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Original Article

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

Amy Niego and Antonio Benítez-Burraco

Abstract

Autism spectrum disorders and Williams syndrome exhibit quite opposite features in the social domain, but also 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 article, we adopted a comparative molecular approach and looked for genes that might be differentially (or similarly) regulated in the blood of subjects with these two conditions. We found a significant overlap between differentially expressed genes compared to neurotypical controls, with most of them exhibiting a similar trend in both conditions, but with genes being more dysregulated in Williams syndrome than in autism spectrum disorders. These 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 autism spectrum disorder and the Williams syndrome etiopathogenesis.

Lay abstract

Autism spectrum disorders and Williams syndrome are complex cognitive conditions exhibiting quite opposite features in the social domain: whereas people with autism spectrum disorders are mostly hyposocial, subjects with Williams syndrome are usually reported as hypersocial. At the same time, autism spectrum disorders and Williams syndrome 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 article, 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 Williams syndrome than in autism spectrum disorders. 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 autism spectrum disorder and the Williams syndrome etiopathogenesis. Overall, these genes emerge as promising candidates for the similarities and differences between the autism spectrum disorder and the Williams syndrome socio-cognitive profiles.

Keywords

autism spectrum disorders, dendritogenesis, differentially expressed genes, social cognition, Williams syndrome

Introduction

Cognitive disorders usually exhibit complex phenotypical profiles. In cases with an unclear molecular etiology, as in autism spectrum disorders (ASDs), certain genes with a high penetrance can be found in some subjects (e.g. *SHANK3* or *CNTNAP2*). Nonetheless, it is more frequently observed that many genes (and many variants of specific

University of Seville, Spain

Corresponding author:
Antonio Benítez Burraco, Área de Lingüística, Departamento de Lengua Española, Lingüística y Teoría de la Literatura, Facultad de Filología, Universidad de Sevilla, C/ Palos de la Frontera s/n, 41004 Sevilla, Spain.
Email: abenitez8@us.es

genes) contribute to the cognitive and behavioral problems exhibited by affected subjects, with each of them conferring low risk to the disorder (Geschwind & State, 2015; Gyawali & Patra, 2019). In cases with a known etiology, like Williams syndrome (WS), which results from the hemideletion of around 30 genes from chromosome 7 (Pober, 2010), robust gene-to-phenotype correlations are also difficult to establish. This is particularly true for cognitive and behavioral deficits (see Ghaffari et al., 2018; Karmiloff-Smith et al., 2012; Korenberg et al., 2000; Tassabehji, 2003 among others for discussion). The difficulty seems to stem from the fact that in most cases, these problems result 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 & Grayson, 2018a, 2018b). 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. This allows for 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 subjects, as well as achieve earlier and more precise diagnoses. For instance, several co-expression modules of genes outside the WS deletion region are found to be dysregulated in the blood of subjects with this condition and to be 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 & 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, ASDs and schizophrenia (SZ) exhibit distinctly contrasting features, from neurodevelopmental pathways to brain structure and function to cognitive (dis) abilities, including language (see Crespi & Badcock, 2008; Murphy & Benítez-Burraco, 2017 among others for discussion). As far as gene expression is concerned, there is also some evidence of mirror gene dosage profiles for each condition (Byars et al., 2014). In some cases, as observed with the gene *SHANK3*, differences can result from differences in mRNA stability caused by specific mutations, with some pathogenic alleles giving rise to SZ features and others causing ASD features (Zhou et al., 2016). Accordingly, it can be hypothesized that SZ and ASDs might share the same genetic determinants, but with some key genes exhibiting opposite patterns of abnormal downregulation 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 for complex cognitive disorders. These findings suggest that common biological mechanisms can in fact be implicated in both SZ and ASDs, despite their distinct clinical profiles and onset times. Such biological mechanisms mostly converge on aberrant synaptic plasticity and remodeling, and ultimately, on altered connectivity between brain regions (X. Liu et al., 2017). Consequently, dosage-sensitive gene expression emerges as a key etiological factor of these complex conditions. This conclusion is reinforced by the finding that copy number variations (CNVs) in the human genome impacting the same genes are a risk factor for different psychiatric disorders, especially SZ and ASDs (Zarrei et al., 2019). In some cases, mechanistic insights can be provided. For instance, altered excitatory/inhibitory balance is implicated in both SZ and ASDs, seemingly accounting for many of their distinctive cognitive features, including language deficits (see Murphy & Benítez-Burraco, 2017 for discussion). More specifically, CNVs in the gene *CYFIP1* have been associated with both conditions, with *CYFIP1* upregulation resulting in increased excitatory synapses and decreased inhibitory synapses, and with *CYFIP1* knockout giving rise to synaptic inhibition (Davenport et al., 2019).

In this article, we have adopted a comparative approach to two prevalent cognitive disorders with the aim of illuminating aspects of the problems that subjects with ASDs and WS experience with social cognition and social behavior. These problems manifest themselves in markedly opposite ways in various domains. For instance, individuals with ASDs normally exhibit difficulties with engaging in social interaction, and are generally uninterested in establishing social links with others (for a general review, see Newschaffer et al., 2007). In contrast, subjects with WS are usually friendly and eager to interact with others (for general reviews, see Bellugi et al., 2000; Doyle et al., 2004; Järvinen et al., 2013; Jones et al., 2000; Martens et al., 2009). Nonetheless, a closer examination reveals an intricate profile of similarities and differences between these two conditions (see Figure 1 for a graphical summary).

A similar picture emerges regarding the brain networks thought to be responsible for the behavioral and cognitive abnormalities observed in both conditions. Common social deficits of ASDs and WS have been associated with the dysfunction of selected networks, particularly the default mode network (Assaf et al., 2010; Lynch

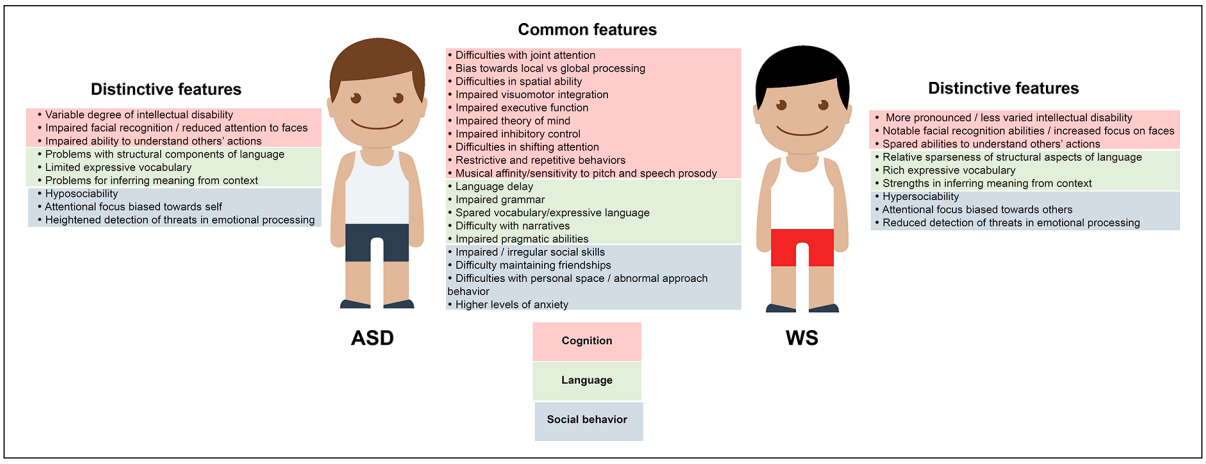

Figure 1. An overview of the socio-cognitive differences between ASDs and WS (based on Asada & Itakura, 2012; Barak & Feng, 2016; Baron-Cohen et al., 1985; Bellugi et al., 1994, 2000; Bhatara et al., 2010; Brock et al., 2007; Charman et al., 1997; Diez-Itza et al., 2016; Doyle et al., 2004; Dykens, 2003; Fein et al., 1996; Fishman et al., 2011; Freeman & Dake, 1996; Gastgeb et al., 2006; Graham et al., 2005; Happé, 1997; Happé & Frith, 1996; Järvinen et al., 2015; Järvinen-Pasley et al., 2008; Jawaid et al., 2012; Klein-Tasman et al., 2009; Klin et al., 1999; Lacroix et al., 2009; 2016; Laws & Bishop, 2004; E. Lough et al., 2015; Mervis & Becerra, 2007; Mervis et al., 2001; Perovic et al., 2013; Perovic & Wexler, 2007; Philofsky et al., 2007; Reilly et al., 2004; Rhodes et al., 2010; Riby et al., 2011; Riby & Hancock, 2008, 2009; Rodgers et al., 2012; Rose et al., 2007; Schultz, 2005; Stojanovik & James, 2006; Sullivan et al., 2003; Swensen et al., 2007; Tager-Flusberg, 2000, 2003, 2004; Tager-Flusberg et al., 2006; Thakur et al., 2018; Vivanti et al., 2016).

et al., 2013; Sampaio et al., 2016), the social brain network (Barak & Feng, 2016; Gotts et al., 2012; Kennedy & Adolphs, 2012), the self-representation network (Haas et al., 2013; Lombardo et al., 2010), reward circuitry (Dichter, Felder, et al., 2012), and the mirror neuron system (MNS; Järvinen et al., 2013). In turn, differences between ASDs and WS in the realm of social behavior and social cognition have been hypothesized to stem from differences in the development and function of other brain areas and networks. For instance, the fusiform gyrus, which is involved in face processing, is twice the volume in subjects with WS compared to neurotypical controls (Golarai et al., 2010; Haas et al., 2012; O'Hearn et al., 2011), whereas in subjects with ASDs, it is hypoactivated during face processing (Nickl-Jockschat et al., 2015). In other cases, however, we observe different outcomes of the same abnormal pattern of brain function. An interesting example of this is the amygdala, which is a key component of the limbic system supporting emotion and motivation, among other functions. Although the amygdala appears to be abnormally hyperactivated in both ASDs and WS during eye gazing, in subjects with ASDs, this hyperactivation results in an aversive response, whereas it results in an appetitive response in subjects with WS (Barak & Feng, 2016). All in all, it appears that similar irregularities in brain structure or function may or may not result in similarly abnormal behaviors at the phenotypic level. This is why we are confident that examining abnormal patterns of gene expression thought to underlie these irregularities will facilitate the formulation of bridging theories, linking abnormal socio-cognitive phenotypes to abnormal brain development and function in these two conditions, including their similarities and differences.

In accordance with the above discussion, in this article, we adopted a molecular comparative approach. We relied on the abnormal transcriptional profiles in the blood of subjects with ASDs or WS 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 etiopathogenesis of these conditions (see Bjørklund et al., 2018 or Shen et al., 2019 for ASDs). Specifically, systems biology analyses of gene expression in the blood and the brain of subjects with ASDs point to a common signature of gene dysregulation in both tissues. This allows the pathological changes in gene expression patterns in the brain to be confidently inferred from abnormal patterns of gene expression in the blood (Diaz-Beltran et al., 2016).

In this article, we determine the genes that are abnormally expressed in the blood of subjects with ASDs or WS compared to 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.

Materials and methods

Gene expression profiles in the blood of affected subjects

To determine the genes that are differentially expressed in the blood of subjects with ASDs or WS, we analyzed the publicly available Gene Expression Omnibus (GEO) dataset (accession number: GSE 89594). The GSE 89594 dataset consisted of 32 subjects with ASDs (mean age 24.0 years, male/female ratio 50:50), 32 subjects with WS (mean age 21.6 years, male/female ratio 50:50), and 30 controls (mean age 23.9 years, male/female ratio 50:50; Kimura et al., 2019). These data were obtained with Agilent SurePrint G3 Human GE v2 8x60K microarray (Agilent Technologies) from peripheral blood samples (all samples had RNA integrity number (RIN) values over 8). 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, this entailing a change in expression of 20%. A total of 20% can be regarded as a safe threshold for DEGs, if one considers that 10% of "error" is normal in an experiment (to put this differently, the FC group between 0.8 and 1.2 can be considered to be genes that do not change in their expression status). The threshold used to define DEGs is slightly less stringent than the threshold used in other similar studies (usually FDR < 0.05), but it is similar to the threshold used in our previous work on gene dysregulation in WS (e.g. Benítez-Burraco, 2000). Using the same threshold in this article is expected to provide more confident comparisons between our findings and the findings in these other papers. The Benjamini–Hochberg procedure was used to control the FDR in multiple testing (Benjamini and Hochberg, 1995). All the human protein-coding genes were considered and 17,446 genes were regarded as background. The list of DEGs in subjects with ASDs 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.

Functional characterization of genes of interest

To provide a detailed characterization of the functions performed by DEGs, we compiled information about their association with ASDs and/or WS, their involvement in comorbid conditions, and/or their role in physiological aspects of relevance (mostly at the brain level) for the etiopathogenesis of the socio-cognitive dysfunctions observed in ASDs and/or WS. To achieve this, we checked the available literature via PubMed (ncbi.nlm.nih.gov/pubmed), but also relied on other common gene databases, particularly GeneCards (https://www.genecards.org/).

Gene ontology analysis

Gene ontology (GO) analyses of the sets of DEGs were performed via Enrichr (amp.pharm.mssm.edu/Enrichr; E. Y. Chen et al., 2013; Kuleshov et al., 2016). We considered biological processes, molecular functions, cellular components, or human pathological phenotypes to be enriched if their $p < 0.05$.

Results

Contrasting gene transcriptional profiles in the blood of subjects with ASDs and WS

In contrast to what is known about the neurobiological causes of socio-cognitive dysfunctions in ASDs and WS, less is known about the genetic factors that might contribute to the observed similarities and differences in the socio-cognitive domain, despite the fact that both are conditions with a clear genetic basis. This stems from the indirect link between genes underneath and behavior at the surface, with many genes affecting a single phenotype (and vice versa). More specifically, however, it stems from the pervasive problems that arise when attempting to map genes to complex phenotypes, which current approaches based on genome-wide association studies (GWASs) can only partially alleviate (Goddard et al., 2016; Guo et al., 2018). As noted in the "Introduction" section, ASDs and WS are no exception; the causes of ASDs 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 (Jawaid et al., 2012; Newschaffer et al., 2007). This circumstance raises the possibility that differences in gene dosage can account for some of the opposite features exhibited by affected subjects in the social cognition domain. An interesting example is the gene *OXTR*, which encodes the oxytocin receptor. Subjects with WS exhibit increased basal levels of oxytocin correlating with social engagement behaviors (Dai et al., 2012). Higher levels of oxytocin in WS have been hypothesized to result from the hypomethylation (and thus, the overexpression) of *OXTR* (Haas & Smith, 2015), seemingly as a result of the deletion of *WBSCR22*, which encodes a methyltransferase (Doll & Grzeschik, 2001; Merla et al., 2002). Higher levels of oxytocin have also been attributed to effects of *GTF2I*, a gene

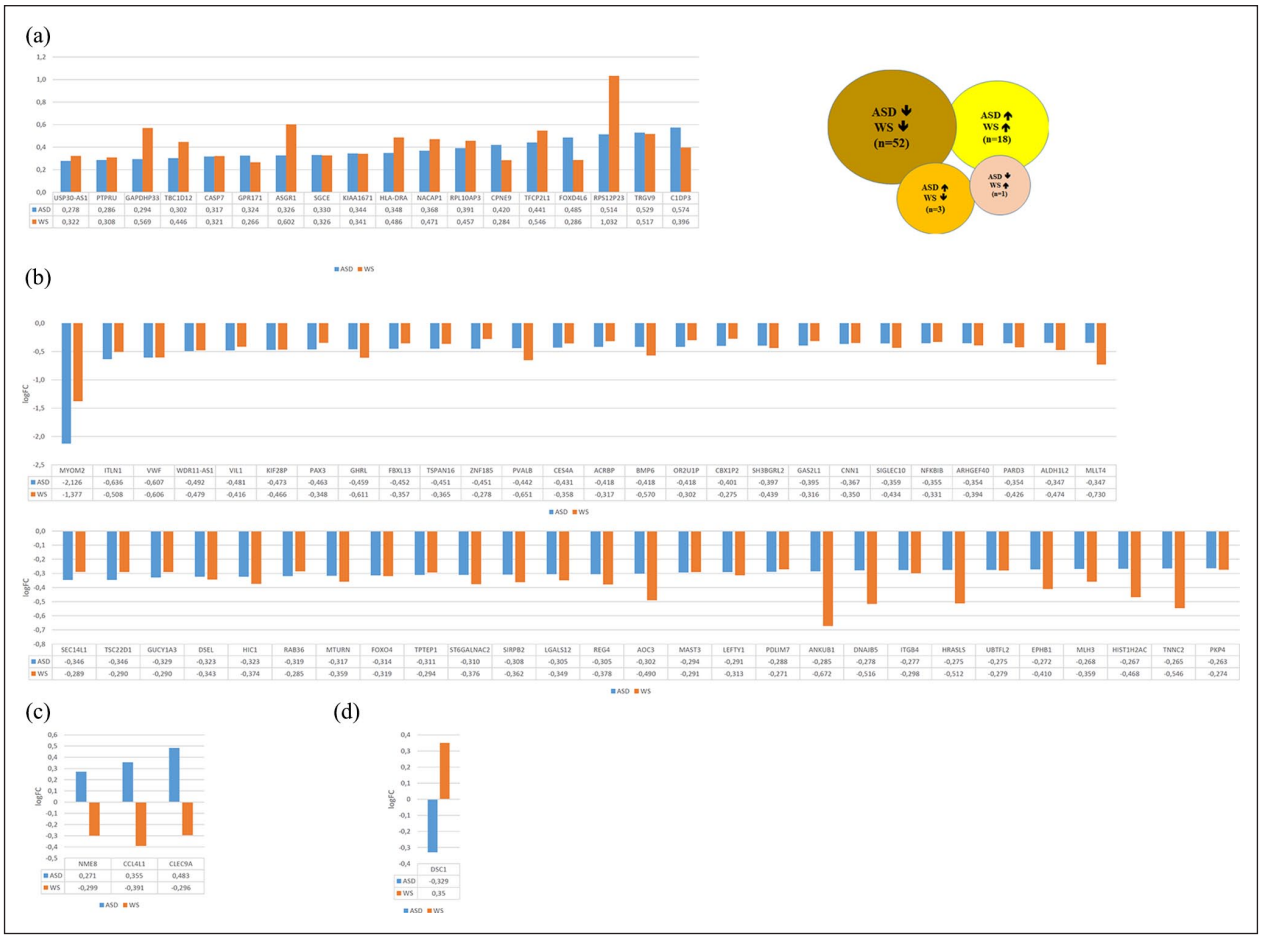

Figure 2. Abnormal expression patterns in the blood of subjects with ASDs or WS. (a) Genes found upregulated in both conditions. (b) Genes found downregulated in both conditions. (c) Genes found upregulated in ASDs but downregulated in WS. (d) Genes found downregulated in ASDs but upregulated in WS. Histograms show changes in the expression level of genes compared to neurotypical controls as fold changes (FCs) if $|FC| > 1.2$ and with false discovery rate ($FDR < 0.1$). Values for ASDs 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.

also deleted in WS, which has proven to affect the reactivity to oxytocin and ultimately, sociability (Procyshyn et al., 2017). In contrast, *OXTR* has been found to be hypermethylated (and thus, less active) in subjects with ASDs; this hypermethylation correlates to abnormal interconnection patterns between brain areas involved in the ASD pathogenesis, as well as to the severity of symptoms, including social cognitive deficits (Andari et al., 2010; see Maud et al., 2018 for review). Such hypermethylation specifically correlates to 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 at uncovering similar and dissimilar patterns of abnormal gene expression in the blood of subjects with ASDs and WS. 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 subjects with ASDs. Interestingly, despite their opposite profile in many domains—particularly in their socio-cognitive abilities—most DEGs exhibit a similar expression profile in the blood of subjects with ASDs and subjects with WS. Specifically, they are either upregulated or downregulated in both conditions. Still, selected genes appear to be more strongly downregulated or upregulated in WS compared to ASDs. Figure 2 shows the overlapping genes that are significantly upregulated in both conditions ($n = 18$; Figure 2(a)), downregulated in both conditions ($n = 53$; Figure 2(a)), upregulated in ASDs but downregulated in WS ($n = 3$; Figure 2(c)), and downregulated in ASDs but upregulated in WS ($n = 1$; Figure 2(d)) compared to controls ($FDR < 0.1$, $|FC| > 1.2$).

We then investigated whether these DEGs have the potential to contribute to the etiopathogenesis of the socio-cognitive deficits of ASDs and WS. Whereas genes found similarly dysregulated in the blood of subjects with ASDs 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 also result from FC differences in the expression of genes that exhibit the same abnormal trends in ASDs and WS.

Functional characterization of genes of interest

As shown in Table 1, most of the DEGs (50 out of 75) that have been associated with ASDs and/or WS are candidates for comorbid conditions, and/or might be involved in physiological aspects of relevance, mostly at the brain level, for the etiopathogenesis of the socio-cognitive dysfunctions observed in ASDs and/or WS. A more detailed characterization of these genes is provided in Supplemental file 2.

GO analyses

We also conducted GO analyses of the sets of DEGs to know more about possible biological functions that might be found similarly or differentially altered in ASDs and WS, particularly in connection with their distinctive socio-cognitive profiles. Because the number of genes showing opposite expression patterns was too small, GO analyses were performed only for genes found either upregulated or downregulated in the blood of subjects with ASDs or WS compared to controls. We found that these two sets of genes are significantly related to processes, functions, cellular components, and pathological phenotypes of interest for the ASD and the WS etiopathogenesis, and some interesting differences between both sets also exist. Specifically, whereas genes found upregulated in both conditions are mostly involved in dendritogenesis, genes found downregulated in both ASDs and WS contribute preferentially to myelinization. Likewise, whereas the former are mostly involved in apoptosis and autophagia, the latter seem to contribute to cell proliferation (see Figure 3 for a graphical summary). We now provide a more detailed account of these findings.

Genes that are found upregulated (Figure 4) 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 ASDs, 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 & Man, 2017; Joensuu et al., 2018; Martínez-Cerdeño, 2017 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, is observed in *Limk1*-knockout mice, supporting a role for 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). In addition, genes upregulated in both ASDs and WS are preferentially associated with aspects of the immune response, particularly with major histocompatibility complex (MHC) class II complex function (GO:0032395; GO:0023026; GO:0042613). MHC genes have been found to be dysregulated in skin fibroblasts from subjects with WS (Henrichsen et al., 2011). Regarding ASDs, 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 & McAllister, 2012 for review). Population-based epidemiological studies have found an association between ASDs and MHC complex haplotypes (reviewed by Gesundheit et al., 2013). In addition, genes upregulated in both ASDs 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 also been associated with neurodegeneration (see J. A. Lee, 2012 for review) and with ASDs (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 with ASDs (Wei et al., 2014), particularly endoplasmic reticulum stress resulting in apoptosis (Dong et al., 2018). Interestingly, genes upregulated in both ASDs and WS are preferentially associated with 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 ASDs 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

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

ASDs ↑ / 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 al., 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 et al., 1998) • Receptor for bigLEN neuropeptide, expressed in the basolateral amygdala (Bobeck et al., 2017) • Interactions in the BigLEN–Gpr171 system, key in anxiety and fear behavior (Bobeck et al., 2017)
HLA-DRA	• Influential in the immune system (Charron & McDevitt, 1979) • HLAB*07 allele significantly associated with ASDs (Al-Hakbany et al., 2014) • HLA-B*13:02 allele significantly increased in ASDs (Puangpetch et al., 2015) • HLA DPB1*1501 allele shows a pronounced protective effect on susceptibility to ASDs (Nudel et al., 2019)
PTPRU	• Regulates differentiation and cell growth (Gonzalez-Brito & Bixby, 2009) • Key in early neural development in mice (Gonzalez-Brito & Bixby, 2009) • Expressed in meso-diencephalic dopamine neurons and potentially implicated in the metabolism of dopamine (Jacobs et al., 2009)
SGCE	• Instrumental in linking the actin cytoskeleton to the extracellular matrix (Grabowski et al., 2003) • Associated with calcium ion binding (Xiao et al., 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, 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)
ASDs ↓ / 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 and 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 the 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 (Mulherkar et al., 2017)
BMP6	• Associated with the MAPK signaling pathway, which is key in embryonic development of the central nervous system, neuronal physiology, and ultimately behavior (L. Chen et al., 2018) • Associated with ASDs through the 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 & 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 & Caplan, 1998; Telang & Morris, 2010) • Potentially involved in stress regulation (Telang & Morris, 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 et al., 2017) • Related to the Eph/ephrin signaling pathway, instrumental in guiding neuron projections, and the neurons themselves during embryonic development (Homman-Ludiye et al., 2017) • Members of the same gene family (e.g. EphB2) have been associated with ASDs in recent GWASs (Pinto et al., 2010; Krishnan et al., 2016) • A polymorphism of this gene is significantly associated with modulating attention to faces (Yang et al., 2016)

(Continued)

Table 1. (Continued)

ASDs ↓ / WS ↓	
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 hub genes in bipolar disorder (Xie et al., 2017)
FOXO4	• Implicated in growth and differentiation, but also in insulin signaling pathway (Schaffner et al., 2018) • 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 (J. Zhang et al., 2015) • Foxo4 downregulation impairs autophagy in developing neurons of the hippocampus in adult mice (Schäffner et al., 2018) • Foxo4 deficiency leads to altered dendritic morphology, spine density, and spine positioning in neurons (Schäffner 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 (M. Ikeda & 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 (Y. Zhang et al., 2014) • Involved in the Wnt signaling pathway, which has been connected to the pathogenesis of ASDs (Freese et al., 2010; Y. 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 & Yost, 2014) • One of the genes found hypermethylated in patients with schizophrenia (S. A. Lee & 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 (Markandona 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 (W. Ikeda et al., 1999) • Related to cleft lip/palate ectodermal dysplasia syndrome (K. J. Lough et al., 2017) • Localized to the nucleus of hippocampal and cortical neurons (Van Leeuwen et al., 2014) • Accumulates in dendrites in a way that suggests it is trafficked from the cytosol to synapses (Van Leeuwen 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 of the cortex (W. A. Liu et al., 2018) • Associated with epilepsy among other conditions (W. A. Liu et al., 2018)
PAX3	• Expressed during embryonic development in the neural crest (X. 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 ASDs (Wang et al., 2018)

(Continued)

Table 1. (Continued)

ASDs ↓ / WS ↓	
PDLIM7	• Involved in cytoskeletal interaction (Krcmery 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 an "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 ASDs, seemingly through sex-biased post-translational phosphorylation (Zhou et al., 2019) • Associated with 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 ASDs (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 ASDs, 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 subregulatory 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 ASDs, 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) • An ASD candidate (Krumm et al., 2015) • Expressed differently in gray and white matter of the visual cortex, hippocampus, precentral gyrus, postcentral gyrus, and rhinal cortex (Mbagwu & Filgueira, 2020) • Higher VWF activity associated with increased risk of dementia (Wolters et al., 2018)
WDR11-AS1	• Implicated in certain types of neurodegeneration (Hohman et al., 2014) • Several SNPs associated with enhancers in fetal brain tissue (Hohman et al., 2014) • Involved in the development of olfactory neurons (Hohman et al., 2014)
ZNF185	• Involved in remodeling the cytoskeleton and polarizing cells after DNA damage (Smirnov et al., 2018)
ASDs ↑ / WS ↓	
CCL4L1	• Potentially associated with 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 & Kamboh, 2014) • An *NME8*-adjacent SNP (rs2718058) plays a preventive role in Alzheimer's disease, particularly in the hippocampus (Y. Liu et al., 2014) • One SNP (rs12155159) of *NME8* associated with reduced cognitive decline in patients with Alzheimer's disease (Bressler et al., 2017)
ASDs ↓ / 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

ASDs: autism spectrum disorders; WS: Williams syndrome; mPFC: medial prefrontal cortex; VWF: von Willebrand factor; SNPs: single-nucleotide polymorphisms; GTP: guanosine-5′-triphosphate; cGMP: cyclic guanosine monophosphate; MHC: major histocompatibility complex; GWASs: genome-wide association studies; MAPK: mitogen-activated protein kinase.

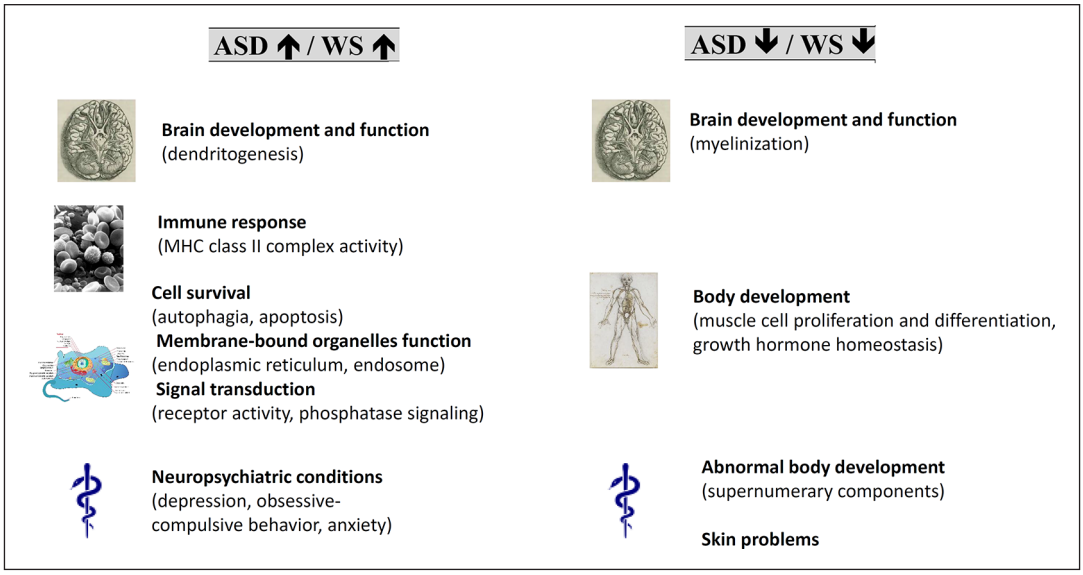

Figure 3. Graphical summary of GO analyses of genes found upregulated in both ASDs and WS (left) and downregulated in both conditions (right). Illustrations are from Wikipedia (www.wikipedia.org), and all of them are in the public domain.

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 ASDs (Matson & Nebel-Schwalm, 2007; Rosen et al., 2018; Vannucchi et al., 2014). Anxiety is also prevalent within subjects with WS, although depression is also occasionally diagnosed in affected subjects (Royston et al., 2017; Stinton et al., 2010, 2012).

As shown in Figure 2, most genes upregulated in ASDs and WS compared to controls exhibit similar FCs in both conditions. However, some of them are more strongly upregulated in WS than in ASDs, particularly *GAPDHP33, ASGR1*, and *RPS12P23*. Interestingly, a GWA analysis has associated *ASGR1* with animal personality and coping styles, particularly with latency, duration, and frequency of struggling attempts by piglets during backtests, with one single-nucleotide polymorphism (SNP) showing differential expression in the hypothalamus (Ponsuksili et al., 2015). Dosage perturbation of this gene has also been shown to negatively impact neurodevelopment in zebrafish, ultimately resulting in microcephaly. Thus, it seems that this gene contributes 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 ASDs and WS compared to controls (Figure 5), we found that they are significantly related not only 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 myelinization (GO:0031643). Children with ASDs are known to exhibit an early generalized overgrowth (Chawarska et al., 2011; Fukumoto et al., 2008; Van Daalen et al., 2007), with postnatal overgrowth correlating with greater severity of social deficits and worse verbal skills (D. J. Campbell et al., 2014; Chawarska et al., 2011). Significantly higher levels of several growth-related hormones have been found in children with ASDs (Mills et al., 2007). Dysregulation of overall systemic growth seems to account for the brain overgrowth also frequently observed in subjects with ASDs, which correlates to lower functioning abilities (Sacco et al., 2015). Higher head circumference and increased brain size values are usually observed only during early childhood (Courchesne et al., 2011; Fukumoto et al., 2008, although see Raznahan et al., 2013). In contrast, children with WS typically show growth retardation, at least during their first years of life (Morris et al., 1998; Pankau et al., 1992). 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 (Jackowski et al., 2009; Jernigan & Bellugi, 1990; Meyer-Lindenberg et al., 2005; Reiss et al., 2004; Schmitt et al., 2001; Thompson et al., 2005), mostly due to a reduction of white matter (Nir & Barak, 2020; Thompson et al., 2005), impacting selected networks such as the prefrontal–amygdala pathways (Avery et al., 2012), which might result in turn from the deletion of *GTF2I* (Barak et al., 2019). Also interesting is the fact that the insulin-like growth factor I, which is primarily involved in the regulation of the effects of growth hormone, contributes as well to neural development, myelinization, and protection (see Puche & Castilla-Cortázar, 2012 for review). Finally, the

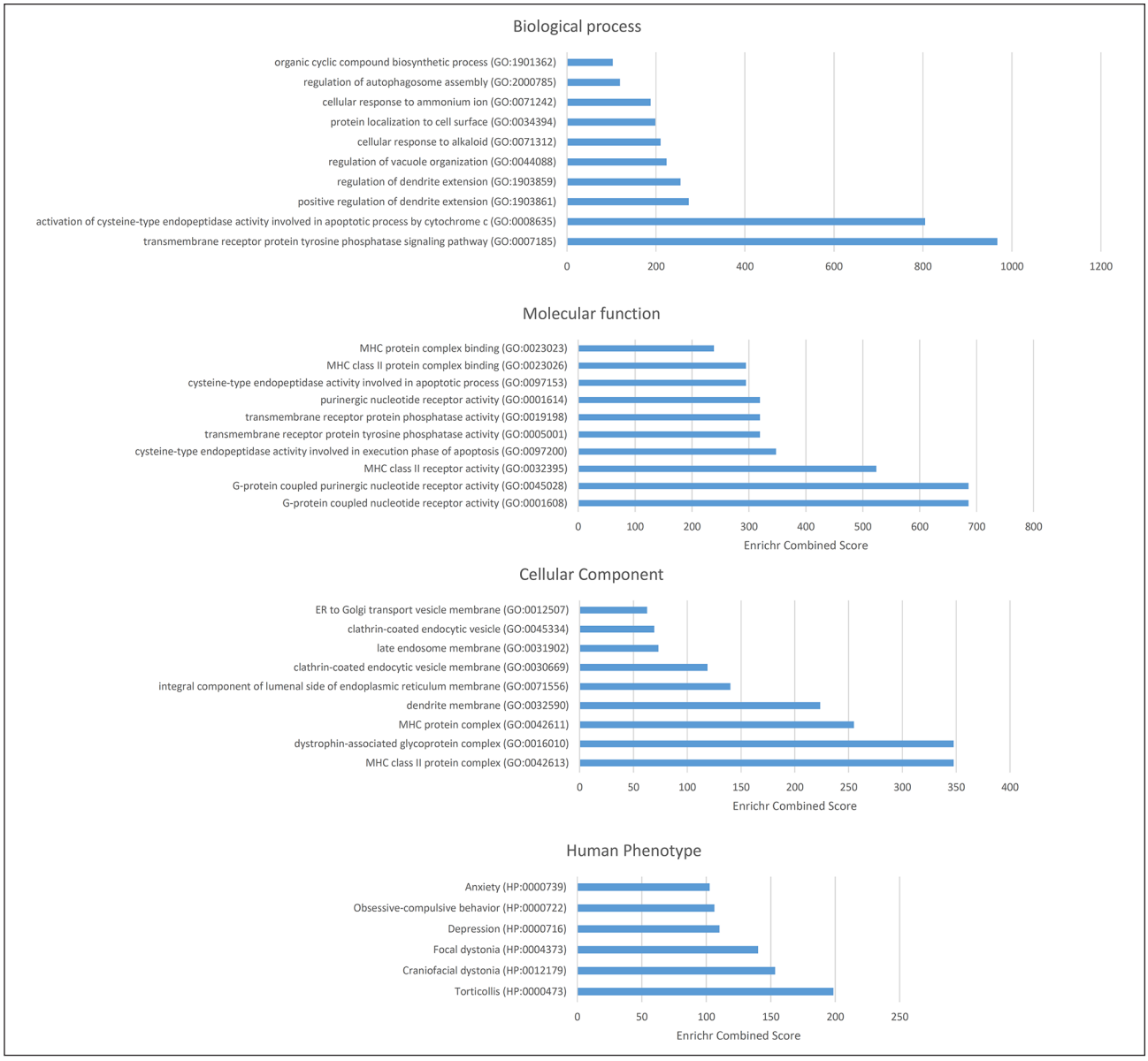

Figure 4. Functional enrichment analysis according to Enrichr of the set of genes that are significantly upregulated in the blood of subjects with WS or ASDs compared to neurotypical controls. The figure shows the enrichment in biological processes, molecular function, cellular components, and human pathological phenotypes (from top to bottom). Top-10 functions have been included 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 assesses 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.

genes found downregulated in both ASDs and WS are significantly associated with 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). These genes are also associated with different skin problems, like white forelock (HP:0002211), aplasia cutis congenita (HP:0001057), and patchy hypopigmentation of hair (HP:0011365); these are of less interest for the socio-cognitive profile of subjects with ASDs and WS.

As shown in Figure 2, most genes downregulated in both ASDs and WS compared to controls exhibit similar FCs in these two conditions. However, some of them are more strongly downregulated in WS than in ASDs, particularly

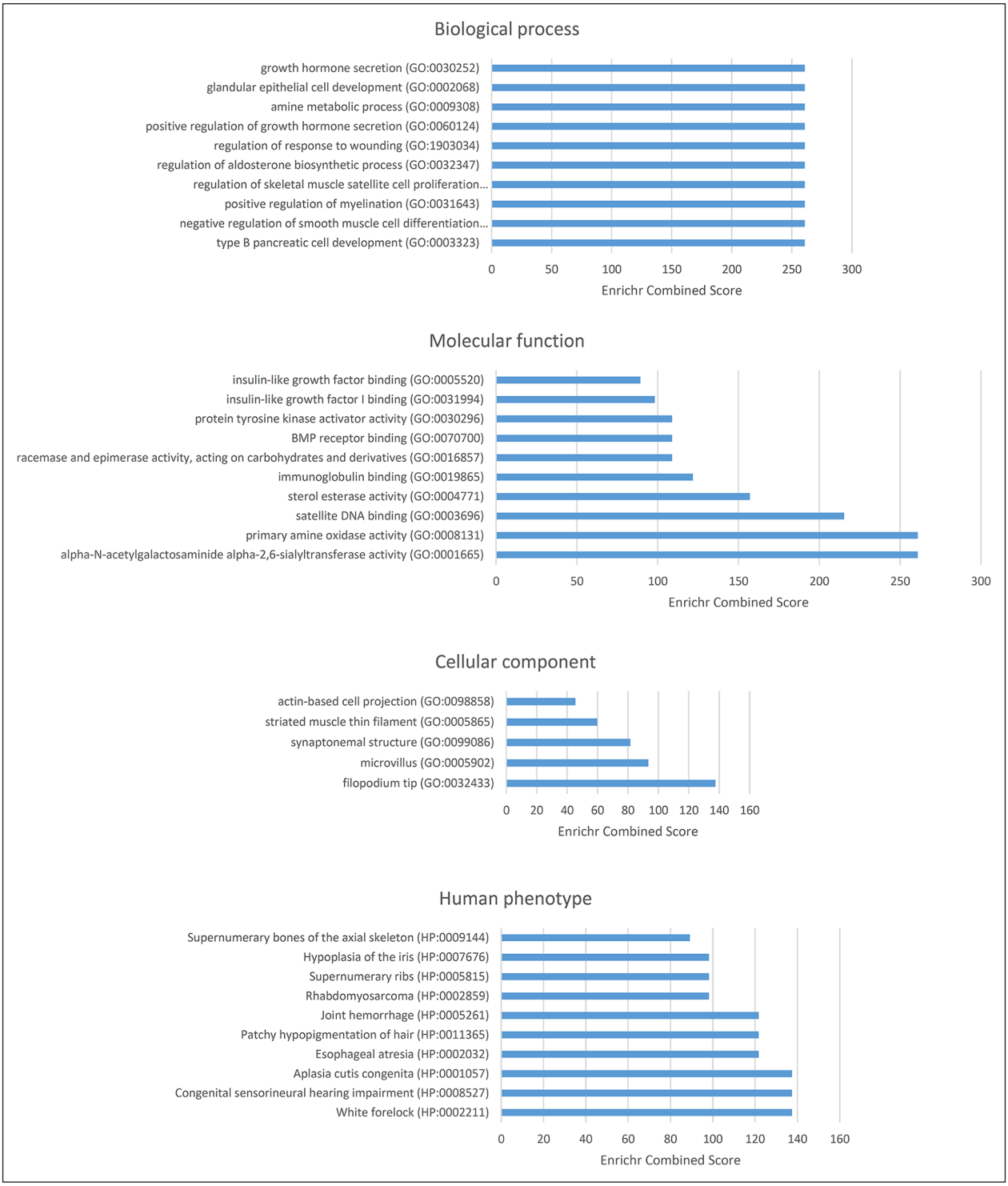

Figure 5. Functional enrichment analysis according to Enrichr of the set of genes that are significantly downregulated in the blood of subjects with WS or ASDs compared to neurotypical controls. The figure shows the enrichment in biological processes, molecular function, cellular components, and human pathological phenotypes (from top to bottom). Top-10 functions have been included 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 assesses 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.

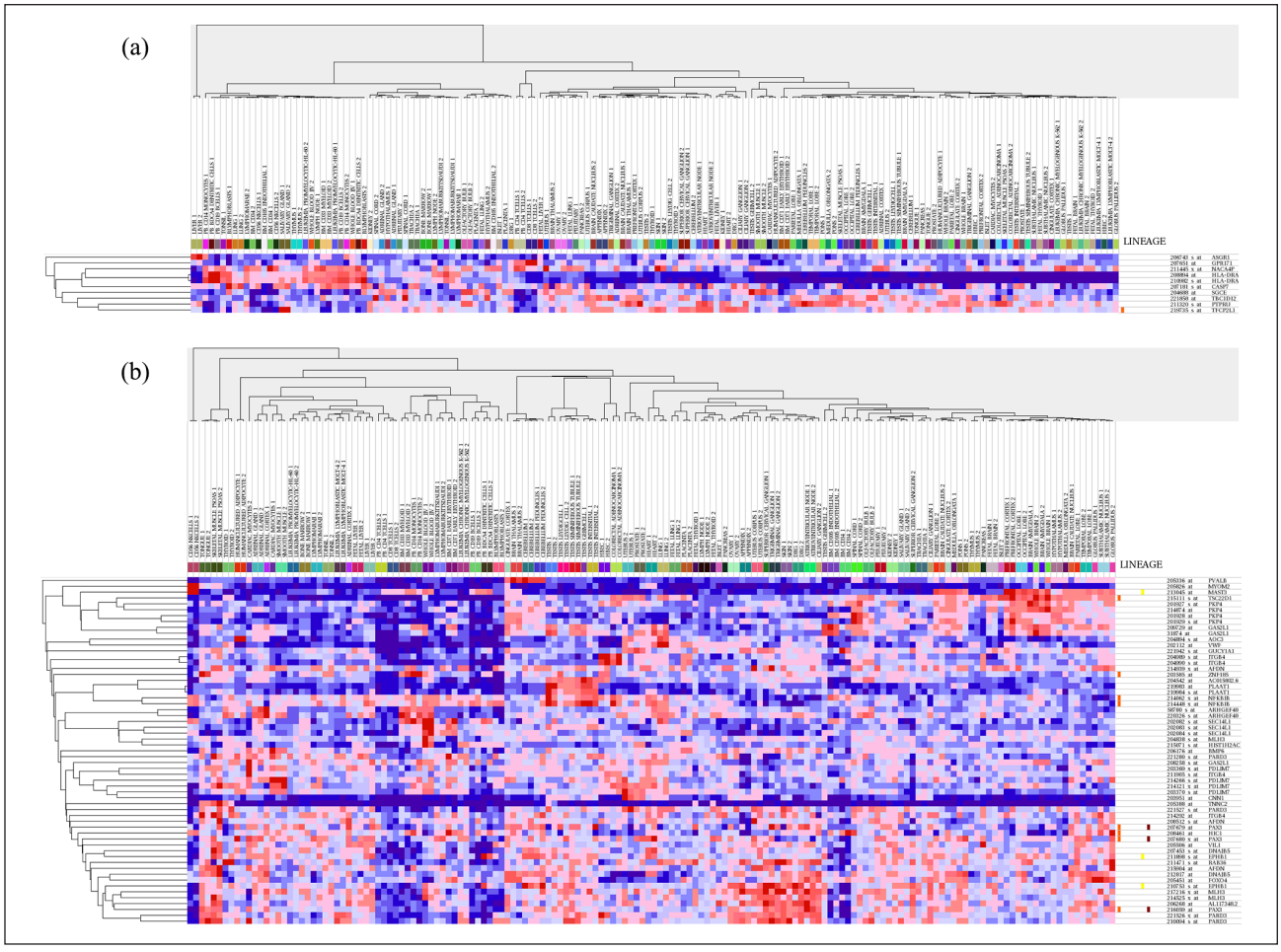

Figure 6. Heat maps of the expression levels of the set of genes that are significantly dysregulated in the blood of subjects with ASDs or WS compared to controls. (a) Heat map of the genes found upregulated in both conditions. (b) Heat map of the genes found downregulated in both conditions. The heat maps were generated by Gene Set Enrichment Analysis (GSEA) software using the samples of the Human tissue compendium (Novartis; A. I. Su et al., 2004). The 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 the probe identifier, gene symbol, description, and gene family. See http://software.broadinstitute.org/gsea/index.jsp for details.

MLT4, *ANKUB1*, *DNAJB5*, *HRASLS*, and *TNNC2*. In contrast, *MYOM2* is more strongly downregulated in ASDs than in WS. Interestingly, *DNAJB5* has been associated with 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 ASDs. We have focused on the brain, given our interest in behavioral and cognitive features. A heat map of the expression levels of these genes in the samples of the Human tissue compendium (Novartis; A. I. Su et al., 2004), as generated by Gene Set Enrichment Analysis (GSEA) software (http://software.broadinstitute.org/gsea/index.jsp), is shown in Figure 6. According to the Human Gene Atlas (A. I. Su et al., 2004), genes found differentially upregulated in ASDs and WS are predicted to be preferentially expressed in the thalamus ($p = 0.06879$; Enrichr combined score = 37.65). In 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 ASDs or WS are expressed in the brain throughout development. However, whereas some of them are expressed at similar levels across regions, others exhibit different expression levels in different brain areas. Specifically, these genes tend to be more expressed outside the neocortex, particularly in the thalamus, but also in the

striatum and the amygdala (Supplemental file 3). Moreover, all the genes that are differentially downregulated in subjects with ASDs 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 not only in the cerebellum but also in the striatum (Supplemental file 3). Overall, these findings suggest that abnormal gene upregulation can be expected to impact primarily the thalamus, whereas downregulated genes tend to be more involved in cerebellar development and function. Both groups are expected to affect striatal regions.

In subjects with WS, the thalamus shows structural and functional differences compared to neurotypical controls, including smaller volumes, reduced gray matter, and enhanced activity (Bódizs et al., 2012; Meyer-Lindenberg et al., 2005; Mobbs et al., 2007; Reiss et al., 2000; Schmitt et al., 2001; Tomaiuolo et al., 2002). Although thalamic gray matter reduction has been associated with visuospatial impairment (L. E. Campbell et al., 2009; Chiang et al., 2007), abnormal thalamic development and function can also be expected to contribute to other cognitive deficits, particularly language problems. This is because of the role of the thalamus as a sort of relay center, connecting many of the brain areas involved in language processing (David et al., 2011; Murdoch, 2010; Wahl et al., 2008). In subjects with ASDs, despite previous inconsistent findings, recent research points to structural abnormalities in the thalamus as well (Schuetze et al., 2016). It also points to a disruption of local thalamic connectivity and a dysregulation of thalamo-cortical networks (Tomasi & Volkow, 2019; Woodward et al., 2017). Likewise, regarding the striatal regions, subjects with WS have reduced basal ganglia volumes (Bellugi et al., 1999; L. E. Campbell et al., 2009; Jernigan et al., 1993; Reiss et al., 2000). Moreover, children with Asperger syndrome show reduced volumes of the caudate, whereas high-functioning children with ASDs exhibit smaller gray matter volumes in the frontostriatal regions (McAlonan et al., 2008). In contrast, adults with ASDs exhibit a relative increase in both caudal putamen and pallidum, with restricted, repetitive behaviors positively correlating to the surface area in the bilateral globus pallidus (Schuetze et al., 2016). The basal ganglia control different cognitive and emotional functions, including language (J. R. Booth et al., 2007; Kotz et al., 2009; Viñas-Guasch & 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 ASDs. Specifically, socio-cognitive similarities between ASDs 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; see Niego & Benítez-Burraco, 2020, for a recent review). Finally, in subjects 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 (Mariën & Borgatti, 2018; Vias & Dick, 2017). In a similar vein, genetic, molecular, behavioral, and neuroimaging findings support the view that, in subjects with ASDs, the cerebellum develops differently at multiple levels of neural structure and function. This circumstance contributes to facets of their distinctive behavioral, cognitive, and affective profile (Becker & Stoodley, 2013; Hampson & Blatt, 2015).

Discussion

In this article, we have adopted a comparative molecular approach to gain insight into the causes of the deficits exhibited by subjects with ASDs or WS, particularly in the domains of social cognition and social behavior. As discussed in the "Introduction" section, the ASD phenotype often directly contrasts 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 ASDs (Sanders et al., 2011), and since people with WS have some risk of suffering from autistic behaviors (Klein-Tasman et al., 2018; Tordjman et al., 2012). 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 with the social phenotype of WS, has been found to be a risk factor for ASDs (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). Nonetheless, these mice exhibit increased maternal separation–induced anxiety (Mervis et al., 2012). This contradicts simplistic models of these disorders, according to which socio-cognitive differences between ASDs and WS might result from dosage changes in selected genes. At the very least, whole-genome analyses should be conducted 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 a restricted set of genes potentially impacting cognition and behavior shares a common pattern of gene dysregulation in the blood of subjects with ASDs and WS. The fact that most of the abnormally expressed genes are found either upregulated or dysregulated in both conditions might account for their similarities in the socio-cognitive domain, particularly if one considers that most of these genes are involved in

aspects of (abnormal) brain development and/or (dys) function. Accordingly, we have found that a significant number of the DEGs contribute to 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. Nonetheless, some remarkable phenotypical and neurobiological differences also exist between ASDs and WS. We hypothesize that they might result in part from the opposite expression pattern exhibited by a small group of genes. This is due in part to the fact that some of the genes showing similar expression trends in ASDs and WS still exhibit quantitative differences between conditions, with most of them being more dysregulated in WS than in ASDs. Overall, the genes we highlight in the article emerge as potentially promising candidates for explaining the similarities and differences between ASDs and WS, particularly those regarding social cognition and social behavior. However, this remains to be demonstrated experimentally, and not only correlatively.

Accordingly, some caution is in order. First, our study has limitations. Besides the small size of our samples of subjects with ASDs or WS, the abnormal patterns of gene expression uncovered by the microarray analyses need to be validated via other techniques, for example, reverse transcription polymerase chain reaction (RT-PCR). Second, a direct translation of gene dosage changes to differences in the severity (or even the nature) of abnormal phenotypical traits or disorder symptoms should be avoided unless empirical evidence does exist. Actually, in many cases, this translation is not observed, even for particular genes, as noted above. When several genes are involved, as in conditions resulting from CNVs, mirror phenotypes are not usually found either. For instance, Smith–Magenis syndrome and Potocki–Lupski syndrome are reciprocal contiguous gene syndromes resulting from the microdeletion and the microduplication, respectively, of the same chromosomal region. Although the affected subjects exhibit some mirror traits, others are shared between conditions, with only a minor number of genes within the critical genomic region being dosage sensitive (Neira-Fresneda & Potocki, 2015). More generally, the mechanisms by which gene dosage changes result in disorder are frequently opaque (see Rice & McLysaght, 2017 for discussion). Third, from a translational medicine point of view, the gene expression changes we highlight in the article should be regarded as more of a biomarker of ASDs and WS than a mechanistic account of specific deficits of ASDs and/or WS via the dysfunction of specific genes. Incidentally, this is why in our analysis, we focused on GO analyses, instead of on the functions performed by each of the DEGs. Alterations in the expression of individual genes can be potentially caused by unknown coincident events, can be of no developmental/biological relevance, and/or can be an adaptive response to the changes affecting other genes which actually contribute to the disorder. Even in this case, however, caution is in order. One reason is that we have attested differences in gene expression levels in adult subjects compared to neurotypical controls. Nonetheless, ASDs and WS are developmental conditions; this entails that changes in gene dosage could differ from one developmental stage to another, and/or impact differentially at different stages of development. Accordingly, even if these abnormal gene expression profiles could be used as reliable biomarkers of these two conditions (and current evidence supports the view that gene dysregulation in the blood significantly echoes gene dysregulation in the brain; see Diaz-Beltran et al., 2016), they should be validated in children, for whom an early diagnosis (particularly of ASDs) is intended.

In sum, more research is needed before promoting the genes we highlight in the article to key causal factors in the emergence of the deficits observed in ASDs and WS. To achieve this, in addition to validating our findings, as noted above, other approaches should be adopted. It is particularly necessary to conduct additional in vitro and in vivo research (including the development of animal models of selected candidates) aimed to gain direct insights into the mechanics of these genes, specifically in terms of their contribution to brain development and function in areas involved in social cognition.

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ORCID iD

Antonio Benítez-Burraco https://orcid.org/0000-0003-4574-5666

Supplemental material

Supplemental material for this article is available online.

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