1 **Title:** Delving into the genetic causes of language impairment in people with partial
2 deletions of *NRXN1*

3 **Running head:** Language and *NRXN1* deletion

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ABSTRACT

Copy-number variations (CNVs) impacting on small DNA stretches and that are associated to language deficits provide a unique window to the role played by specific genes in language function. We report in detail on the cognitive and language features of a girl bearing a small deletion (0,186 Mb) in the 2p16.3 region (arr[hg19] 2p16.3(50761778-50947729)x1), affecting to exons 3-7 of *NRXN1*, a neurexin-coding gene previously related to schizophrenia (SZ), autism (ASD), attention deficit hyperactivity disorder (ADHD), mood disorder, and intellectual disability (ID). The proband exhibits many of the features commonly found in subjects with deletions of *NRXN1*, like ASD-like traits (including ritualized behaviors, disordered sensory aspects, social disturbances and impaired theory of mind), ADHD symptoms, moderate ID, and impaired speech and language. Regarding this latter aspect, we observed altered speech production, underdeveloped phonological awareness, minimal syntax, serious shortage of active vocabulary, impaired receptive language, and inappropriate pragmatic behavior (including lack of metapragmatic awareness and communicative use of gaze). Although these problems might arise from some basic cognitive deficit, such as the impairment of executive function, we provide evidence that several genes important for language function are dysregulated in the proband compared to their healthy parents.

Keywords: 2p16.3 deletion; *NRXN1*; cognitive impairment; language deficits; pragmatic impairment; language-related gene networks

INTRODUCTION

Copy number variants (CNVs) found in individuals with language and pragmatic deficits provide a unique window to the genetic foundations of the human ability to learn and use languages. This is particularly true of CNVs affecting a reduced number of genes and resulting in a common phenotypic profile. In this paper, we report on a girl with a microdeletion in the 2p16.3 region affecting the *NRXN1* gene. This gene encodes a neurexin (Rowen et al., 2002). Neurexins are polymorphic cell surface proteins implicated in synapse development and maintenance (Missler and Südhof, 1998). The *NRXN1* protein has been shown to regulate synaptic activity, neuritogenesis, and neuronal network assembly during neocortical development (Südhof, 2008; Gjørland et al., 2012; Jenkins et al., 2016). Genomic losses involving *NRXN1* have been associated to different neurocognitive conditions, including schizophrenia (SZ), autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), seizures, mood disorder, or intellectual disability (ID) (see Lowther et al., 2017; Hu et al., 2019; Castronovo et al., 2020; Tromp et al., 2020 for recent reviews). Whereas, as noted, the clinical profile of patients with deletions in this gene is pretty variable, language and communication deficits are commonly reported in most of them (Béna et al., 2013; Curran et al., 2013; Al Shehhi et al., 2019). To date, the most detailed report on language and speech problems in patients with deletions in *NRXN1* is Brignell et al.'s (2018), who observed that children (aged 1.8-17 years) with *NRXN1* deletions affecting to exons 1-3 or 1-5 of the gene exhibited a pretty variable phenotype with regards to language problems. Speech sound problems were frequent, but not severe, whereas many children also had difficulties with receptive language. Language use in social settings was impaired as well.

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70 The reported heterogeneity in the severity and the type of speech and language
71 problems associated to deletions in this gene urges to find and characterize in detail the
72 clinical presentation of new CNVs affecting the gene, so that a more precise profile of
73 the affected subjects can be established that enables for more accurate and timely
74 interventions during childhood. Moreover, as genes work in a coordinated way and
75 mutations in many genes are known to impact on language abilities, it is well possible
76 that changes in the dosage of *NRXN1* affect to downstream genes and that speech and
77 language problems observed in patients are partially due to the alteration of other genes
78 besides *NRXN1*. Having this in mind, in this paper we provide a detailed
79 characterization of the speech, language, and communication deficits observed in our
80 patient. Additionally, we build on our current knowledge of the genetic aspects of
81 language development and language evolution, as well as on the expression pattern of
82 selected genes in the blood of our proband, for refining our current knowledge of the
83 molecular causes of language dysfunction associated to *NRXN1* deletions.

84

85 **MATERIAL AND METHODS**

86 **Linguistic, cognitive, and behavioral assessment**

87 The global developmental profile of the proband was evaluated with the Spanish
88 version of the Batelle Developmental Inventory (De la Cruz López and González
89 Criado, 2011), which consists of 341 items aimed to evaluate the subject's
90 personal/social development, adaptive capabilities, gross and fine motor abilities,
91 receptive and expressive communication skills, and cognitive development. In addition,
92 the proband's language features and communication skills were assessed in detail
93 through the analysis of a 10 minutes sample of an interaction between the child and her

sister while playing in a room at her speech language therapist's place. Her mother was in the room as well so that the child would feel in a familiar atmosphere. The conversation was video-recorded and then transcribed and coded using the CHAT (*Codes for the Human Analysis of Transcripts*) software, a tool of the CHILDES Project (MacWhinney 2000). CHAT allows to code for speech production phenomena on the main lines of the transcript, and for phonological, morphological, syntactic and pragmatic phenomena on dependent lines. Information about prosody, dialectal articulation, communicative gestures, and communicative use of gaze is included within square brackets in the main lines. Pauses are also coded in the main lines following CHAT conventions for estimated duration. After tagging every language mistake with an indication of the structural components affected, we evaluated their impact on communication and labelled them accordingly on the pragmatic level using PREP-CORP (PRagmatic Evaluation Protocol for the analysis of oral CORPpora, Fernández-Urquiza et al. 2017a). This protocol has been previously used for establishing the pragmatic profiles of other neurodevelopmental disorders (e.g. Diez-Itza et al. 2018; Fernández-Urquiza et al. 2015; Fernández-Urquiza et al. 2016; Fernández-Urquiza et al. 2017b; Shiro et al. 2016; Shiro et al. 2019).

Molecular analyses

Microarrays for whole-genome CNVs search and chromosome aberrations analysis

Peripheral venous blood lymphocytes were grown following standard protocols and collected after 72 hours. DNA from the patient and her parents was extracted from 100 µl of EDTA-anticoagulated whole blood using MagNA Pure (Roche Diagnostics, West Sussex, UK). The DNA was then hybridized on a CGH platform (Agilent Technologies). The derivative log ratio spread (DLRS) value was 0.13. The platform

included 60.000 probes. Data were analyzed with the Agilent Genomic Workbench 7.0, and the ADM-2 algorithm (threshold = 6.0; aberrant regions had more than 5 consecutive probes).

Microarrays for whole-genome expression analysis

In order to determine the genes that could be differentially expressed in the proband (DEGs) compared to her healthy parents, microarray analyses of blood samples from the three of them were performed. Total RNA was extracted with the PAXgene Blood RNA Kit IVD (Cat No./ID: 762164). RNA quality and integrity were confirmed with a Bioanalyzer RNA 6000 Nano. All samples had RNA integrity number (RIN) values above 9. An Affymetrix® Scanner 3000 7G was then used for analyzing transcriptome changes. The resulting raw data were processed with the Affymetrix® GeneChip® Command Console® 2.0 program. Next, *.CEL files were checked to certify the RNA integrity and the suitability of the labeling and the hybridization processes. Finally, the raw data from the different arrays were normalized with the SST (Signal Space Transformation)-RMA (Robust Microarray Analysis) tool (Irizarry et al., 2003). Normalized data (*.CHP files) were subsequently used to search for DEGs in the proband compared to his parents. Statistical analyses were conducted with the LIMMA (Linear Models for Microarray Analysis) package of BioConductor, using the TAC 4.0 software.

RESULTS

Clinical History

The proband was born by caesarean section after an uncomplicated pregnancy. She weighted 2.6 kg at birth and presented with a congenital torticollis that required a year

of rehabilitation. She was fed with artificial lactation and the transition to solid feeding went smoothly. At 9 months, she was referred to the Paediatric Neurology Unit, because her parents reported that the girl's development was delayed compared to her older sister. She was diagnosed with global psychomotor developmental delay. At 13 months, a cranial MRI was performed. Results suggested an increase in extra-axial spaces, supratentorial ventriculomegaly, and mega cisterna magna. The girl began to attend day care. At 15 months, the girl seemed to evolve favourably despite her maturational delay. At 17 months, urine and metabolic studies were required, as the girl suffered from anemia. At 21 months, a low-protein diet was recommended by the doctors because of increasing evidence of some type of congenital metabolic problem. At this point, the proband's verbal comprehension seemed to have slightly improved, but her expressive impairment was still dramatic, as she was able to produce only a few single words. Regarding her family history, it is of interest that her paternal uncle suffered from SZ and ID, her father presented with motor tics, and her paternal great-grandmother died with cognitive and motor impairment beyond the age of 70.

Language and cognitive development

At 27 months, the proband was assessed with the Batelle Developmental Inventory (see Figure 1). At this point, the girl exhibited a 16-month delay in her adaptive abilities and her expressive communication skills, and a 14-month delay in her receptive communication abilities. She also presented with a 10-month cognitive delay. Her personal social skills and her gross motor abilities were less impaired.

Figure 1. Results of the assessment with the Battelle Developmental Inventory at 27, 85, and 97 months of age.

At 42 months, when the proband began to attend school, she was diagnosed with a severe developmental delay. Regarding her cognitive (dis)abilities, the girl showed scattered attention, problems for making associations, poor imitation capacity, absence of symbolic play, and difficulties with adequate social interaction. She also experienced difficulties expressing and identifying emotions, although she did not present with behavioral problems. Concerning her language development, the girl exhibited a severe mixed language delay. She was unable to construct simple sentences and their speech was barely intelligible.

At 60 months, the proband's language abilities had improved only slightly. On the expressive level, she occasionally uttered two-word phrases, and her speech difficulties persisted. The girl started to attend a speech therapist.

At the age of 72 months, when the girl entered the primary school, she was subject again to cognitive and behavioral evaluation. At this time, the girl exhibited a moderate ID and emotional and behavioral deficits, as well as learning difficulties, since she needed a very structured learning environment with constant monitoring and aid from adults. Overall, she showed a notable developmental delay compared to her peers.

At 85 months, the proband was assessed again with the Batelle Developmental Inventory. As shown in Figure 1, the gap between the girl's chronological age and her developmental age had increased in all the assessed areas, being expressive language the most impaired domain. At that moment, the proband presented with ID and significant alterations in the areas of social interaction and verbal communication. She also exhibited some ritualized and disordered behaviors, such as smelling objects, as well as high levels of impulsivity and attention deficit. Her general independence and adaptive skills were also below expectations for her chronological age.

At 97 months, a third evaluation with the Batelle Developmental Inventory was carried out, which showed a significant setback with respect to the two previous assessments, being the proband's personal/social and adaptive skills the most affected domains, along with her expressive language (see Figure 1).

In addition, we examined in detail the structural and functional features of the child's language, as well as her communication skills through the analysis of a naturally-occurring interaction with her mother and sister. The full record can be found in the Supplemental file 1. The proband's speech featured frequent omissions of initial consonants (e.g. siguiente> iguiente* 'following'; quita > ita* 'remove'; ventana >

209 entana* ‘window’), as well as consonant clusters simplification (e.g. verde > vele*
210 ‘green’; espejo > epejo* ‘mirror’; pastel > fafé* ‘cake’; armario > ababio* ‘closet’),
211 and sound substitutions (e.g. ducha > lucha* ‘shower/fight’; roja > doja* ‘red’; armario
212 > armadio* ‘closet’; aquí > adí* ‘here’; música > muzita* ‘music’; pastel > fafé*
213 ‘cake’). Consonant frontalization was also frequently observed (e.g. aquí > adí* ‘here’;
214 armario > ababio* ‘closet’; pastel > fafé* ‘cake’), particularly, of alveolar /s/ into
215 interdental /θ/ (e.g. silla > zilla* ‘chair’; esto > ezto* ‘this’; eso > ezo* ‘that’; sí > zí*
216 ‘yes’; música > muzita* ‘music’).

217

218 Concerning language structure and complexity, the mean length of utterance in words
219 (MLUw) of the girl’s discourse was very low, of 0.981. This roughly corresponds to a
220 limited holophrastic language which is typically found in one-year-old children.
221 Although the proband did not produce truly syntactic structures, a hallmark of her
222 discourse was the avoidance or the phonetic alteration of definite and indefinite articles
223 (e.g. la ropa > e dopa* ‘the clothes’; las manos > a mano* ‘the hands’).

224

225 With regards to the pragmatic component, the child did not seem able to properly
226 engage in conversation. Most of her turns at talk, even being verbal by nature (Figure
227 2), were reactive, in response to her interlocutor’s requests. Usually, the interlocutor
228 needed to repeat the question twice or three times in order to obtain a minimal answer
229 (verbal or non-verbal). In the infrequent cases when the child took the floor, she could
230 generate echolalic utterances only.

■ empty ■ non-verbal ■ paralinguistic ■ holophrastic

Figure 2. Nature of the conversational turns provided by the child during a spontaneous conversation with a peer. Empty turns: the child provided no answer at all, ignoring her interlocutor and focusing on the objects she was playing with. Non-verbal turns: the child produced an action in response to her interlocutor's request. Paralinguistic: the child tried to take the turn but was only able to produce fillers, such as non-verbal vocalizations. Holophrastic: the child generated single-word responses.

Furthermore, the pragmatic skills related to the understanding of the logic of conversation as described by Grice (1975) were seriously impaired. Specifically, transgressions of the maxim of relation (i.e. say things relevant to the topic under discussion) were pervasive (e.g. when asked to name a music player, she might say "dance", when asked about a picture she might reply "paper" or when asked about some windows in the room she might reply by counting them: "one, two"), as well as transgressions of the maxim of quantity (i.e. provide the right amount of information), so that the child might refer to the majority of the things around her by means of demonstrative pronouns like "this" and "that", which are not informative enough. Finally, her communicative use of gaze was also impaired, not establishing visual

contact with her conversational partner, and experiencing difficulties with joint attention when she was asked to name an object. No compensatory strategies aimed to improve her communication deficits were observed (e.g. asking for help when she was unable to find a word).

To sum up, our proband exhibited severe speech and language deficits, with her expressive skills being dramatically affected, to the point that she was unable to pronounce words correctly, to build up simple canonical sentences, and to name the everyday things around her. These deficits hindered the intelligibility of her discourse and her communicative success. Comprehension of language was also seriously impaired, as well as her pragmatic abilities: she showed no metapragmatic awareness (i.e. she did not realize which of her utterances were problematic, and she was unable to produce compensatory strategies to reach communicative success); she frequently produced non-related, tangential and/or insufficiently informative answers; she was not able to properly engage in conversation according to the turn-taking system (Sacks et al. 1974), and she made no communicative use of gaze. Finally, her literal interpretation of utterances revealed an underdeveloped theory of mind.

Cytogenetic and molecular analyses

A comparative genomic hybridization array (array-CGH) was performed when the proband was 5 years and 1 month old. The array confirmed the presence of a deletion of 0,186 Mb in the 2p16.3 region (arr[hg19] 2p16.3(50761778-50947729)x1), predicted to be pathological, and affecting exons 3-7 of the gene *NRXNI* (figures 3A and 3B). The deletion was inherited from the proband's healthy father.

Figure 3. Chromosomal alterations found in our proband. A. Screen capture of the array-CGH of the proband’s chromosome 2 showing the microdeletion at 2p16.3. B. Screen capture of the UCSC Genome Browser (<https://genome.ucsc.edu/>) showing the extension of the deletion in NRXN1.

In order to delve into the molecular causes of the speech and language problems exhibited by the girl, we conducted several silico analyses. Specifically, we used String 11.0 (www.string-db.org) for finding putative functional links between NRXN1 and the products of genes important for language. We focused on two types of genes: i) candidates for highly prevalent (specific) language disorders, i.e. developmental dyslexia (DD) and specific language impairment (SLI), as listed by Paracchini et al., 2016, Pettigrew et al., 2016, and Chen et al., 2017); and ii) candidates for language evolution, as discussed by Boeckx and Benítez-Burraco (2014a,b) and Benítez-Burraco and Boeckx (2015); many of these genes are also candidates for language dysfunction in broader cognitive disorders, particularly, ASD and SZ (see Benítez-Burraco and Murphy, 2016; Murphy and Benítez-Burraco, 2016; Murphy and Benítez-Burraco, 2017 for details). Both sets of genes are listed in the Supplemental file 2. String 11.0 predicts physical and functional associations between proteins relying on different sources (genomic context, high-throughput experiments, conserved coexpression, and

294 text mining) (see Szklarczyk et al., 2015 for details). Because we were interested in
295 finding robust functional links, we limited our search to protein-protein interaction
296 databases and curated databases of protein interactions (Biocarta, BioCyc, GO, KEGG,
297 and Reactome). String did not predict any functional link between NRXN1 and the
298 products of candidates for language disorders and/or evolution (data not shown).
299 Besides in silico analyses, we also conducted in vitro analyses. Specifically, we
300 performed microarray analyses of blood samples from the proband to determine
301 whether she exhibited altered patterns of gene expression that may account for the
302 observed deficits. We used her healthy carrier father and her healthy non-carrier mother
303 as controls. The results of the microarrays are shown in the Supplemental file 3. We
304 found that *NRXN1* was only slightly upregulated in the proband (1.27 fold change (FC)
305 compared to her healthy non-carrier mother; 1.1 FC compared to her healthy carrier
306 father). Additionally, we checked whether the candidate genes for language disorders
307 and/or evolution used in our in silico analyses were differentially expressed in the girl
308 compared to her parents. For most of the candidates for language disorders, we found
309 no significant differences (i.e. $FC > 1.5$ compared to both healthy parents). However,
310 some of them (*CNTNAP2*, *ROBO1*, and *SETBP1*) were significantly downregulated in
311 the proband, whereas some others (*KIAA0319*, *KANSL1*, *NFXL1*, and *SI00B*) were
312 significantly upregulated (Figure 4A). Regarding candidates for language evolution, we
313 found that most genes that were differentially-expressed genes ($FC > 1.5$ compared to
314 both healthy parents) were upregulated in the proband (including *DYRK1A*, *ASPM*,
315 *NCAM1*, *BAZ2A*, *SLIT2*, *DUSP1*, *FLNA*, *PLAUR*, *CDC42*, *SLIT1*, *RUNX2* and *TLE3*)
316 (Figure 4B). Finally, we searched for additional candidates for the proband's language
317 deficits, looking for genes exhibiting the strongest FC in our subject (i.e. $FC > 5$
318 compared to both unaffected parents). We found that several genes were strongly

downregulated (*KIAA1324*, *GSTM1*, *PDZK1IP1*, and *LIN7A*), whereas only one gene (*RAP1GAP*) was strongly upregulated (Figure 4C).

Figure 4. Variation in the expression levels of genes of interest in the proband's blood compared to her healthy parents. A. Fold changes in the expression levels of candidates for language disorders. B. Fold changes in the expression levels of candidates for language evolution. C. Genes exhibiting fold changes > 5 in the proband compared to both healthy parents.

ith regards to the candidates for language disorders and/or evolution that are significantly down- or upregulated in the blood of our proband, we found that around 50% are more expressed in the brain than in the blood. These include *S100B* (strongly expressed in the spinal cord, the substantia nigra, the hypothalamus and the hippocampus), *NCAM1* (highly expressed across the whole brain), *SLIT1* (expressed throughout the brain), *CNTNAP2* (more expressed in the cortex), and *KIAA0319* (highly

expressed in the cortex and parts of the basal ganglia). Finally, with regards to the genes that are strongly downregulated in the proband, we found that *LIN7A* is expressed at similar levels in the nervous system and in the blood, although it is upregulated in the cerebellum. *PDZK1IP1* is expressed at lower levels in the brain than in the blood. Transcripts of this gene are preferentially found in the spinal cord. *GSTM1* is expressed at similar levels in the blood and in the brain, where it is mostly expressed in the frontal cortex and the basal ganglia. *KIAA1324* is expressed at higher levels in the brain, particularly in the cortex, the hypothalamus and parts of the basal ganglia. Lastly, *RAP1GAP* is expressed at higher levels in the brain than in the blood, particularly, in the cortex and the basal ganglia.

Figure 5. Expression pattern in the blood and the brain of genes of interest. Expression levels of the genes were retrieved from the Genotype-Tissue Expression (GTEx) project (GTEx Consortium, 2013) (<https://www.gtexportal.org/home/>). Statistical analysis and data interpretation were performed by The GTEx Consortium Analysis Working Group using the . Legend: TPM, transcripts per million.

Finally, we used String 11.0 for knowing more about functional interactions of interest between the proteins encoded by the genes found strongly dysregulated in the proband and the proteins encoded by candidate genes for language disorders and/or evolution.

We found predicted functional links between LIN7A and GRIN2B, ERBB4, and EGFR, as well as between RAP1GAP and CDC42 and HRAS (Figure 6).

Figure 6. Interaction network of genes found strongly dysregulated in the proband and the proteins encoded by candidate genes for language disorders and/or evolution. The network was drawn with String (version 11.0; Szklarczyk et al., 2015) license-free software (<http://string-db.org/>), using the molecular action visualization. Colored nodes symbolize gene/proteins included in the query (small nodes are for proteins with unknown 3D structure, while large nodes are for those with known structures). The color of the edges represents different kind of evidence, as shown in the legend. Stronger associations between proteins are represented by thicker lines. The medium confidence value was .0400 (a 40% probability that a predicted link exists in a particular database). The diagram only represents the potential connectivity between the involved proteins, which has to be mapped onto particular biochemical networks, signaling pathways, cellular properties, aspects of neuronal function, or cell-types of interest.

DISCUSSION

The widespread application of next generation sequencing facilities, particularly array-CGH, to people with conditions featuring cognitive and language deficits has resulted in an increasing list of candidate genes for these problems. Nonetheless, it is usually difficult to arrive to robust genotype-to-phenotype links, particularly in the case of complex, multifactorial traits like language. In this paper, we have provided a detailed characterization of the language problems exhibited by a girl with a microdeletion in 2p16.3 affecting to part of the *NRXN1* gene. Mutations or genomic losses in this gene have been associated to diverse cognitive and behavioral problems, including language and communication deficits (Béna et al., 2013; Curran et al., 2013; Brignell et al., 2018; Al Shehhi et al., 2019), although we still lack a mechanistic account of these problems.

Our proband exhibits most of the cognitive, behavioral and neurological anomalies observed in patients with losses of *NRXN1*. This is specifically true for her speech, language, and communication (dis)abilities (Table 1).

Cognitive/behavioural features	
Intellectual disability (ID)	x
Autism spectrum disorder (ASD)	x
Attention deficit hyperactivity disorder (ADHD)	x
Schizophrenia (SZ)	
Anxiety	
Speech impairment	x
Expressive language impairment	x

Receptive language impairment	x
Impaired pragmatics (social communication difficulties)	x
Brain/Neurological findings	
Childhood Apraxia of Speech	x
Dysarthria	
Hipotonia	x
Epilepsy	
Complex neurodevelopmental disorder	x

Table 1. Summary table with the most relevant clinical features of our proband compared to patients with deletions of *NRXN1* (according to Brignell et al., 2018 and DECIPHER). The observed features are marked with x.

From our detailed analysis of the proband's speech problems, we conclude that they are indicative of Childhood Apraxia of Speech (CAS), a condition characterized by inconsistent errors on consonants and vowels in repeated productions of words and inappropriate prosody. Nonetheless, we have also found evidence of an underdeveloped phonological awareness. Our results are thus in line with findings by Brignell et al. (2018), who suggest that articulation and phonological problems co-occur in children with *NRXN1* deletions.

We have also found that besides her severe expressive language delay, the receptive skills of our proband are also notably affected. This finding is also in line with previous research (e.g. Ching et al., 2010; Gregor et al., 2011; Béna et al., 2013; Curran et al., 2013; Dabell et al., 2013).

406

407 Finally, we report for the first time on the pragmatic impairment associated to deletions
408 of *NRXNI*. This pragmatic deficit consists on an inability to properly engage in turn-
409 taking during conversation together with a reduced metapragmatic awareness, that
410 impedes to perceive the violation of the logic of conversation. This results in different
411 abnormal behaviors during conversation, like producing tangential or perseverating
412 answers to new questions or interpreting utterances in a literal way. These pragmatic
413 problems seemingly become exacerbated by other co-occurring problems, like her
414 reduced vocabulary, attention deficit, and ASD-like features.

415

416 Overall, this language and communication profile partially overlaps with the deficits
417 found in other neurodevelopmental disorders, such as ASD, ADHD, and moderate to
418 severe ID, which are commonly comorbid conditions in children with *NRXNI* deletions
419 (ASD: 43–65%; Schaaf et al., 2012; Béna et al., 2013; Dabell et al., 2013; González-
420 Mantilla et al., 2016; ADHD: 9–41%; Schaaf et al., 2012; Lowther et al., 2017; ID: 77–
421 92%; Schaaf et al., 2012; Béna et al., 2013; Dabell et al., 2013). In fact, as pointed out
422 by Lowther et al. (2017), around 46% of individuals with *NRXNI* deletions present with
423 dual neurodevelopmental disorder diagnoses, as it is the case of our proband, who was
424 diagnosed with a moderate ID, but who also exhibits ADHD features, as well as ASD-
425 like traits, including problems with social interactions, some ritualized behaviors,
426 altered sensory experience, and an underdeveloped theory of mind. Brignell et al.
427 (2018) have suggested that the speech and language problems of individuals with
428 *NRXNI* deletions could result from their ID and ASD features, a possibility that is
429 supported by several studies pointing to a correlation between ID, ASD, and language
430 difficulties (Levy et al., 2010; Liao et al., 2015).

431

432 Besides providing a profile of the problems with language exhibited by our proband, as
433 well as some hints about their cognitive causes, we also aimed to advance a hypothesis
434 about the molecular causes of the language problems resulting from losses of the
435 *NRXN1* gene. In our proband, the gene is not significantly dysregulated compared to
436 her healthy parents. We have not found in silico evidence of a functional connection
437 between the protein NRXN1 and the products of strong candidates for language
438 development, impairment, and/or evolution. Nonetheless, the known roles of *NRXN1*
439 in synapse development and maintenance, and neuron network assembly during cortical
440 development (Missler and Südhof, 1998; Südhof, 2008; Gjølund et al., 2012; Jenkins
441 et al., 2016), are compatible with a putative role in the development and maintenance,
442 specifically, of brain circuits underlying language function. This possibility is
443 reinforced by the fact that the gene is expressed in areas involved in language
444 processing, particularly, the cerebellum, which contributes significantly to motor
445 planning, but also to many aspects of language processing (Vias and Dick, 2017;
446 Mariën and Borgatti, 2018), along with the prefrontal cortex region, which is a core
447 region for speech and language (Jenkins et al., 2016). Deficits in the frontal cortex are
448 known to impact on executive function and problems with executive function have been
449 hypothesized to contribute to diverse neurodevelopmental disorders, including ASD,
450 ADHD, and SZ (Ozonoff, and Jensen, 1999; Martos-Pérez and Paula-Pérez, 2011). As
451 we have repeatedly pointed out, our proband exhibits ASD- and ADHD-like features.
452 Additionally, her paternal uncle, who was also a carrier of the *NRXN1* deletion inherited
453 by our proband, presented with SZ. Furthermore, executive dysfunction has been
454 claimed to account for the generativity deficit observed in ASD (i.e. the lack of new
455 ideas, behaviors, and utterances tailored to new contexts) and ultimately, for the

456 stereotypies, echolalic utterances and restrained interests typical of this condition
457 (Turner, 2000; Gilotty et al., 2002). Additionally, some studies (e.g. Perner, and Lang,
458 2000; Russell, 2000; Ibáñez-Barassi, 2005) have associated executive dysfunctions to
459 an impaired theory of mind. Overall, one could hypothesize that the *NRXN1* deletion
460 found in our proband may impact on her executive function, thus affecting a wide range
461 of cognitive abilities, such as attention (which plays a central role in learning and
462 communication), theory of mind (necessary for the development of adequate
463 communication skills) and, of course, speech and language.

464
465 Brignell et al. (2018) support the view that there is no specific linguistic profile for
466 deletion of *NRXN1*. We agree that the speech, language and communication deficits
467 found in our proband seemingly result from the impairment of more basic cognitive
468 functions, which are also affected in other high-prevalent, co-morbid
469 neurodevelopmental conditions in children with *NRXN1* deletions. Nonetheless, we
470 think that it is possible going beyond Brignell et al.'s general claim that this
471 circumstance precludes the identification and the characterization of a neurobiological
472 pathway relating to the speech and language problems observed in deletions of *NRXN1*
473 (2018).

474
475 In our research, we have found that several candidates for language disorders and/or
476 language evolution are dysregulated in the proband's blood. While we have no evidence
477 of a direct effect of the loss of *NRXN1* on the dysregulation of these genes, these
478 changes could potentially contribute to the language deficits observed in the proband.
479 Accordingly, we have found that several candidates for DD show altered levels of
480 expression in our subject. Among the genes found downregulated, we wish to highlight

481 *ROBO1* and *SETBP1*. The former encodes a protein involved in thalamocortical axon
482 development and plays a critical role in the establishment of vocal learning pathways
483 in many species (Pfenning et al., 2014). Mutations in the latter give rise to Schinzel-
484 Giedion Syndrome, a clinical condition entailing occasional epilepsy and severe
485 developmental delay (Ko et al., 2013; Miyake et al., 2015), as well as behavioral and
486 social deficits (Coe et al., 2014). Also the DD candidate *CNTNAP2* is found strongly
487 downregulated in our proband. This gene encodes a protein associated with K⁺ voltage-
488 gated channels in the pyramidal cells of the temporal cortex (Inda et al., 2006), which
489 contributes to regulate brain connectivity and morphology (Scott-Van Zeeland et al.,
490 2010; Tan et al., 2010; Dennis et al., 2011), dendritic arborization and spine
491 development (Anderson et al., 2012), and axonogenesis in conjunction with ROBO
492 factors (Banerjee et al., 2010). *CNTNAP2* has been also associated to language and
493 speech regression (Strauss et al., 2006; Marchese et al., 2016; Smogavec et al., 2016),
494 SLI (Newbury et al., 2011), ASD (Alarcón et al., 2008; Bakkaloglu et al., 2008), CAS
495 (Worthey et al., 2013), and language impairment in SZ (Poot, 2015). As noted, CAS is
496 a core symptom in our proband, whereas one of her relatives has been diagnosed with
497 SZ. Moreover, several candidates for DD are upregulated in the proband, including
498 *KIAA0319*, *KANSL1* and *S100B*. *KIAA0319* encodes a membrane protein contributing
499 to the interactions between neurons and radial glial cells during neuronal migration
500 (Paracchini et al., 2006; Velayos-Baeza et al., 2008). Mutations in *KANSL1*, which
501 encodes a component of the NSL1 complex, important for chromatin organization and
502 gene transcription regulation, result in Koolen-de Vries Syndrome (OMIM#610443).
503 This clinical condition features epilepsy, developmental delay, and moderate ID, which
504 impacts mostly on expressive language development (Koolen et al., 2016). Finally,

SL00B encodes a calcium-binding protein involved in neurite extension, axonal proliferation, and synaptic plasticity and learning (Sorci et al., 2013).

Among the candidates for language evolution (many of them resulting in cognitive disorders like ASD or SZ when mutated) that are found dysregulated in the proband we wish to highlight *SLIT1*, *SLIT2*, and *HES1*. The SLIT/ROBO pathway is thought to play a crucial role in the externalization of language (i.e. speech) (see Boeckx and Benítez-Burraco, 2014b for details). Several other genes related to (the evolution of) speech are upregulated in the girl, including *DUSP1*, involved in vocal learning in songbirds (Horita et al., 2010, 2012); *PLAUR*, part of FOXP2's interactome (Roll et al., 2010; Royer-Zemmour et al., 2008) and a candidate for speech dyspraxia (Roll et al., 2006); *TLE3*, a target of FOXP2 in the inferior prefrontal cortex (Spiteri et al., 2007); and *FLNA*, which encodes an actin-binding protein needed for cytoskeleton remodeling and neuronal migration (Fox et al., 1998) that binds FLNA interacts as well with *CDC42*, which is also found upregulated in our proband. CDC42 regulates cortical interneuron migration (Katayama et al., 2013) and dendritic spine growth and function (Datta et al., 2015). In mice, *Slit2* reduces *Cdc42* activity in living growth cones (Myers et al., 2012), whereas depletion of *Robo1* prevents *Slit2* inhibition of *Cdc42* activity (Yiin et al., 2009). The abnormal expression pattern of these candidates for DD and speech-related genes might account from the speech and phonological problems exhibited by our proband.

Also of interest for explaining the language deficits observed in the proband is the upregulation of *NCAM1*, a gene related to working memory performance (Bisaz et al., 2013), but also to neuropsychiatric conditions like SZ, bipolar disorder, and

Alzheimer's disease (Atz et al., 2007). *NCAM1* is a target of FOXP2 (Konopka et al., 2009), but also of RUNX2 (Kuhlwilm et al., 2013). *RUNX2* is strongly upregulated in the proband. This is a key gene hypothesized to account for some of the changes in the human brain morphology and configuration resulting in our cognitive uniqueness, particularly, our cross-modal thinking (see Boeckx and Benítez-Burraco, 2014a for a detailed discussion). Also *ASPM* is found upregulated in our proband. This is a strong candidate for microcephaly, but also for the increase in brain size in the human lineage (Bond et al., 2002; Zhang, 2003). Finally, it is of interest the finding that *DYRK1A* is upregulated in the girl. Mutations in this gene result in microcephaly, as well as in intellectual disability and absence of speech (Van Bon et al., 2011; Courcet et al., 2012). The gene seems to play a role in learning and memory (Hämmerle et al., 2003) via its effects on synaptic plasticity and on the balance between excitation and inhibition (Souchet et al., 2014). The abnormal expression pattern of these genes can also contribute to the speech problems of the proband through its effect on the FOXP2 interactome, but also to her problems with grammar through its effect on the RUNX2 network.

Lastly, it is worth considering the biological roles played by the genes that are strongly dysregulated in the blood of the girl compared to her healthy parents. The most promising genes for explaining her language deficits are *LIN7A* (found strongly downregulated) and *RAP1GAP* (found strongly upregulated). Both genes are expressed in the brain, particularly in the cerebellum (*LIN7A*) and the striatum (*RAP1GAP*), which are two regions that are crucially involved in language processing (Silveri, 2020), particularly, in speech production (Konopka and Roberts, 2016). Deletions in *LIN7A*, a gene encoding a scaffold protein important for synaptic function, impact on the

development of the cerebral cortex and result in ID (Matsumoto et al., 2014). Regarding *RAP1GAP*, it encodes a GTPase-activating-protein acting as a negative regulator of RAP1, which is involved in cell proliferation, adhesion, differentiation, and embryogenesis, and specifically, in neuronal migration (Yang et al., 2019) and the regulation of dendritic spine morphology in the striatum (McAvoy et al., 2009) and the cortex (Chen et al., 2005). *RAP1GAP* mediates aversive behaviors in the nucleus accumbens (Lin et al., 2020). Interestingly, we have found that the products of these two genes interact with the products of several candidates for language impairment and/or evolution, particularly, *GRIN2A*, *GRIN2B*, *HRAS*, and *ERBB4*. *GRIN2A* and *GRIN2B* are two of the components of the NR2 subunit of a receptor for N-methyl-D-aspartate (NMDA), involved in long-term potentiation and ultimately, in memory and learning. Mutations in *GRIN2A* give rise to speech impairment and language regression, as part of epileptic syndromes like Landau-Kleffner Syndrome, Continuous Spike and Waves during Slow-Wave Sleep Syndrome (CSWSS), or rolandic epilepsies (Carvill et al., 2013; Lesca et al., 2013; Dimassi et al., 2014). The speech problems observed in patients include syllable repetitions, imprecise articulation, and problems with pitch and prosody, which are usually labelled as dyspraxia or dysarthria (Turner et al., 2015), and which parallel the speech deficits observed in our proband. By contrast, mutations in *GRIN2B* are mostly related to behavioral problems, but also to motor and cognitive problems (Freunscht et al., 2013; Hu et al., 2016; Smigiel et al., 2016). Concerning *HRAS*, it is a candidate for DD and ASD, and encodes a GTPase that contributes to regulate neural growth and differentiation, long-term potentiation, and synaptic plasticity (Comings et al., 1996). Lastly, *ERBB4* is involved in the regulation of interneuron migration and in synchronizing neural oscillations in the cortex (Li et al., 2012; Hou et al., 2014). Mutations in *ERBB4* result in ID and speech delay

(Kasnauskiene et al., 2013). In our view, the strong dysregulation of these genes could contribute to explain the speech, language, cognitive, and behavioral problems exhibited by our proband.

CONCLUSIONS

Although the exact molecular causes of the speech and language problems observed in our proband remain to be fully elucidated, we think that they might result from the dysregulation of several known candidates for language impairment and/or evolution with a known function on brain development and with a role in cognitive diseases impacting on speech and language, particularly, ASD, ID, and DD. This hypothesis needs to be properly tested. Particularly, the link between the loss of *NRXN1* and the dysregulation of these genes needs to be probed. Still, we hope that our findings contribute to a better understanding of the speech, language, cognitive, and behavioral phenotype resulting from mutations and CNVs of this key neurexin. More detailed accounts of the neurobiological basis of the deficits (and strengths) exhibited by patients are necessary for improving (psycho)pedagogical strategies aimed to ameliorate their problems.

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1138 **SUPPLEMENTAL DATA**

1139

1140 **Supplemental file 1.** Transcriptions of the conversational exchanges in natural settings
1141 used for the analyses of the proband's language in use.

1142

1143 **Supplemental file 2.** The whole set of genes important for language used for the in
1144 silico analysis.

1145

1146 **Supplemental file 3.** Data resulting from the microarray analyses comparing gene
1147 expression levels in the blood of the proband and her healthy parents.

1148