Williams syndrome and autism: dissimilar socio-cognitive profiles with similar patterns of abnormal gene expression in the blood

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Abstract

Autism Spectrum Disorders (ASD) and Williams Syndrome (WS) are complex cognitive conditions exhibiting quite opposite features in the social domain: whereas people with ASD are mostly hyposocial, subjects with WS are usually reported as hypersocial. At the same time, ASD and WS share some common underlying behavioral and cognitive deficits. It is not clear, however, which genes account for the attested differences (and similarities) in the socio-cognitive domain. In this paper we adopted a comparative-molecular approach and looked for genes that might be differentially (or similarly) regulated in the blood of people with these conditions. We found a significant overlap between genes dysregulated in the blood of patients compared to neurotypical controls, with most of them being upregulated or, in some cases, downregulated. Still, genes with similar expression trends can exhibit quantitative differences between conditions, with most of them being more dysregulated in WS than in ASD. Differentially-expressed genes are involved in aspects of brain development and function (particularly, dendritogenesis) and are expressed in brain areas (particularly, the cerebellum, the thalamus and the striatum) of relevance for the ASD and the WS etiopathogenesis. Overall, these genes emerge as promising candidates for the similarities and differences between the ASD and the WS socio-cognitive profiles.

Keywords: Autism Spectrum Disorders; Williams Syndrome; Differentially-expressed genes, language evolution, neural crest, language impairment; gene expression

Introduction

Cognitive disorders usually exhibit complex phenotypical profiles. In cases with an unknown molecular etiology, as in autism spectrum disorders (ASD), many genes (and many variants of specific genes) have been found to contribute to the cognitive and behavioral problems exhibited by affected people, with each of them conferring low risk to the disease (Geschwind and State, 2015; Gyawali and Patra, 2019). In cases with a known etiology, like in Williams syndrome (WS), robust gene-to-phenotype correlations are also difficult to establish, particularly, for cognitive and behavioral deficits (see Korenberg et al., 2000; Tassabehji, 2003; Karmiloff-Smith et al., 2012; Ghaffari et al., 2018 among others for discussion), seemingly because these problems result in most cases from the dysregulation of several other genes outside the affected genomic regions (e.g. Lalli et al., 2016 or Kimura et al., 2019 for WS). Consequently, for these clinical conditions, it is of particular interest to examine the expression pattern of genes across the whole genome. This approach ultimately follows the 'omnigenic' theories of complex diseases, according to which such diseases result from the altered expression of most of the genes expressed in the affected tissues, with many of them located well outside the core pathways leading to disease (Boyle et al., 2017; Peedicayil and Grayson, 2018a,b). Still, even if hundreds of genes are found to be dysregulated in patients, specific pathways or specific biological processes are expected to be differentially affected in different conditions, enabling the identification of intermediate, disease-specific phenotypes (e.g. abnormal, disease-specific gene expression profiles). This should help clarify the genetics of these conditions and the clinical symptoms observed in affected people, as well as achieve earlier and more precise diagnoses. For instance, several co-expression modules of genes

outside the region deleted in WS are found to be dysregulated in the blood of subjects with this condition and enriched in genes related to RNA processing and RNA transport (Kimura et al., 2019). Eventually, traits that appear to be omnigenic in lesser studies seem to have finite genetic determinants (Jakobson and Jarosz, 2019). Consequently, more studies of this sort are needed if we want to achieve robust conclusions about the etiology of complex cognitive disorders.

At the same time, it has been argued that a promising way of bridging the gap between the genome and the phenotype in these conditions is to adopt a comparative approach, instead of focusing on each disorder separately. For instance, ASD and schizophrenia (SZ) exhibit distinctly contrasting features, from neurodevelopmental pathways to brain structure and function to cognitive (dis)abilities, including language (see Crespi and Badcock 2008, Murphy and Benítez-Burraco, 2017 among others for discussion). As far as gene expression profiles are concerned, there is also some evidence of diametric gene-dosage in some cases (Byars et al. 2014). Thus it can be hypothesized that SZ and ASD might share the same genetic determinants, but with some key genes exhibiting opposite patterns of abnormal down- or upregulation compared to controls. The development of next-generation sequencing facilities and the analyses of thousands of cases by large consortia have exponentially increased the number of available genetic variants. These suggest that common biological mechanisms can be in fact implicated in both SZ and ASD in spite of their distinct clinical profiles and onset times, mostly converging on aberrant synaptic plasticity and remodeling, and ultimately, on altered connectivity between brain regions (Liu et al., 2017). Accordingly, dosage-sensitive gene expression emerges as a key etiological factor of complex diseases. This is reinforced by the finding that copy number variations (CNVs) in the human genome impacting on the same genes are a risk factor for different psychiatric disorders, especially SZ and ASD (Zarrei et al., 2019). In some cases, mechanistic insights can be provided. For instance, altered excitatory/inhibitory balance is implicated in both SZ and ASD, seemingly accounting for many of their distinctive cognitive features, including language deficits (see Murphy and Benítez-Burraco, 2017 for discussion). CNVs in the gene *CYFIP1* have been associated to both conditions, with *CYFIP1* upregulation increasing excitatory synapse and decreasing inhibitory synapses and with *CYFIP1* knockout resulting in synaptic inhibition (Davenport et al., 2019).

In this paper, we have adopted a comparative approach to cognitive disease with the aim of illuminating aspects of the problems that people with ASD and WS experience with social cognition and social behavior; two aspects which exhibit quite opposite features in many domains. Also in line with our discussion above, we have further adopted a molecular comparative approach. Accordingly, we have relied on the abnormal transcriptional profiles in the blood of affected people to identify genes that can be similarly or dissimilarly dysregulated between conditions and that can account for some of the similarities and the differences observed at the cognitive and behavioral levels. Certainly, as far as cognitive conditions are concerned, the most important changes are expected to occur in the brain. However, because blood and brain transcriptional profiles exhibit a notable overlap, ranging from 20% (Rollins et al., 2010) to 55% (Witt et al., 2013), blood expression profiles can be employed to infer changes of relevance for the etiopathogensis of these conditions (see Bjørklund et al., 2018 or Shen et al., 2019 for ASD). The paper is structured as follows. First, we provide a comparative characterization of the socio-cognitive and socio-behavioral profiles of people with ASD and WS. Afterwards, we discuss several neurobiological hypotheses aimed to account for the observed deficits and strengths in the social domain. Then, because much less is known about the genes accounting for these problems, we have determined the genes that are abnormally expressed in the blood of people with ASD or WS compared to the neurotypical controls. We discuss the biological roles played by the genes that exhibit similar abnormal expression patterns in both conditions, as well as the role of those showing opposite expression trends. We conclude with some reflections about our findings and more generally, about the utility of our approach for achieving a better understanding of the etiology of these two conditions.

2. Contrasting the ASD and the WS socio-cognitive phenotypes

General overview

At first sight, ASD and WS can be viewed as opposite conditions, at least as far as social behavior is concerned. Individuals with ASD are normally characterized as withdrawn, difficult to engage in social interaction, ignorant of social norms, and generally uninterested in social relationships with others (for a general review, see Newschaffer et al., 2007). This hyposocial phenotype starkly contrasts with the hypersocial phenotype exhibited by people with WS, who are usually characterized as overly friendly, gregarious, and eager to interact with others, sometimes to an excessive degree (for a general review, see Bellugi et al., 2000; Jones et al. 2000, Doyle et al. 2004; Martens, et al. 2008; Järvinen et al. 2013). However, this is just a rough picture that deserves a closer examination, not just because such a close look reveals an intricate profile of similarities and differences, as we show in this section, but because these two conditions have been claimed to share genetic determinants (Newschaffer et al 2007, Jawaid et al 2012). Ultimately, social aspects and the management of the social context can be crucial for understanding the different clinical presentation of both conditions, considering that in terms of general cognition, ASD and WS are much more similar when social motivation is removed. Hence, Vivanti and colleagues (2016) found that when the objective of a task is learning and not social interaction, both ASD and WS subjects are equally able to imitate and learn in social situations (see Ingersoll et al., 2013; Berger and Ingersoll, 2015 for similar findings). Eventually, exploring these overlaps and divergences is expected to reveal more about the etiology of atypical social behavior in humans and about the evolution of human social cognition. Our findings are summarized in Figure 1 and are discussed in more depth below.

Socio-cognitive similarities between ASD and WS

In spite of people with WS being labeled as 'overly friendly' and 'hypersocial', they exhibit many difficulties in the social arena that overlap in part with ASD. Accordingly, parents of children with WS often report that they have poor social skills, difficulties with understanding important social cues or information, and difficulty maintaining friendships (Mervis et al., 2001; Sullivan et al., 2003; Stojanovik, 2006; Klein- Tasman et al., 2009; Jarvinen et al., 2015). Included in these similarities are "…social isolation, and other types of social impairment, distractibility, inflexibility, ritualism, obsessiveness, and pragmatic deficits" (Gillberg and Rasmussen, 1994). Both groups also show difficulties with the typical boundaries of personal space (Lough et al., 2015). These shared social difficulties make them more vulnerable socially, prone to disadvantages when it comes to forming productive relationships and social connections. Social vulnerability is thought to be the source of some of the anxiety documented in both groups, which report higher levels compared to neurotypical people (Dykens, 2003; Graham et al., 2005; Jawaid et al., 2012). This elevated anxiety is coupled in many cases with restricted and repetitive behaviors (Rodgers et al., 2012).

To an important extent, these problems in the social sphere are expected to arise from deeper cognitive and behavioral dysfunction. Young children with ASD or WS show delays in pointing behaviors and joint attention, and underperform in theory of mind (ToM) tasks, such as the false belief test (Baron Cohen et al., 1985; Charman et al., 1997; Klein-Tasman et al., 2009; Vivanti et al., 2016). Also documented are difficulties in inhibitory control and shifting attention (Rhodes et al. 2010; Riby et al., 2011). Sparaci and colleagues (2014) found that both participants with ASD and WS had difficulty specifying the 'why' of an experimenter's actions. That is, in a task where they were asked to observe a hand-object action (e.g. grasping a mug to drink tea or touching the handle to put it in a cupboard), both groups had difficulty specifying why they were doing so (i.e. they couldn't say they were grasping the object to put it away). In contrast to their similarities in 'why understanding', participants with ASD showed superior ability in specifying the 'what' of an experimenter's actions. That is, they were better at specifying that the individual was grasping a mug vs. simply touching it, while those with WS showed more difficulty with this task. As Sparaci and colleagues (2015) point out, this difference in 'what' ability coupled with a similarity in 'why' ability is indicative of the fact that certain low level abilities may shape higher level processes in unexpected ways (Sparaci et al., 2015). In a similar vein, the difficulty ASD and WS individuals have with predicting others' intentions and actions have been hypothesized to arise from deficits in predicting physical actions. Indeed, motor impairments have been widely documented in both ASD (e.g. Teitelbaum et al., 1998; Jansiewicz et al., 2006; Dewey et al., 2007) and WS (see Trauner et al. 1989; Elliott et al. 2006; Gagliardi et al. 2007).

Finally, the socio-cognitive problems exhibited by people with ASD or WS are expected to have an impact on (and result in part from) their language deficits. Language development is generally delayed in both conditions, although it tends to follow the typical progression (Asada and Itakura, 2012). In both ASD and WS, grammar was originally thought to be relatively spared, although more recent research has highlighted the fact that it is more impaired than in appears at the surface (see Perovic et al. 2013 and Lacroix et al., 2016 for direct comparisons). In both WS and ASD, grammatical impairment has been shown to happen with aspects of grammar defined later in typical development, like raising and passives (Tager Flusberg 1981; Perovic et al., 2007; Perovic and Wexler, 2007), grammatical morphology (Kjelgaard and Tager –Flusberg, 2001; Roberts et al., 2004), relative clauses (Riches et al., 2009), and subject-control structures (Perovic and Janke, 2013). Importantly for our concerns here, pragmatics (that is, the ability to use language for communicating in a social context) is impaired in both conditions (see Tager-Flusberg, 2000; Doyle et al., 2004: Laws and Bishop, 2004; Stojanovik, 2006; Philofsky et al., 2007; Jarvinen-Pasley et al., 2008; Asada and Itakura, 2012; Lacroix et al. 2016 among others), although, as we will show in the next section, it is more so in ASD. Specifically, both ASD and WS individuals have been rated as impaired in the quality of their conversational initiations with others, with WS subjects underperforming people with ASD (Philofsky et al., 2007). Likewise, narration, a basic pragmatic skill, has also been shown to be impaired in both conditions. Accordingly, Diez-Itza and Martinez (2016) reported in their study that WS individuals often give the impression of having in-tact narrative skills because of their overuse of discourse markers and exclamations, but in-depth analyses further reveal deficiencies in sequencing narratives. Similar deficits in sequencing narratives have been reported in ASD (see Freeman and Dake, 1996; Happé and Frith, 1996).

Studies have shown a direct correlation between socio-cognitive skills and deficits and pragmatic language (dis)abilities in both WS and ASD (Happé, 1993; Surian et al., 1996; Hale and Tager-Flusberg, 2005; John et al., 2009), suggesting that deficits in the social domain impact negatively on language use in both conditions. Difficulties with pragmatics can be hypothesized to derive from specific deficits that both groups have, particularly, problems with inferring the mental states of others (Asada and Itakura, 2012). Likewise, problems with narration, and specifically, the lack of ability to sequence events, might stem from difficulties in spatial cognition, at least in the case of WS (Phillips et al., 2004). At the same time, socio-cognitive deficits impacting language use certainly contribute to language delay in both conditions, as many aspects of language acquisition require inference of the speaker's intentions (Preissler and Carey, 2005). Other probable factors contributing to language delay are deficits in joint attention, which especially impact the acquisition of vocabulary and semantic meaning of words (Baron Cohen et al., 1985; Charman et al., 1997; Klein Tasman et al., 2007; Mervis and Becerra, 2007; Mervis and John, 2012). At the same time, as noted, there are aspects of language that appear similarly preserved in both conditions in spite of socio-cognitive impairment. For instance, in their study on grammatical binding, Perovic and colleagues (2013) came to the conclusion that the impairment of grammatical knowledge on binding in both conditions is independent of difficulties in social interactions and pragmatics (Perovic et al., 2013).

Socio-cognitive differences between ASD and WS

Although, as discussed above, similarities between ASD and WS can indeed be found and while the social profiles of both conditions are in no way homogeneous, research consistently shows that those with WS have less socio communicative deficits than those with ASD do (e.g. Bellugi et al., 2000; Lincoln et al., 2007; Klein-Tasman et al., 2009; Lacroix et al., 2016). In general, people with WS and ASD have been shown to have opposite preferences in terms of their orientation to social vs. nonsocial information, as reported by eye tracking studies such as Riby and Hancock (2008, 2009). More specifically, in social situations, individuals with ASD tend to direct their attention inward towards themselves and prioritize information related to them as individuals, while those with WS direct their attention to others. As pointed out by Kuang (2016) in a social setting, neurotypical people rely on both systems of attention (attention to self and attention to others) in order to interact properly. This increased attention towards others may in turn help individuals with WS to preserve more emotional empathy than those with ASD can, in spite of the fact that, as discussed previously, both exhibit difficulties with

imagining mental states of others (Tager-Flusberg and Sullivan, 2000). As a consequence, individuals with WS are eager to engage socially and are highly motivated to approach familiar and unfamiliar people (Bellugi et al., 2000). In contrast, people with ASD attend much less to socially salient features and are generally reluctant to engage with others, regardless of whether they are familiar or not (Sigman et al., 2006; Riby and Hancock, 2009). Specifically, ASD and WS show distinct differences in the area of face recognition skills; people with WS are hyper-atentive to faces and reportedly perform better than mental age matched controls on standardized tests of face recognition skills, while those with ASD attend much less to faces and perform distinctly worse (Bellugi et al 1994; Kiln et al., 1999; Schultz, 2005; Tager Flusberg et al., 2006; Rose et al., 2007). The results vary, however, when emotional recognition is involved, as people with WS have more difficulty recognizing emotions from facial expressions than those with ASD do (Lacroix et al., 2009). Interestingly, the results are the opposite when subjects are asked to analyze emotion in music, with individuals with WS outperforming those with ASD (Bhatara et al., 2010), in spite of both conditions exhibiting similar affinity and interest towards music in general (Heaton et al., 1998; Bonnel et al., 2003; Heaton, 2003; Bhatara et al., 2010). In truth, enhanced musical abilities of people with WS do not concern the structural aspects of music, but instead are related to musicality and expressivity, commonly expressed through a heightened emotional responsiveness to music (Thakur et al., 2018).

Both conditions contrast as well in the management of anxiety in social settings. In both WS and ASD levels of anxiety correlate with their degree of social impairment, although those with ASD are thought to have higher levels of anxiety in general (Rodgers et al., 2012). Higher levels of restricted and repetitive behaviors correlated to higher levels of anxiety in ASD but not WS (Rodgers et al., 2012), which suggests that these behaviors may serve different functions in both conditions. Barak and Feng (2016) posited that these differences in anxiety levels correlate to social cognition, that is, it may be that the social drive of WS acts as a buffer against social anxiety, while in ASD social impairments might make them more vulnerable to anxiety (see also Frigeria et al., 2006). White et al., 2010).

Regarding language, and particularly, language use in social settings, differences between conditions can be observed as well. As noted above, generally individuals with ASD show a more marked overall deficit in communicative use of language, while those with WS show certain strengths including ample, descriptive vocabularies, often with elaborate attention to detail and expressive phrases that are full of emotion and affect (Udwin and Yule, 1990; Bellugi et al., 1994; Bellugi et al., 2000; Reilly et al 2004; Brock et al., 2007; Gothelf et al., 2008; Fishman et al., 2011;). Still, there are indications that the processes involved in acquiring and using these characteristics are irregular, as can be seen from research exploring atypical activation of semantic networks after pointing (Lukács et al., 2004). By contrast, in ASD, vocabulary progresses steadily with age, but it contains a disproportionately high number of nouns and a much lower number of mental state terms when compared to typically developing children (Fein et al., 1996; Gastgeb et al., 2006; Kelley et al., 2006; Swensen et al., 2007; Tek et al., 2008). Regarding the access to implicatures (i.e. non-explicit meaning of utterances), Fishman and colleagues (2011) found that individuals with WS show larger N400 effects (N400 is an ERP component which is inversely correlated with the semantic fit of a word or phrase), suggesting that they do rely on context to infer meaning. This contrasts with the significantly smaller N400 effect found in individuals with ASD, which suggests that they make less use of contextual information when it comes to language use (Fishman et al., 2011). Other studies (e.g. Firth and Snowling, 1983; Happé 1997; Tager-Flusberg, 2003 and 2004; Harris et al., 2006; Walenski et al., 2006,) also document difficulties with comprehension of meaning from context in ASD; even individuals with high-functioning ASD show irregularities in an otherwise typical IQ profile, with significantly lower scores in comprehension tasks, such as comprehending idioms (Siegel et al., 1996; Goldstein et al., 2002). Fishman et al. (2011) highlight as well the fact that ASD individuals have been shown to rely on visual imagery instead of linguistic cues to comprehend sentences (Kana et al., 2006), while people with WS tend to rely on sentence-level context cues. Pragmatic problems, and differences between conditions, have been documented in other studies. For instance, in their comparative study of the pragmatic language profiles of children with ASD and WS, Philofsky and colleagues (2007) found that in certain areas (coherence, stereotyped language, nonverbal communication, and social relations scales) individuals with WS performed better than subjects with ASD, although in other areas (inappropriate

initiation, use of context, and interests scales) the impairment was similar. Also, WS children were rated by their parents as being slightly better than ASD individuals at communicative tasks like appropriately sequencing and referencing events for a listener, but they still had difficulties (Philofsky et al., 2007). As expected, these differences in language use between ASD and WS can be attributed to their divergent socio-cognitive profiles: after all, language is learned and used in social situations, and attention to the facial area and emotional state of the speaker, as well as interest in the interlocutor play a crucial role at these levels. Hence, Fishman and colleagues (2011) suggest that the different patterns of attention exhibited by people with ASD and subjects with WS may lead to different perceptual inputs, which in turn lead to different communicative behaviors. Likewise, the decreased sensitivity to speech prosody documented in ASD (e.g. Korpilahti et al., 2007) could explain their impaired ability to infer meaning from context, whereas the auditory hypersensitivity documented in WS (e.g. Klein et al., 1990; Blomberg et al., 2006) could account for their enhanced ability at this level (see Fishman et al. 2011 for discussion).

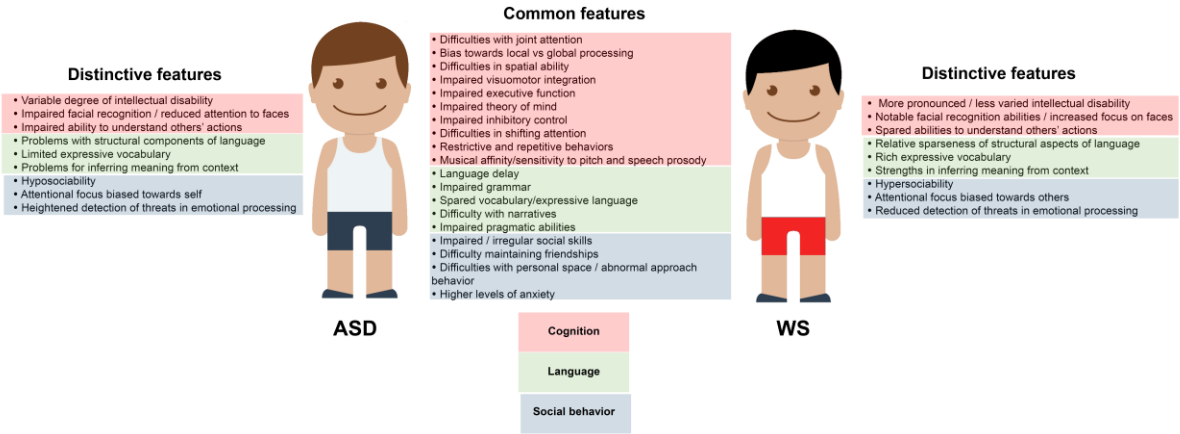

Figure 1. An overview of the socio-cognitive differences between ASD and WS.

3. Contrasting the (neuro)biological causes of the ASD and the WS abnormal socio-cognitive phenotypes

In studies of both ASD and WS, a wealth of research has focused on specific brain networks thought to be implicated in behavioral and cognitive abnormalities of both conditions. Here we provide a brief overlook of research focused on the social realm. Such networks provide a more biologically-grounded account of the similarities and differences in the socio-cognitive phenotypes of these conditions and are expected to facilitate the formulation of bridging theories linking these phenotypes to the underlying genetic factors (our focus of interest in the next section of the paper). An important outcome of the neurobiological characterization of ASD and WS is that similar irregularities in brain structures and their functional connectivity do not always translate to similar behaviors. As research repeatedly shows, what may look like a similar impairment at the neurobiological level can translate to a completely different trait at the phenotypic level. Overall, studies of WS and ASD consistently provide additional evidence of the brain's flexibility and its ability to adapt its connections and functions when irregularities and deficits arise.

Socio-cognitive similarities in ASD and WS: explanatory hypotheses

Regarding the associations between irregularities in certain brain networks and some core social deficits found in both ASD and WS, four networks are worth considering. The first is the default mode network, associated with various elements of social cognition, which includes the medial prefrontal cortex (mPFC), the posterior cingulate cortex (PCC), the precuneus, the inferior parietal lobes (IPL), and medial temporal regions; its functional connectivity has been found to be irregular in ASD (Assaf et al., 2010; Lynch et al., 2013) as well as WS (Sampaio et al., 2016). Even more relevant is the second

network, namely, the social brain network, which includes the superior temporal sulcus (STS), the anterior cingulate cortex (ACC), the medial prefrontal cortex (mPFC), the inferior frontal gyrus (IFG), and the anterior insula and the amygdala. Research has uncovered atypical connections and irregularities in this circuitry in both ASD (Gotts et al., 2012; Kennedy and Adolphs, 2012) and WS (Barak and Feng, 2016). Also of interest is the circuitry involved in self-representation, which includes the mPFC, the PCC/precuneus, the temporo-parietal junction (TPJ), the anterior insula, the middle cingulate cortex (mCC), the ventral premotor cortex (PMv), and the somatosensory cortex, which have also been deemed atypical in ASD (Lombardo et al., 2010) and WS (Haas et al., 2013). Specifically, in their voxel-level study of resting state functional connectivity in ASD, Cheng and colleagues (2015) found that the medial temporal gyrus exhibits reduced cortical connectivity and increased connectivity to the medial thalamus in ASD participants, and posited that this may be related to face processing deficits and ToM impairments (Cheng et al., 2015). Cheng and colleagues (2015) also found in people with ASD a key system in the precuneus/superior parietal lobe with reduced functional connectivity, which is implicated in spatial functions, including those related to self and the environment. These elements are substrates of ToM, so it stands to reason that reduced connectivity in these regions may help to explain key elements in the social phenotype of ASD. In studies of WS, Sampaio and colleagues. (2016) also found decreased functional connectivity in the precuneus, as well as the posterior cingulate of the left hemisphere, which is also implicated in the default mode network. Finally, also of interest is the reward circuitry, including the ventral tegmental area (VTA), the striatum, the orbitofrontal cortex (OFC), the ventromedial prefrontal cortex (vmPFC) and the ACC, which have been shown to be irregular in ASD and WS (Dichter et al., 2012).

Special attention regarding the similarities between both conditions has been paid to two particular brain structures mentioned above: the amygdala and the frontal lobes. Although differences are attenuated as subjects get older (Martens et al., 2009), the amygdala is disproportionately large in both ASD and WS (Reiss et al., 2004; Schumann et al., 2004; Martens et al., 2009; Mosconi et al., 2009; Haas et al., 2012; Murphy et al., 2012; Jarvinen et al., 2013; Gibbard et al., 2018). The amygdala shows atypical functional connections to several brain regions, specifically with the ACC, the PFC, and the OFC (all of which are implicated in cognitive processing, attention, and inhibition) (Martens et al., 2008; Dedovic et al., 2009; Haas et al., 2014; Gibbard et al., 2018), and importantly, with various components of the social brain, particularly, the frontal lobes (Meyer- Lindenberg, 2005; Paul et al., 2010; Jawaid et al., 2012). A key component of the limbic system, the amygdala is a set of brain structures that support emotion and motivation, among other functions (see Rolls, 2015 for review), and is forefront in much of the research about the social (dys)function in both conditions (Stefanacci and Amaral, 2000; Meyer-Lindenberg et al., 2005; Haas et al., 2010; Paul et al., 2010; Jawaid et al., 2012; Zalla and Sperduti, 2013; Barak and Feng, 2016). The amygdala is also instrumental in the anxiety reported in both ASD and WS; a common source of this anxiety has been found to be irregular hyper- and hypo- activation of the amygdala in response to both social and non-social stimuli in both conditions (see Reiss et al., 2004; Martens et al., 2009; Jarvinen et al., 2013 for WS; see Baron-Cohen and Wheelwright, 1999; Critchley et al., 2000; Dalton et al., 2005; Corbett et al., 2009; Kliemann et al., 2012; for ASD). Specifically, Barak and Feng (2016) highlight that the amygdala is the source of the non-social anxiety and phobias which are typical of WS, pointing to deficits in the prefrontal-amygdala white matter pathways as the cause (see also Avery et al., 2012). Research on a salience network including the amygdala, the ventral striatum, the dorsomedial thalamus, the hypothalamus, and the substantia nigra (SN)/VTA has shown these functional connections to be atypical in ASD (Uddin et al., 2013) as well as in WS (Haas and Reiss, 2013). This network has been linked to attention switching, as well as detection and attention to sensory and emotional stimuli. Regarding the frontal areas, it should be noted that individuals with WS exhibit similar approach behavior to people with frontal lobe damage, suggesting that this abnormal approach behavior could be due to a lack of inhibitory control in the frontal lobe (Porter et al., 2007). Specifically, abnormal functional connectivity between the OFC and the amygdala has been linked to the uninhibited social nature in WS, since the frontal lobes have been shown to regulate and inhibit inappropriate social behavior (Meyer-Lindberg et al., 2005; Mobbs et al., 2007; Porter et al., 2007; Little et al., 2013; Barak and Feng, 2016). Similar lack of inhibitory control has also been shown in people with ASD, but in terms of abnormal personal space boundaries (Christ et al., 2007). Moreover, language deficits and language delay have been associated to a frontal lobe dysfunction and irregular functional connectivity

to the amygdala, seemingly impacting on aspects like inferencing or joint attention (Lincoln et al., 2002; Cornish et al., 2007; Martens et al., 2008; Barak and Feng, 2016).

Research has also implicated the mirror neuron system (MNS) in social dysfunction in ASD and WS (e.g. Jarvinen et al., 2013). This network includes the frontal gyrus, the STS, and the IPL (Van Overwalle and Baetens, 2009). Apart from its role in imitation, decoding, and implementation of actions (see e.g. Rizzolatti and Craighero, 2004), the MNS is also related to the social realm in terms of empathy (e.g. Gallese, 2001; Iacoboni, 2009). Reduced cortical surface area, but preserved cortical thickness, in structures implicated in the MNS have been found in WS (Ng et al., 2016). Studies of the MNS in ASD report cortical thinning in selected areas, which positively correlate to degree of social dysfunction (Hadjikhani et al., 2006; Wallace et al., 2012). These findings indicate that the common social deficits found in both WS and ASD may stem from an atypical MNS, while the distinct social drive in WS is most likely derived from systems independent of this network (Ng et al., 2016).

Finally, the HPA axis (a major neuroendocrine system resulting from the interaction between the hypothalamus, the pituitary gland, and the adrenal glands) comes into play here, because of its involvement in stress response---particularly, the response to cortisol in the amygdala, the PFC, and the hippocampus-- all of them areas implicated in situations of fear and social stress (see Martens et al, 2008; Dedovic et al., 2009; Lense and Dykens, 2013; Bitsika et al., 2015). Both ASD and WS individuals have been shown to exhibit interrupted HPA axis function (Spratt et al., 2012; Jacobson, 2014; Benítez-Burraco et al., 2016; Niego and Benítez-Burraco, 2019, among many others). This might explain in part the prevalence of anxiety in the two disorders, although as mentioned above, the anxiety generally seems to happen in separate arenas for each group: social in ASD and non-social in WS (see also Dykens, 2003; Graham et al. 2005; Rodgers et al., 2012; Lense and Dykens, 2013).

Socio-cognitive differences in ASD and WS: explanatory hypotheses

Just as the observed similarities in their respective social phenotypes happen to follow from similar dysfunctions in similar brain areas and circuits, the differences between ASD and WS in the realm of social behavior and social cognition stem from the impairment of different devices. One focus of attention has been the amygdala. As noted above, ASD and WS share similar irregularities in the amygdala. Nonetheless, some of the differences between these two conditions in the social domain can be hypothesized to lie in certain sub circuits of the amygdala, its differential response to stimuli, and/or its different connections to brain regions upstream or downstream from it. For instance, during eye gazing, a positive activation of the amygdala has been reported in participants with WS while aversive activation was reported in people with ASD (Barak and Feng, 2016). An interesting point about this activation is that, according to Barak and Feng (2016), in both cases the amygdala is hyperactivated. However, this hyperactivation takes on different forms in the two conditions. In ASD, it seems that this hyper activation is negatively valenced, creating an aversive response in those with ASD. In contrast, those with WS experience an appetitive response from this hyperactivation, making them more apt to continue the eye gaze (Riby et al, Barak and Feng, 2016). In terms of processing faces, there seems to be a difference at the level of responsiveness of the amygdala; it is hyper responsive to unfamiliar faces in ASD and hypo responsive to the same stimulus in WS (Lough et al., 2015).This might explain their distinctive response to faces and eye gaze. Accordingly, as mentioned above, the the aversive response triggered by hyperactivation of the amygdala would cause an aversive response to faces, resulting in a reduced sustained attention to the facial region, and hence, problems for facial recognition (Dalton, 2005; Kliemann et al., 2012; Strauss et al., 2009). The opposite may happen in WS: the appetitive response triggered by amygdala hyperactivation may be a motivating factor to spend more time assessing facial features (Riby et al., 2009; Barak and Feng, 2016). It has also been shown that individuals with WS have a heightened amygdala reaction to images depicting non-social fear, but a somewhat muted amygdala response to fearful social images and faces. In contrast, subjects with ASD seem to present a negative over arousal of the amygdala when looking at faces (not necessarily fearful ones) which seems to follow the pattern of their social behavior (Meyer-Lindenberg et al., 2005; Haas et al., 2009; Mimura et al., 2010; Munoz et al., 2010; Barak and Feng, 2016). Eventually, one possible (complementary) explanation of all these differences is that the neurons within the amygdala responding

to social stimuli come from different classes in each condition, e.g. glutamatergic or GABAergic (Barak and Feng, 2016). Still, it should be noted here that the results are far from straightforward and contrasting results have also been reported (e.g. Thornton-Wells et al., 2011).

Other brain areas have been implicated in the differences between ASD and WS in the socio-cognitive domain. These include the fusiform gyrus (Haxby et al., 2000), the pSTS (Allison et al., 2000; Nummenmaa and Calder, 2009), the amygdala (Adolphs and Spezio, 2006), and parietal-frontal areas such as the TPJ and the mPFC (Gallese and Goldman, 1998; Decety and Jackson, 2004; Amodio and Frith, 2006; Lieberman, 2007; Sui et al., 2013). Specifically, recent research indicates that the mPFC and the pSTS both have crucial roles in both sides of the attention spectrum, i.e., attention to self vs. attention to others, responding to each function with an activation response or an inhibition response: whereas the pSTS area is key in 'attention to others' functions, the mPFC seems to support the 'attention to self' function (Sui et al., 2013; Kuang, 2016). Not surprisingly, atypical connectivity and/or structures have been found in both the pSTS and the mPFC in both ASD and WS (Pelphrey et al., 2004; Amaral et al., 2008; Järvinen et al., 2013). Significant differences have also been found in the fusiform face area, an area in the fusiform gyrus involved in face processing. Accordingly, this area is twice the volume in individuals with WS than it is in typically developing individuals (Golarai et al., 2010, O'Hearn et al 2011; Haas and Reiss, 2012). In subjects with ASD, similar areas within the left fusiform gyrus have been shown to be hypo-activated during face processing (Nickl-Jockschat et al., 2015). Finally, differences in the structure and the connection patterns of the frontal lobes (particularly, with the amygdala) may contribute to distinctive features of the WS social phenotype, like sustained gaze towards faces, increased approachability perception for unfamiliar faces, difficulty in disengaging attention from faces, and difficulties with perceiving emotion from facial expressions (Bellugi et al., 1999; Porter et al., 2007). In contrast, it seems that altered connectivity with the frontal cortex in ASD is instrumental in decreased habituation of the amygdala response to emotional facial expressions, which correlates to their gaze aversion (Zalla and Sperduti, 2013; Swartz et al., 2013).

Finally, it is worth mentioning the role of oxytocin, a hormone known to regulate social behavior and interaction (Wojciak et al., 2012). Specifically, oxytocin inhibits the HPA axis' stress triggered activity (Neumann, 2002). Individuals with WS show an increased basal level of oxytocin, and levels of the hormone have been positively correlated with social engagement behaviors which are typical of this condition, such as tendency to approach strangers and emotionality (Dai et al., 2012). In contrast, lower levels of oxytocin have been reported in people with ASD (Modahl et al., 1998), with higher plasma concentrations of oxytocin correlating with enhanced verbal abilities (Zhang et al., 2016) and the retention of social information, like affective speech (Hollander et al., 2007). Administering oxytocin to individuals with ASD has been shown to help with attention to and retention of social cues, as well as promote eye contact (Hollander et al., 2007; Andari et al., 2010; Domes et al., 2013).

4. Contrasting gene transcriptional profiles in the blood of subjects with ASD and WS

In contrast to what is known about the neurobiological causes of socio-cognitive dysfunctions in ASD and WS, less is known about the genetic factors that might contribute to the observed similarities and differences in the socio-cognitive domain, in spite of being conditions with a clear genetic basis. This is a consequence of the indirect link between genes, at the bottom, and behavior, at the surface, with many genes affecting a single phenotype (and vice versa), but more specifically, of the pervasive problems for mapping genes to complex phenotypes, which current approaches based on genome-wide association studies (GWAS) can only partially alleviate (Goddard et al., 2016, Guo et al., 2018). As noted in the Introduction, ASD and WS are no exception;the causes of ASD are not entirely known and no robust gene-to-phenotype correlations have been established for the cognitive features of WS. Still, as also noted, it is interesting that some genetic elements have been claimed to be shared between both conditions (Newschaffer et al 2007, Jawaid et al 2012). This circumstance raises the possibility that differences in gene dosage can account for some of the opposite features exhibited by affected people in the social cognition domain. An interesting instance is the gene *OXTR*, which encodes the oxytocin receptor. As noted in the previous section, individuals with WS exhibit increased basal levels of oxytocin correlating with social engagement behaviors. Higher levels of oxytocin in WS have been

hypothesized to result from the hypomethylation (and thus, the overexpression) of *OXTR* (Haas and Reiss, 2015), seemingly as a result of the deletion of *WBSCR22*, which encodes a methyltransferase (Doll and Grzechik, 2001; Merla et al., 2002), and/or some effect of *GTF2I*, a gene also deleted in WS, which has proven to affect the reactivity to oxytocin and ultimately, sociability (Prosyshyn et al., 2017). By contrast, *OXTR* has been found to be hypermethylated (and thus, downregulated) in subjects with ASD, with this hypermethylation correlating with abnormal interconnection patterns between brain areas involved in the ASD pathogenesis, as well as with the severity of symptoms, including social cognitive deficits (Andari et al., 2020; see Maud et al., 2018 for review), particularly, with a decrease in the extent to which social information automatically captures attention (Puglia et al., 2018).

For all these reasons we conducted a comparative in vivo analysis aimed to uncover similar and dissimilar patterns of abnormal gene expression in the blood of subjects with ASD and WS. In order to determine the genes that are differentially expressed, we first performed microarray analyses of blood samples from subjects with ASD or WS and compared them with samples from neurotypical controls. Concerning WS, we compared samples from 32 patients with this condition (mean age 21.6 years, male/female ratio 50:50) with samples from 30 age–sex–race balanced controls (mean age 23.9 years, male/female ratio 50:50). Concerning ASD, we compared 32 patients with this condition (mean age 24.0 years, male/female ratio 50:50) with samples from 30 age–sex–race balanced neurotypical controls (mean age 23.9 years, male/female ratio 50:50). Total RNA was extracted from peripheral blood. All samples had RNA integrity number (RIN) values over 8. An Agilent SurePrint G3 Human GE v2 8x60K Microarray (G4851B) (Agilent Technologies) was subsequently used for analyzing transcriptome changes, as described in more detail in Kimura et al. (2019). Gene expression data can be retrieved from Gene Expression Omnibus (GSE 89594). Differentially expressed genes (DEGs) were calculated based on diagnosis, age, gender, and RIN using the Limma R package (Smyth, 2005). Genes were considered to be differentially expressed when the false discovery rate (FDR) <0.1 and the |fold change (FC)| > 1.2. The Benjamini-Hochberg procedure was used for controlling the FDR in multiple testing (Benjamini and Hochberg, 1995). All the human protein-coding genes were considered and 17446 genes were regarded as background. The list of DEGs in subjects with ASD compared to controls encompasses 242 genes (Supplemental file 1; column A). The list of DEGs in subjects with WS compared to controls encompasses 882 genes (Supplemental file 1; column B). A hypergeometric test was used to determine the significance of the overlapping DEGs between the two clinical conditions.

We found a very significant overlap ($p = 7.93E-40$) between DEGs in the blood of subjects with WS and DEGs in the blood of people with ASD. Interestingly, in spite of their opposite profile in many domains, particularly, in their socio-cognitive abilities, most DEGs exhibit a similar expression profile in the blood of ASD and WS patients, being either up-regulated or down-regulated in both conditions. Still, selected genes appear to be more strongly down- or upregulated in WS compared to ASD. Figure 2 shows the overlapping genes that are significantly upregulated in both conditions (Figure 2A), downregulated in both conditions (Figure 2B), upregulated in WS but downregulated in ASD (Figure 2C), and downregulated in WS but upregulated in ASD (Figure 2D) compared to controls (FDR <0.1, |FC| > 1.2).

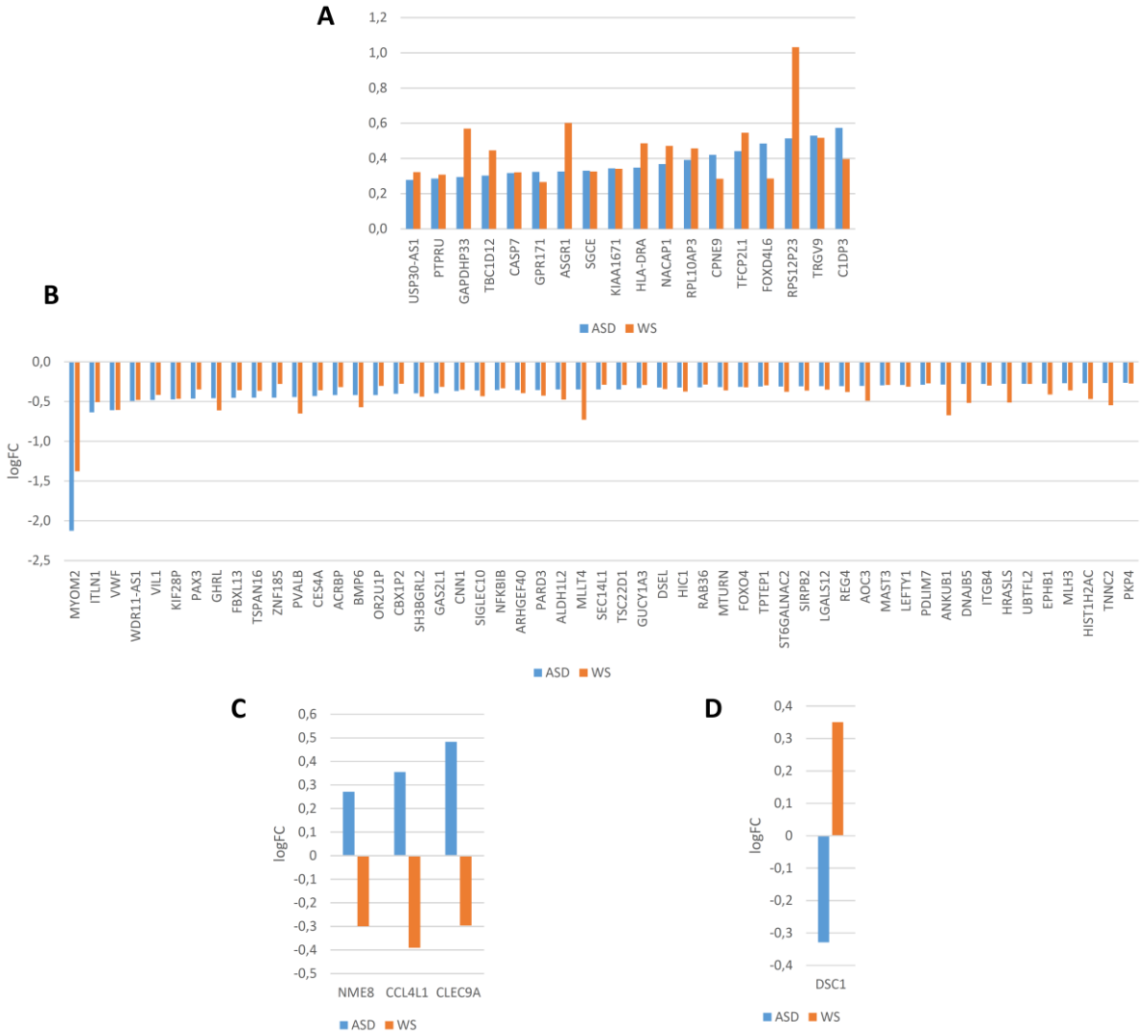

Figure 2. Abnormal expression patterns in the blood of subjects with ASD or WS. A. Genes found upregulated in both conditions. B. Genes found downregulated in both conditions. C. Genes found upregulated in ASD, but downregulated in WS. D. Genes found downregulated in ASD, but upregulated in WS. Histograms show changes in expression level of genes compared to neurotypical controls as fold changes (FC) if |FC| >1.2 and with false discovery rate (FDR<0.1). Values for ASD are colored in blue, whereas values for WS are colored in orange. Gene names are ordered according to the FC values for the ASD group.

We will now discuss these results in more detail, focusing on the potential contribution of these DEGs to the etiopathogenesis of the socio-cognitive deficits of these two conditions: whereas genes found similarly dysregulated in the blood of people with ASD and WS can be expected to account for aspects of their similarities in the social cognition phenotype, the genes that exhibit opposite expression patterns might explain aspects of their differences in the socio-cognitive domain. Differences between these two conditions could result as well from fold change differences in the expression of genes that exhibit the same abnormal trends in ASD and WS.

Functional characterization of genes of interest

Table 1 highlights the DEGs that have been associated to ASD and/or WS, that are candidates for comorbid conditions, and/or that might be involved in physiological aspects of relevance, mostly at the brain level, for the etiopathogenesis of the socio-cognitive dysfunctions observed in ASD and/or WS. For compiling this, we checked the literature via PubMed (ncbi.nlm.nih.gov/pubmed), but also other

common gene databases, like GeneCards (https://www.genecards.org/). Among the genes found upregulated in both conditions we wish highlight *GPR171* and *SGCE*. The former encodes a protein related to the G protein coupled receptor, which acts as a receptor for the neuropeptide bigLEN as part of the system regulating anxiety and fear responses, and which is expressed in the basolateral amygdala (Bobeck et al. 2017). The latter encodes a member of the sarcoglycan family and causes myoclonus dystonia, a hyperkinetic movement disorder frequently associated to social phobia (Peall et al., 2015), as well as anxiety and obsessive compulsive disorder (Saunders–Pullman et al., 2002; van Tricht et al., 2012).

Among the genes found downregulated in both ASD and WS, several genes are of interest for the socio-cognitive profile of these conditions. *DSEL* encodes a protein involved in the metabolism of chondroitin sulfate/dermatan and glycosaminoglycan which is expressed in the brain and which has been associated to bipolar disorder (Verheyen et al., 1999) and depression (Shi et al., 2011). A polymorphism in *EPHB1*, which encodes a receptor for ephrin-B family members, has been associated to attentive behavior to faces (Yang et al., 2016). *EphB1* knocked-out mice exhibit aberrant thalamic-cortical axon guidance (Robichaux et al., 2014), which, as discussed in the previous section, is a usual finding in both ASD and WS. *FBXL13* encodes a protein ubiquitin ligase associated with the Class 1 MHC mediated antigen processing and presentation and has been highlighted as one core gene involved in bipolar disorder (Xie et al., 2017). *FOXO4* encodes a fork-head transcription factor targeted by USP7, a candidate for ASD and for neurodevelopmental disorders involving speech delay and altered behavior (Fountain et al., 2019). *FOXO4* is involved dendrite development, with *FOXO4* deficiency resulting in altered dendritic morphology and abnormal spine density and positioning (Schaffner et al., 2018). As discussed below, dendrite abnormalities are regularly associated to both ASD and WS. *ITGB4* encodes one component of a receptor for laminin, an extracellular matrix protein involved in cellular interaction, motility and signaling (Tarone et al., 2000). The gene has been associated to schizophrenia and bipolar disorder (O'Brien et al., 2018). Interestingly, ITGB4 binds NRG1 as part as Neuregulin-ERBB signaling, which plays a key role in neuronal migration and differentiation, synaptogenesis, neural myelination, neurotransmission, and synaptic plasticity (Mei and Nave, 2014; Kataria et al., 2019). Interestingly too, neuregulins interact with *LIMK1*, one of the genes deleted in WS, which encodes a protein kinase involved in visuospatial cognition (Wang et al., 1998). One important neuregulin, namely NRG1, is seemingly involved in social behavior, as Nrg1(+/-) mice show reduced social activity, mimicking aspects of the social dysfunctional behaviour observed in subjects with ASD (Ehrlichman et al., 2009). *PKP4* encodes a protein involved in cellular adhesion, motility and division, as well as neurite outgrowth (Keil et al., 2013). The gene has been implicated in the sexual dimorphism observed in ASD (Zhou et al., 2019), but it has been associated as well to bipolar disorder, major depression, and schizophrenia (Witt et al., 2017). *PVALB*, which encodes parvalbumin, is expressed in GABAergic interneurons in many brain regions of interest for the ASD and WS pathogenesis, including the thalamus, the cortex, and the basal ganglia (Schwaller et al., 2002). *PVALB* has been directly related to the ASD phenotype. Accordingly, reduced transcription of *PVALB* caused by the happloinsufficiency of the ASD-candidate *ARID1B* has been hypothesized to contribute to the cognitive and social deficits observed in subjects with this condition (Jung et al., 2017). Likewise, *PVALB* expression is dysregulated in mice knocked-out for *Cntnap2*, a robust candidate for ASD (Lauber et al., 2018). Interestingly, activation of selected paravalbumin pathways is involved in triggering fear responses and induced conditioned aversion (Shang et al., 2015), which are abnormal in people with ASD or WS. Finally, *VIL1*, which encodes an actin-binding protein, has been highlighted as a risk factor for ASD (De Rubeis et al., 2014).

Also the genes found upregulated in ASD but downregulated in WS are involved in functions of interest for the socio-cognitive profile of these two conditions. Accordingly, *CCL4L1* encodes a cytokine seemingly involved in inflammatory and immunoregulatory processes (Colobran et al., 2010). The gene has been identified as a risk factor for panic disorder, with patients exhibiting increased methylation of one intron of the gene compared to controls (Ziegler et al., 2019). Whereas panic disorder is not usually described in people with WS, it has been reported in subjects with ASD, who score high in the anxiety subscale of panic (Gillott et al., 2007). Panic behaviors by individuals with ASD have also been found to be associated with a specific allele of the *OTXR* gene, which encodes the oxytocin receptor (de

Oliveira Pereira Ribeiro et al., 2018). *CLEC9A* is involved in cell reprogramming into dendritic cells (Pires et al., 2019), but also in the response to dying cells, as it triggers endocytosis (Schulz et al., 2002; Sancho et al., 2009). Finally, *NME8* encodes a protein involved in ciliary dynamics and it has been associated with Alzheimer's disease and specifically, with the abnormal cognitive processes involved in the disease. Accordingly, an *NME8*-adjacent SNP (rs2718058) seems to play a preventive role in this condition, reducing brain neurodegeneration, as well as brain atrophy and brain hypometabolism (Liu et al., 2014). Likewise, one particular SNP (rs12155159) of *NME8* has been associated to less cognitive decline on a domain-specific cognitive test score (the delayed word recall test) in people with Alzheimer's disease (Bressler et al., 2017).

Lastly, only one gene is found significantly downregulated in subjects with WS but upregulated in patients with ASD, namely, *DSC1*. This gene encodes a member of the cadherin superfamily which is involved in the formation of desmosomes, as well as in cell adhesion and signal transduction (Wang et al., 2016). The gene is expressed in the mouse corpus callosum (Miyata et al., 2015). People with WS exhibit a shorter corpus callosum with altered morphology compared to controls, and this circumstance has been hypothesized to account for some of their cognitive impairments (Tomaiuolo et al., 2002; Sampaio et al. 2013). Decreased volumes and signs of less myelination of the corpus callosum have been observed as well in people with ASD, although contradictory results can be found in the literature, suggesting that within-group differences in callosal morphology may be related to within-group differences in cognitive performance (see Travers et al., 2012 for review and discussion).

ASD ↑ / WS ↑	
CASP7	• Instrumental in apoptosis (McIlwain et al., 2015)
CPNE9	• Involved in calcium mediated intracellular processes (Creutz et al., 1998) • Plays a role in membrane trafficking (Creutz et la., 1998)
FOXD4L6	• Involved in DNA binding (Humphray et al., 2004) • FOXD4L set is recently evolved in humans, due to a duplication event unique to our species (Jackson et al., 2010)
GPR171	• Related to G protein coupled receptor, key in cell-to cell communication, hormone activity, and sensory transduction (Ji and Grossmann, 1998) • Receptor for bigLEN neuropeptide, expressed in basolateral amygdala (Bobeck et al., 2017) • Interactions in BigLEN-Gpr171 system key in anxiety and fear behavior (Bobeck et al. 2017).
HLA-DRA	• Influential in the immune system (Charron et al., 1979) • HLAB *07 allele significantly associated with ASD (Al Hakbany, et al, 2014) • HLA-B*13:02 allele significantly increased in ASD (Puangpetch et al., 2015) • HLA DPB1* 1501 allele shows a pronounced protective effect on susceptibility to ASD (Nudel et la., 2019)
PTPRU	• Regulates differentiation and cell growth (Gonzalez-Brito and Bixby, 2009) • Key in early neural development in mice (Gonzalez-Brito and Bixby, 2009) • Expressed in meso-diencephalic dopamine neurons and potentially implicated in the metabolism of dopamine (Jacobs et al. (2009)
SGCE	• Instrumental in linking actin cytoskeleton to extracellular matrix (Grabowski et al., 2003) • Associated with calcium ion binding (Xio et la., 2017) • Has a brain-specific isoform, highly expressed in Purkinje cells and neurons in the cerebellar dentate nucleus (Xiao et al, 2017) • Carriers of mutations in the gene shown to have higher incidence of psychiatric disorders such as anxiety and panic disorder (Peall et al., 2015)
TBC1D12	• Linked to endocytic recycling as well as cytokinesis (Oguchi et al., 2017) • Modulates neurite outgrowth of PC12 cells (Oguchi et al., 2017)
TFCP2L1	• Involved in establishing and maintaining pluripotency in embryonic stem cells (Wang et al., 2019) • Plays a role in regulation of the cell cycle (Taracha et al, 2018) • Implicated in Alzheimer's disease (Taracha et al., 2018)
ASD ↓ / WS ↓	
ALDH1L2	• Key for the maintenance of mitochondrial morphology and the energy balance of cells (Sarret et al., 2019) • Linked to neuro-ichthyotic syndromes, which cause dysfunction in lipid metabolism, glycoprotein synthesis, and other irregularities in facial morphology and intracellular vesicle trafficking (Sarret et al., 2019)
AOC3	• Linked to leukocyte trafficking (Pannecoeck et al., 2015) • Associated with diabetes (Pannecoeck et al., 2015)
ARHGEF40	• Regulates types of cytoskeletal reorganization, binding to keratin filaments through various sites (Fujiwara et al. 2019)
	• Slows collective cell migration by way of Rho-ROCK pathway (Isozaki et al., 2020) • Through involvement with Rho-ROCK pathway, it is implicated in facets of cognitive machinery including amelioration of detrimental effects of traumatic brain injury, improving synaptic connections and ultimately enhancing functional recovery in patients (Mulerkar et al., 2017)
BMP6	• Associated with MAPK signaling pathway, which is key in embryonic development of the central nervous system, neuronal physiology, and ultimately behavior (Chen et al., 2018) • Associated with ASD through MAPK signaling pathway (Vithayathil et al., 2018) • Linked to various neuro-cardio-facio-cutaneous syndromes (Vithayathil et al. 2018).
CES4A	• Encodes an enzyme involved in detoxifying drugs from neural tissue and cerebrospinal fluid (Yao et al., 2017) • Involved in E2F transcription factor network, responsible for activating and repressing transcription and regulating cell death (Dimova and Dyson, 2005) • Located in specific regions of the brain, including the cerebellum (Yao et al., 2017)
DNAJB5	• Involved in molecular folding/unfolding and chaperone binding (Cheetham and Caplan, 1998; Telang, 2010) • Potentially involved in stress regulation (Telang, 2010)
DSEL	• Expressed in the brain (Verheyen et al. 1999) • Implicated in bipolar disorder (Verheyen et al. 1999) • Implicated in early onset of major depressive disorder (Shi et al. 2011)
EPHB1	• Codes a receptor for ephrin-B family members, which play a role in various developmental processes in the nervous system (Homman-Ludiye and Kwan, 2017) • Related to the eph/ephrin signaling pathway, instrumental in guiding neuron projections, and the neurons themselves during embryonic development (Homman-Ludiye and Kwan (2017) • Members of the same gene family (e.g. EphB2) have been associated with ASD in recent GWAs studies (Pinto et al., 2010; Krishnan et. al., 2016) • A polymorphism of this gene is significantly associated to modulating attention to faces (Yang et al., 2016)
FBXL13	• Acts as a protein ubiquitin ligase, associated with the Class 1 MHC mediated antigen processing and presentation (Xie et al., 2017) • Implicated as one of the four core Inh genes in bipolar disorder (Xie et al., 2017)
FOXO4	• Implicated in growth and differentiation, but also in insulin signaling pathway (Schaffner et al., 2015) • Is targeted by the ASD-candidate USP7 (Fountain et al., 2019). • Linked to a neurodevelopmental disorder characterized by speech delays, altered behavior, and neurological irregularities (Fountain et al., 2019) • Upregulated by puerarin, which impedes vascular dementia by improving memory and learning (Zhang et al., 2015) • Foxo4 downregulation impairs autophagy in developing neurons of the hippocampus in adult mice (Schaffner et al., 2018) • Foxo4 deficiency leads to altered dendritic morphology, spine density, and spine positioning in neurons (Schaffner et al., 2018).
GAS2L1	• Involved in cytoskeleton assembly and possibly, in interactions between microtubules and microfilaments (Goriounov et al., 2003)
	• Related to the ectoderm differentiation pathway, which gives rise to major structures including the central nervous system and neural crest (Goriounov et al., 2003)
GHRL	• Encodes a preproprotein that yields two peptides: Ghrelin, which plays a role in hunger, reward perception, gastrointestinal mobility, and glucose-stimulated insulin secretion; Obestatin, the other protein, is thought to regulate glucose metabolism (Tyra et al., 2019).
GUCY1A3	• Associated with the cerebrovascular condition known as Moyamoya Disease (Wallace et al., 2016). • Instrumental in the nitric oxide/cGMP signaling pathway (Kessler et al., 2017), a pathway linked to olfactory learning and memory in insects (Ikeda and Yoshino, 2018) • Reduced Gucy1A3 in mice causes neurite retraction of medial ganglionic eminence cells which eventually form parts of the basal ganglia (Mandal et al., 2013)
HIC1	• As part of the Wnt pathway, it is involved in cell proliferation, cell differentiation, and cell migration, most importantly during the development of the nervous system (Zhang et al., 2014) • Involved in Wnt signaling pathway, which has been connected to the pathogenesis of ASD (Freese et al, 2010; Zhang et al., 2014) and WS via *FZ9* (a gene within the WS region which encodes a Wnt receptor) (Freese et al., 2010)
HIST1H2AC	• Encodes a member of the H2A histone family, responsible for structuring the nucleosome by compacting and wrapping DNA into chromatin (Albig and Doenecke 1998)
ITGB4	• Encodes a receptor for laminin and plays a critical role in cellular interactions, particularly in motility and signaling during development (Jaakkola et al., 1993) • Implicated in schizophrenia and bipolar disorder, likely due to its involvement with multiple neuronal and stem /precursor cells (O'Brien et al., 2018) • Expressed in neurons and apt to be responsible for neuronal survival and apoptosis signal pathways (Jaakkola et al., 1993)
KIF28P	• Codes a gene in the kinesin protein family, crucial for cellular morphology and function (Miki et al., 2005) • Specifically involved in vesicle-mediated transport and also related to microtubule binding/ motor activity (Miki et al., 2015)
LEFTY1	• An asymmetrically expressed brain marker affected by fibroblast growth factor proteins and implicated in left-right brain asymmetry (Neugebauer and Yost, 2013) • One of the genes found hypermethylated in patients with schizophrenia (Lee and Huang, 2016)
MAST3	• Part of the microtubule-associated serine/threonine kinase family (Garland et al., 2008) • Differentially expressed in the striatum, the hippocampus, and the cerebral cortex of the rat brain (Garland et al., 2008)
MLH3	• Responsible for maintaining the integrity of the genome during DNA replication and after meiotic recombination (Markadona et al., 2015) • Plays a role in DNA mismatch repair, and a polymorphism of this gene has been associated with male infertility (Markandona et al., 2015).
MLLT4	• Related to signaling and organizing cell junctions during embryogenesis (Ikeda et al., 1999) • Related to cleft lip/palate ectodermal dysplasia syndrome (Lough et al., 2017). • Localized to the nucleus of hippocampal and cortical neurons (VanLeeuwen et al., 2014)
	• Accumulates in dendrites in a way that suggests it is trafficked from the cytosol to synapses (VanLeeuwen et al., 2014) • Regulates presynaptic differentiation of hippocampal neurons (Toyoshima et al., 2014)
MTURN	• Essential for neural differentiation during primary neurogenesis (Martinez-De Luna et al., 2013) • Overexpression of this gene stimulates neurogenesis, while downregulation inhibits neuronal progenitor differentiation, ultimately leading to neural plate expansion (Martinez-De Luna et. al., 2013).
PARD3	• Plays a role in asymmetrical cell division and also directs polarized cell growth (Gao et al., 2018) • Crucial in neural tube closure (Hapak et al., 2018). • Contributes to the development of radial glial progenitors (RGPs), which are involved in the development the cortex (Liu et al., 2018) • Associated with epilepsy among other conditions (Liu et al., 2018)
PAX3	• Expressed during embryonic development in the neural crest (Su et al., 2016) • Contributes to neural stem cell development (Sudiwala et al., 2019) • A candidate for Waardenburg syndrome, a clinical condition entailing sensorineural hearing loss and developmental delay (Tassabehji et al., 1992; Chen et al., 2010) • Associated with gastrointestinal problems in ASD (Wang et al., 2018)
PDLIM7	• Involved in cytoskeletal interaction (Kremery et al., 2010) • A related gene, *LIM*, shows significant increased expression in bipolar patients as well as those with schizophrenia and major depression (Kato et al., 2005)
PKP4	• Codes a 'armadillo-like' protein involved in intercellular adhesion, motility, cell division, and neurite outgrowth through control of GTPases (Keil et al., 2013) • A potential factor contributing to the downregulation of activities related to transport of synaptic vesicles as well as neurotransmitter release (Navarro et al., 2017) • Implicated in the sexual dimorphism of ASD, seemingly through sex-biased post-translational phosphorylation (Zhou et al., 2019) • Associated to bipolar disorder, major depression, and schizophrenia (Witt et al., 2017)
PVALB	• Expressed in GABAergic interneurons from the thalamus, the cortex, and the hippocampus and projecting to the basal ganglia (Schwaller et al., 2002) • Reduced *PVALB* expression via the ASD-candidate *ARID1B* may be instrumental in the abnormal cognitive and social behaviors associated with ASD (Jung et al., 2017) • Altered parvalbumin levels found in ASD patients with mutations in the ASD-candidate *CNTNAP2* (Lauber et al., 2018) • Decrease in *PVALB* expressing interneurons found in the prefrontal cortex of people with ASD, with a potential impact on excitation/inhibition balances (Hashemi et al., 2017) • Parvalbumin neurons project to the amygdala via the parabigeminal nucleus (Shang et al., 2015) • Activation of parvalbumin neurons is key in triggering fear responses and induced conditioned aversion (Shang et al., 2015). • Parvalbumin neurons in the mPFC are involved in goal-driven attentional processing (Kim et al., 2016) • Increased methylation of *PVALB* found in the hippocampus of individuals with schizophrenia (Fachim et al., 2018)
RAB36	• Involved in GTP binding and activity, as well as protein transport and neurite outgrowth (Kobayashi et al., 2014)
REG4	• Related to calcium binding (Azman et al., 2011) • Linked to regeneration, cell growth, apoptosis resistance, and cell adhesion (Azman et al., 2011)
SEC14L1	• Involved in an intracellular transport system (Chinen et al., 1996).
SH3BGRL2	• Implicated in neural development (Tong et al., 2016)
TSC22D1	• Codes a transcriptional repressor (Gluderer et al., 2010) • Implicated in the sub regulatory network of Alzheimer's disease in the hippocampus, a region that undergoes severe loss of volume in people with the condition (Vargas et al., 2018)
TSPAN16	• Mediates signal transduction, playing a role in cell development, motility, activation, and growth (Puls et al., 1999) • Involved in cell activation and adhesion in neural tissues (Puls et al., 1999).
VIL1	• Involved in cytoskeletal remodeling (Khurana et al., 2010) • A risk factor for ASD, probably through effects on chromatin remodeling, which ultimately leads to altered transcription and impaired synaptic function (De Rubeis et al., 2014)
VWF	• Involved in hemostasis and protein transport in the blood (Krumm et al., 2015) • A ASD candidate (Krumm et al., 2015). • Expressed differently in gray and white matter of the visual cortex, hippocampus, precentral gyrus, postcentral gyrus, and the rhinal cortex (Mbagwu and Filgueira (2020) • Higher VWF activity associated with increased risk of dementia (Wolters et al. 2018)
WDR11-AS1	• Implicated in certain types of neurodegeneration (Holman et al., 2014) • Several SNPs associated with enhancers in fetal brain tissue (Holman et al., 2014) • Involved in the development of olfactory neurons (Holman et al., 2014)
ZNF185	• Involved in remodeling the cytoskeleton and polarizing cells after DNA damage (Smirnov et al., 2018)
ASD ↑ / WS ↓	
CCL4L1	• Potentially associated to inflammatory and immunoregulatory processes (Colobran et al., 2010) • A risk gene for panic disorder (Ziegler et al., 2019)
CLEC9A	• Involved in the development of dendritic cells (Pires et al., 2019)
NME8	• Associated with abnormal cognitive processes in Alzheimer's disease (Rosenthal and Kamboh, 2014) • An *NME8*-adjacent SNP (rs2718058) plays a preventive role in Alzheimer's disease, particularly in the hippocampus (Liu et al., 2014) • One SNP (rs12155159) of *NME8* associated with reduced cognitive decline in patients with Alzheimer's disease (Bressler et al., 2017)
ASD ↓ / WS ↑	
DSC1	• Encodes a member of the cadherin superfamily involved in the formation of desmosomes as well as in cell adhesion and signal transduction (Wang et al., 2016) • Expressed in the corpus callosum

Table 1. Summary list of the genes found dysregulated in subjects with ASD or WS that have a potential role in the etiopathogenesis of these conditions.

Gene Ontology analyses

We also conducted gene ontology analyses of the sets of DEGs, whenever possible, to know more about possible biological functions that might be found similarly or differentially altered in ASD and WS, particularly, in connection with their distinctive socio-cognitive profiles. Functional enrichment analyses were performed with Enrichr (amp.pharm.mssm.edu/Enrichr; Chen et al., 2013; Kuleshov et al., 2016). We considered biological processes, molecular functions, cellular components, or human pathological phenotypes as enriched if their $p<0.05$. Because the number of genes showing opposite expression patterns was too small, ontology analyses were performed only for genes found either upregulated (Figure 3) or downregulated (Figure 4) in the blood of subjects with ASD or WS compared to controls. We found that these two set of genes are significantly related to processes, functions, cellular components, and pathological phenotypes of interest for the ASD and the WS etiopathogenesis, with some interesting differences between both sets also existing.

Accordingly, genes that are found upregulated in both conditions compared to controls are significantly enriched in molecular, cellular, and biological processes important for neuron function, particularly dendrite extension (GO:1903861; GO:1903859). Multiple studies have pointed to alterations in dendrite growth, number, and morphology as a key aspect of the pathophysiology of ASD, with most alterations involving a generalized reduction in dendrite size and number, as well as an increase in spine densities with immature morphology (see Gilbert and Man, 2017, Martínez-Cerdeño, 2017, Joensuu et al., 2018 for selected reviews). Likewise, the neurons of animal models of selected genes within the WS region also exhibit an anomalous dendrite morphology. Accordingly, abnormal spine morphology, as well as abnormal synaptic function resulting in enhanced long-term potentiation (LTP) and altered fear responses and spatial learning, are observed in *Limk1*-knockout mice, supporting a role of this gene in the regulation of cofilin and actin cytoskeleton (Meng et al., 2002). Similarly, *FZD9* regulates dendritic spine formation in hippocampal neurons via its effect on Wnt5a signaling (Ramírez et al., 2016). Finally, neurite length is greater in mice lacking one copy of *Gtf2i*, another of the genes located within the chromosomal fragment deleted in WS (Deurloo et al., 2019). Additionally, genes upregulated in both conditions ASD and WS are preferentially associated to aspects of the immune response, particularly, to MHC class II complex function (GO:0032395; GO:0023026; GO:0042613). MHC genes have been found to be dysregulated in skin fibroblasts from people with WS (Henrichsen et al., 2011). Regarding ASD, because of the important role of the MHC in brain development and plasticity, changes in MHC expression resulting from mutations and/or immune dysregulation have been hypothesized to contribute to the altered brain connectivity and function typically found in subjects with this condition (see Needleman and McAllister, 2012 for review). Population-based epidemiological studies have found an association between ASD and MHC complex haplotypes (reviewed by Gesundheit et al., 2013). Additionally, genes upregulated in both ASD and WS are significantly associated with processes related to cell survival via autophagia, as in autophagosome assembly (GO:2000785), and to cell death via apoptosis, mostly in connection to cysteine-type endopeptidase activity (GO:0008635, GO:0097200, GO:0097153). In neurons, autophagy is involved in axon guidance, dendritic spine development and pruning, and synaptic plasticity (Hwang et al. 2019); altered autophagy has been associated as well to neurodegeneration (see Lee, 2012 for review) and to ASD (Hwang et al., 2019). Apoptosis is also crucially involved in brain development and wiring, and pathological activation of apoptotic death pathways resulting in neural cell death has been equally associated to ASD (Wei et al. 2014), particularly, endoplasmic reticulum stress resulting in apoptosis (Dong et al., 2018). Interestingly, genes upregulated in both ASD and WS are preferentially associated to the endoplasmic reticulum membrane (GO:0071556), as well as the endocytic vesicle membrane (GO:0030669; GO:0045334), the endosome membrane (GO:0031902) and the endoplasmic reticulum to Golgi vesicle membrane (GO:0012507). In a similar vein, increased apoptosis has been observed in animal models of WS, particularly, after knocking out several of the genes within the WS fragment, specifically, *WSTF* (Barnett et al., 2012) and *FZD9* (Zhao et al., 2005). Genes upregulated in both ASD and WS are also enriched in proteins involved in signal transduction activities, particularly receptor activity, mostly linked to G-protein (GO:0001608; GO:0045028) and protein tyrosine phosphatase signaling (GO:0007185; GO:0005001; GO:0019198).

Finally, it is worth highlighting that these genes are significantly related to neuropsychiatric conditions like depression (HP:0000716), obsessive-compulsive behavior (HP:0000722), and anxiety (HP:0000739), all of which are comorbid or share core symptoms with ASD (Matson and Nebel-Schwalm, 2007; Vannucchi et al., 2014; Rossen et al., 2018). As discussed in the previous section, anxiety is also prevalent within people with WS, although depression is also occasionally diagnosed in affected people (Stinton et al., 2010; 2012; Royston et al., 2017).

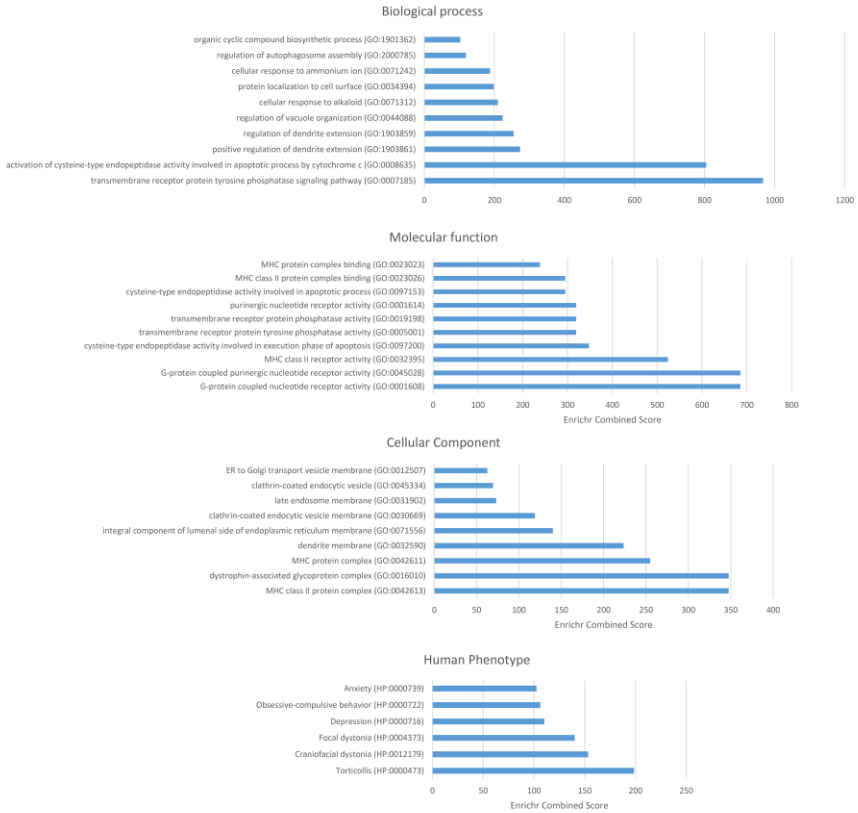

Figure 3. Functional enrichment analysis according to Enrichr of the set of genes that are significantly upregulated in the blood of subjects with WS or ASD compared to neurotypical controls. The figure shows the enrichment in biological processes, molecular function, cellular components, and human pathological phenotypes (from top to bottom). Only the top-10 functions have been included and only if their $p<0.05$. The p-value was computed using Fisher's exact test. Enriched categories are ordered according to their Enrichr Combined Scores. This is a combination of the p-value and the z-score calculated by multiplying the two scores (Combined Score = ln(p-value) * z-score). The z-score is computed using a modification to Fisher's exact test and assess the deviation from the expected rank. The Combined Score provides a compromise between both methods and it is claimed to report the best rankings when compared with the other scoring schemes. See http://amp.pharm.mssm.edu/Enrichr/help#background&q=5 for details.

As shown in Figure 2, most genes upregulated in ASD and WS compared to controls exhibit similar fold changes in both conditions. However, some of them are more strongly upregulated in WS than in ASD, particularly, *GAPDHP33*, *ASGR1* and *RPS12P23*. Interestingly, a GWA analysis has associated *ASGR1* to animal personality and coping styles, particularly to latency, duration and frequency of struggling attempts by piglets during backtests, with one SNPs showing differential expression in the hypothalamus (Ponsuksili et al., 2015). Dosage perturbation of this gene has also probed to impact negatively on neurodevelopment in zebrafish, ultimately resulting in microcephaly, thus seemingly contributing to the cognitive symptoms of the 17p13.1 microdeletion syndrome, which include intellectual disability and poor to absent speech, as well as occasional autistic features (Carvalho et al., 2014).

Regarding the genes that are downregulated in both ASD and WS compared to controls, we found that they are significantly related to muscle cell proliferation and differentiation (GO:0014842; GO:0051151), but also to growth hormone homeostasis, particularly, growth hormone secretion (GO:0060124; GO:0030252) and insulin-like growth factor binding (GO:0031994; GO:0005520). These genes are also related to aspects of brain development, particularly, synaptonemal structure (GO:0099086) and myelinization (GO:0031643). Children with ASD are known to exhibit an early generalized overgrowth (Van Daalen et al. 2007, Fukumoto et al. 2008, Chawarska et al. 2011), with postnatal overgrowth correlating with greater severity of social deficits and poorer verbal skills (Chawarska et al. 2011, Campbell et al. 2014). Significantly higher levels of several growth-related hormones have been found in children with ASD (Mills et al., 2007). Dysregulation of the overall systemic growth seems to account for the brain overgrowth also frequently observed in people with ASD, which correlates with lower functioning abilities (Sacco et al. 2015). Higher head circumference and increased brain size values are usually observed only during early childhood (Fukumoto et al. 2008, Courchesne et al. 2011, although see Raznahan et al. 2013). By contrast, children with WS typically show growth retardation, at least during their first years of life (Pankau et al., 1992; Morris et al., 1998). Still, growth hormone deficiency is rarely diagnosed (e.g. Levy-Shraga et al., 2018). Likewise, subjects with WS have smaller brain volumes compared to controls (Jernigan and Bellugi, 1990; Schmitt et al., 2001a; Reiss et al., 2004, Thompson et al., 2005 Meyer-Lindenberg et al., 2005; Jackowski et al., 2009), mostly due to a reduction of white matter (Thompson et al., 2005). Interestingly too, the insulin-like growth factor I, which is primarily involved in the regulation of the effects of growth hormone, also contributes to neural development, myelinisation, and protection (see Puche and Castilla-Cortázar, 2012 for review). Finally, the genes found downregulated in both ASD and WS are significantly associated to clinical phenotypes mostly involving an abnormal body development, like rhabdomyosarcoma (HP:0002859), supernumerary ribs (HP:0005815) or supernumerary bones of the axial skeleton (HP:0009144); or different skin problems, like white forelock (HP:0002211), aplasia cutis congenita (HP:0001057), patchy hypopigmentation of hair (HP:0011365), which are of less interest for the socio-cognitive profile of people with ASD and WS.

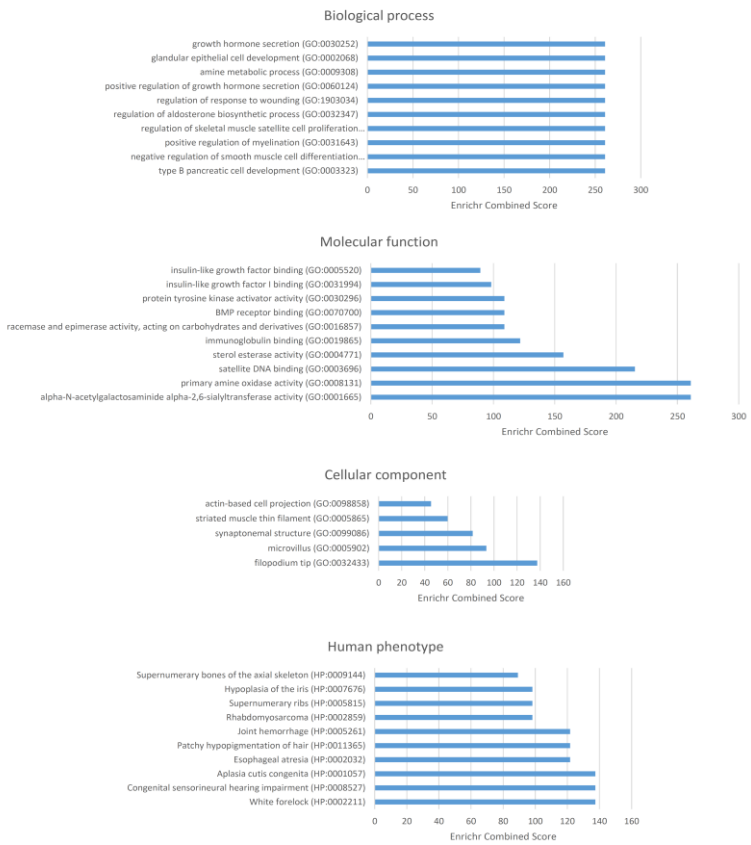

Figure 4. Functional enrichment analysis according to Enrichr of the set of genes that are significantly downregulated in the blood of subjects with WS or ASD compared to neurotypical controls. The figure shows the enrichment in biological processes, molecular function, cellular components, and human pathological phenotypes (from top to bottom). Only the top-10 functions have been included and only if their $p<0.05$. The p-value was computed using Fisher's exact test. Enriched categories are ordered according to their Enrichr Combined Scores. This is a combination of the p-value and the z-score calculated by multiplying the two scores (Combined Score = ln(p-value) * z-score). The z-score is computed using a modification to Fisher's exact test and assess the deviation from the expected rank. The Combined Score provides a compromise between both methods and it is claimed to report the best rankings when compared with the other scoring schemes. See http://amp.pharm.mssm.edu/Enrichr/help#background&q=5 for details.

As shown in Figure 2, most genes downregulated in both ASD and WS compared to controls exhibit similar fold changes in these two conditions. However, some of them are more strongly downregulated in WS than in ASD, particularly, *MLT4*, *ANKUB1*, *DNAJB5*, *HRASLS* and *TNNC2*. By contrast, *MYOM2* is more strongly downregulated in ASD than in WS. Interestingly, *DNAJB5* has been associated to response to social eavesdropping in zebrafish, particularly, to changes in the alertness status (Lopes et al., 2015).

Expression pattern analyses

Finally, we report on the expression profiles of the genes that have been found to be dysregulated in the blood of subjects with WS or ASD, with a focus on the brain, considering our interest on behavioral and cognitive features. A heat map of the expression levels of these genes in the samples of the Human tissue compendium (Novartis) (Su et al., 2004), as generated by Gene Set Enrichment Analysis (GSEA) software (http://software.broadinstitute.org/gsea/index.jsp), is shown in Figure 5. According to the Human Gene Atlas (Su et al., 2004), genes found differentially upregulated in ASD and WS are predicted to be preferentially expressed in the thalamus ($p = 0.06879$; Enrichr combined score = 37.65). By contrast, genes found differentially downregulated in both conditions are predicted to be significantly expressed in the cerebellum ($p = 0.03330$; Enrichr combined score = 23.78). We also checked the expression profile of these two groups of genes during development via the Human Brain Transcriptome Database (http://hbatlas.org). We found that all the genes that are differentially upregulated in subjects with ASD or WS are expressed in the brain thorough development, but whereas some of them are expressed at similar levels across regions, others exhibit different expression levels in different brain areas, tending to be more expressed outside the neocortex, particularly, in the thalamus, but also in the striatum and the amygdala (Supplemental file 2). Also all the genes that are differentially downregulated in subjects with ASD or WS are expressed in the brain during development. However, among these genes, those exhibiting different levels of expression in different brain areas tend to be more expressed in the cerebellum, but also in the striatum (supplemental file 2). Overall, these findings suggest that abnormal gene upregulation can be expected to impact mostly on the thalamus, whereas downregulated genes tend to be more involved in cerebellar development and function. Both groups are expected to affect striatal regions.

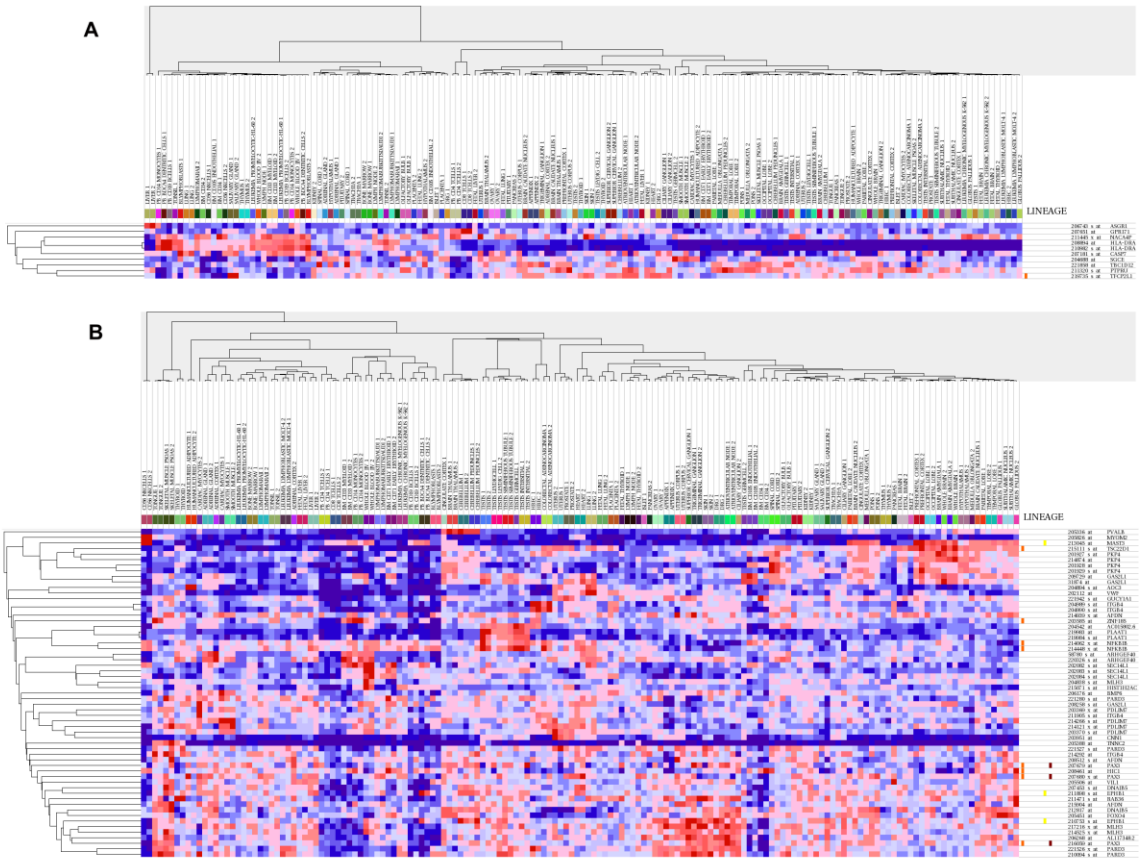

Figure 5. Heat maps of the expression levels of the set of genes that are significantly dysregulated in the blood of subjects with ASD or WS compared to controls. A. Heat map of the genes found upregulated in both conditions. B. Heat map of the genes found downregulated in both conditions. The heat maps were generated by the Gene Set Enrichment Analysis (GSEA) software using the samples of the Human tissue compendium (Novartis) (Su et al., 2004). GSEA is a computational method that determines whether an a priori defined set of genes shows statistically significant, concordant differences between two biological states. The heat maps include dendrograms clustering gene expression by gene and samples. Genes are identified by probe identifier, gene symbol, description, and gene family. See http://software.broadinstitute.org/gsea/index.jsp for details.

In subjects with WS, the thalamus shows structural and functional differences compared to neurotypical controls, including smaller volumes, reduced gray matter, and enhanced activity (Reiss et al., 2000; Schmitt et al., 2001; Tomaiuolo et al., 2002; Meyer-Lindenberg et al., 2004; Mobbs et al., 2007; Bódizs et al., 2012). Although thalamic gray matter reduction has been associated to their visuospatial impairment (Chiang et al., 2007; Campbell et al., 2009), abnormal thalamic development and function can be expected to contribute as well to other cognitive deficits, particularly language problems, because of the role of the thalamus as a sort of relay center, connecting many of the brain areas involved in language processing (Wahl et al., 2008; Murdoch, 2010; David et al., 2011). In people with ASD, in spite of previous inconsistent findings, recent research points to structural abnormalities in the thalamus too (Schuetze eal., 2016), as well as a to a disruption of local thalamic connectivity and a dysregulation of thalamo-cortical networks (Woodward et al., 2017; Tomasi and Volkow, 2019). Likewise, regarding the striatal regions, people with WS have reduced basal ganglia volumes (Jernigan et al., 1993, Bellugi et al., 1999, Reiss et al, 2000; Campbell et al., 2009). Moreover, children with Asperger syndrome show reduced volumes of the caudate, whereas high-functioning children with ASD exhibit smaller gray matter volumes in the frontostriatal regions (McAlonan et al., 2008). By contrast, adults with ASD exhibit a relative increase of both caudal putamen and pallidum, with restricted, repetitive behaviors positively correlating with surface area in bilateral globus pallidus (Schuetze et al., 2016). The basal

ganglia control different cognitive and emotional functions, including language (Booth et al., 2007; Kotz et al., 2009; Viñas-Guasch and Wu, 2017). Overall, these findings point to changes in intrathalamic and transthalamic routes as an important cause of the perceptual, motoric, interoceptive, emotional, and cognitive impairments found in ASD. Specifically, as we discussed in depth in the previous section, socio-cognitive similarities between ASD and WS may stem from the disruption of striatal and thalamic connections, particularly in the domain of face processing and theory of mind (involving the thalamus), reward behavior (involving the striatum), and attention switching (involving the striatum and the thalamus). Finally, in people with WS, the cerebellum exhibits volume alterations that can be associated with their distinctive cognitive, affective and motor features (Osório et al., 2014). This is particularly true of language, given the role of the cerebellum in language processing and its impairment in language-related pathologies (Vias and Dick, 2017; Mariën and Borgatti 2018). In a similar vein, genetic, molecular, behavioral, and neuroimaging findings support the view that in people with ASD the cerebellum develops differently at multiple levels of neural structure and function, this circumstance contributing to facets of their behavioral, cognitive and affective distinctive profile (Becker and Stoodley, 2013; Hampson and Blatt, 2015).

5. Discussion

In this paper we have adopted a comparative-molecular approach in order to gain some insights about the causes of the deficits exhibited by people with ASD or WS in the domain of social cognition and social behavior. As discussed in sections 2 and 3, the ASD phenotype widely mirrors the WS phenotype, although some overlap exists between both conditions. The same can be said of some of the genes contributing to these conditions, since genes within the WS region are also candidates for ASD (Sanders et al., 2011), and with subjects with WS having some risk of suffering from autistic behaviors (Tordjman et al., 2012, Klein-Tasman et al., 2018). However, to date most studies have focused on individual genes. For instance, one key gene within the WS region, namely *GTF2I*, which is regularly associated to the social phenotype of WS, has been found to be a risk factor for ASD (Malenfant et al., 2012). Interestingly, whereas hypersocial behavior has been observed in mice carrying a deletion of *Gtf2i*, no evidence of hyposocial behavior has been observed in mice with the *Gtf2i* duplication (Martin et al., 2017). This contradicts simplistic models of these diseases according to which socio-cognitive differences between ASD and WS might result from dosage changes in selected genes. At the very least, whole-genome analyses should be conducted in order to provide a more comprehensive view of the genetic mechanistics of the similarities and particularly, the differences between these two conditions.

In our study we have found that ASD and WS share a common pattern of gene dysregulation in the blood of affected people. Still, some of the genes showing similar trends in ASD and WS exhibit quantitative differences between conditions, with most of them being more dysregulated in WS than in ASD. Only a minor set of genes show opposite patterns of expression. We have also shown that a significant number of the dysregulated genes are involved in aspects of brain development and function (particularly, dendritogenesis) and are expressed in brain areas (particularly, the cerebellum, the thalamus and the striatum) of relevance for the ASD and the WS etiopathogenesis. Overall, the genes we highlight in the paper emerge as promising candidates for the similarities and differences between ASD and WS in their social cognition and social behavior. More research is needed before promoting these genes to key casual factors in the emergence of the observed deficits. To achieve this, developing animal models of selected candidates seems to be a promising move. In addition, further insight into detailed functional characterizations of these genes should help us gain a better understanding of their contribution to brain development and function in areas involved in social cognition.

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Supplemental data

Supplemental file 1. List of genes considered in this analysis

Supplemental file 2. Developmental expression profiles of the genes dysregulated in the blood of people with ASD or WS compared to controls according to the Human Brain Transcriptome Database.