, L., Haas, B. W., Sheau, K., Mimura, M., Mills, D., et al. (2014). Mapping genetically controlled neural circuits of social behavior and visuo-motor integration by a preliminary examination of atypical deletions with Williams syndrome. *PLoS ONE, 9*(8), e104088.

Järvinen, A., Crivelli, D., Arnold, A., Woo-Von Hoogenstyn, N., & Bellugi, U. (2015). Relations between social-perceptual ability in multi and unisensory context, autonomic reactivity, and social functioning in individuals with Williams syndrome. *Neuropsychologia, 73*, 127–140.

Järvinen, A., Korenberg, J., & Bellugi, U. (2013). The social phenotype of Williams syndrome. *Current Opinion in Neurobiology, 23*, 414–422. https://doi.org/10.1016/j.conb.2012.12.006.

Järvinen-Pasley, A., Bellugi, U., Reilly, J., Mills, D., Galaburda, A., Reiss, A., et al. (2008). Defining the social phenotype in Williams syndrome: A model for linking gene, the brain, and behavior. *Development and Psychopathology, 20*, 1–35. https://doi.org/10.1017/S0954579408000011.

Karmiloff-Smith, A., Broadbent, H., Farran, E., Longhi, E., D´Souza, D., Metcalfe, K., et al. (2012). Social cognition in Williams Syndrome: genotype/phenotype insights from partial deletion patients. *Frontiers in Psychology*. https://doi.org/10.3389/fpsyg.2012.00168.

Karmiloff-Smith, A., Klima, E., Bellugi, U., Grant, J., & Baron-Cohen, S. (1995). Is There a Social Module? Language, Face Processing, and Theory of Mind in Individuals with Williams Syndrome. *Journal of Cognitive Neuroscience, 7*(2), 196–208. https://doi.org/10.1162/jocn.1995.7.2.196.

Kopp, N., McCullough, K., Maloney, S. E., & Dougherty, J. D. (2019). Gtf2i and Gtf2ird1 mutation do not account for the full phenotypic effect of the Williams syndrome critical region in mouse models. *Human molecular genetics, 28*(20), 3443–3465.

Kovas, Y., & Plomin, R. (2006). Generalist genes: implications for the cognitive sciences. *Trends in cognitive sciences, 10*(5), 198–203.

Lalli, M. A., Jang, J., Park, J. H. C., Wang, Y., Guzman, E., Zhou, H., et al. (2016). Haploinsufficiency of BAZ1B contributes to Williams syndrome through transcriptional dysregulation of neurodevelopmental pathways. *Human molecular genetics, 25*(7), 1294–1306.

Laerd Statistics (2015). Kruskal-Wallis H test using SPSS Statistics. Statistical tutorials and software guides. Retrieved from https://statistics.laerd.com/

Levy, Y., & Eilam, A. (2013). Pathways to language: a naturalistic study of children with Williams syndrome and children with Down syndrome. *Journal of Child Language, 40*(1), 106–138. https://doi.org/10.1017/S0305000912000475.

Makeyev, A., Erdenechimeg, L., Mungunsukh, O., Roth, J., Enkhmandakh, B., Ruddle, F., et al. (2004). GTF2IRD2 is located in the Williams-Beuren syndrome critical region 7q1123 and encodes a protein with two TFII-I-like kelix-loop-helix repeats. *PNAS, 101*(30), 11052–11057.

Malenfant, P., Liu, X., Hudson, M., Qiao, Y., Hrynchak, M., Riendeau, N., et al. (2012). Association of GTF2i in the Williams-Beuren syndrome critical region with Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders, 42*, 1459–1469. https://doi.org/10.1007/s10803-011-1389-4.

Martens, M., Wilson, S., & Reutens, D. (2008). Research Review: Williams syndrome, a critical review of the cognitive, behavioral, and neuroanatomical phenotype. *The Journal of Child Psychology and Psychiatry, 49*(6), 576–608.

Martínez-Castilla, P., Burt, M., Borgatti, R., & Gagliardi, C. (2015). Facial emotion recognition in William Syndrome and Down Syndrome: A matching and developmental study. *Child Neuropsychology., 21*(5), 668–692.

Mervis, C., & Morris, C. A. (2007). Williams Syndrome. In M. Mazzocco & J. Ross (Eds.), *Neurogenetic Developmental Disorders*. London: The MIT Press.

Meyer-Linderberg, A., Mervis, C., & Berman, K. F. (2006). Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nature Reviews, 7*, 380–393. https://doi.org/10.1038/nrn1906.

Miezah, D., Porter, M., Batchelor, J., Boulton, K., & Veloso, G. C. (2020). Cognitive abilities in Williams syndrome. *Research in Developmental Disabilities, 104*, 103701.

Pavlova, M., Heliz, J., Sokolov, A., & Barisnikov, K. (2016). Social cognition in Williams Syndrome: Face tuning. *Frontiers in Psycholog., 7*, 1131. https://doi.org/10.3389/fpsyg.2016.01131.

Palmer, S., Taylor, K. M., Santucci, N., Widago, J., Chan, Y.-K. A., Yeo, J.-L., et al. (2012). GTF2IRD2 from the Williams-Beuren critical region encodes a mobile-element-derived fusion protein that antagonizes the action of its related family members. *Journal of Cell Science, 125*, 5040–5050. https://doi.org/10.1242/jcs.102798.

Plesa Skwerer, D., Verbalis, A., Schofield, C., Faja, S., & Tager-Flusberg, H. (2006). Social-perceptual abilities in adolescents and adults with Williams syndrome. *Cognitive Neuropsychology, 23*(2), 338–349. https://doi.org/10.1080/02643290542000076.

Pober, B. (2010). Williams-Beuren Syndrome. *The New England Journal of Medicine, 362*, 239–352.

Porter, M. A., & Coltheart, M. (2005). Cognitive heterogeneity in Williams syndrome. *Developmental neuropsychology, 27*(2), 275–306.

Porter, M., Coltheart, M., & Langdon, R. (2008). Theory of Mind in Williams Syndrome Assessed Using a Nonverbal Task. *Journal of Autism and Developmental Disorders, 38*, 806–814. https://doi.org/10.1007/s10803-007-0447-4.

Porter, M., Dobson-Stone, C., Kwok, J., Schofield, P., Beckett, W., & Tassabehji, M. (2012). A role of transcription factor GTF2IRD2 in Executive Function in Williams-Beuren Syndrome. *PLoS ONE, 7*(10), e47457. https://doi.org/10.1371/journal.pone.0047457.

Quinn, K., Macrae, C. Neil, & Bodenhausen, G. (2006). Social Cognition. In *Annual Review of Psychology* (Vol. 51).

Ramírez-Velasco, A., & Domínguez-Quezada, M. (2017). Deleciones atípicas en el síndrome de Williams-Beuren. *Revista Mexicana del Instituto Mexicano del Seguro Social, 55*(5), 5615–5620.

Serrano-Juárez, C. A., Venegas-Vega, C. A., Yáñez-Téllez, M. G., Rodríguez-Camacho, M., Silva-Pereyra, J., Salgado-Ceballos, H., et al. (2018). Cognitive, behavioural, and adaptive profiles in Williams syndrome with and without loss of GTF2IRD2. *Journal of the International Neuropsychological Society, 24*, 896–904. https://doi.org/10.1017/S1355617718000711.

Tager-Flusberg, H., & Baron-Cohen, S. (1998). Reading the Windows to the Soul: Evidence of Domain-Specific Sparing in Williams Syndrome. *Journal of Cognitive Neuroscience, 10*(5), 631–639. https://doi.org/10.1162/089892998563031.

Tipney, H., Hinsley, T., Brass, A., Metcalfe, K., Donnai, D., & Tassabehji, M. (2004). Isolation and characterisation of GTF2IRD2, a novel fusion gene and member of the TFII-I family of transcription factors, deleted in Williams-Beuren syndrome. *European Jorunal of Human Genetics, 12*, 551–560.

Tirapu-Ustárroz, J., Pérez-Sayes, G., Erekatxo-Bilbao, M., & Pelegrín-Valero, C. (2007). Qué es la teoría de la mente? *Revista de Neurología, 44*, 479–489.

Uhlén, M., Fagerberg, L., Hallström, B., Lindskog, C., Oksvold, P., Mardinoglu, A., et al. (2015). Tissue-based map of the human proteome. *Science*. https://doi.org/10.1126/science.1260419.

van der Fluit, F., Gaffrey, M., & Kelin-Tasman, B. (2012). Social cognition in Williams syndrome: relations between performance on the social attribution task and cognitive and behavioral characteristics. *Frontiers in Psychology., 3*, 197. https://doi.org/10.3389/fpsyg.2012.00197.

Venegas Vega, C. A. (2012). Pruebas citogenéticas basadas en microarreglos. In V. Del Castillo Ruiz, R. D. Uranga Hernández, & G. Zafra de la Rosa (Eds.), *Genética Clínica*. México: Manual Moderno.

Wechsler, D. (2007). *Escala Wechsler de Inteligencia para Niños y Adolescentes-IV*. México: Manual Moderno.

Wechsler, D. (2014). *Escala Wechsler de Inteligencia para Adultos-IV*. México: Manual Moderno.

Zegarra-Valdivia, J., & Chino Vilca, B. (2017). Mentalización y teoría de la mente. *Revista de Neuro-Psiquiatría, 80*(3), 189–199.