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Review article

Repint of "Reframing autism as a behavioral syndrome and not a specific mental disorder: Implications of genetic and phenotypic heterogeneity"

S. Tordjman[a,b,*], D. Cohen[c], G.M. Anderson[d], M. Botbol[e], R. Canitano[f], N. Coulon[b], P.L. Roubertoux[g]

[a] Pôle Hospitalo-Universitaire de Psychiatrie de l'Enfant et de l'Adolescent, Université de Rennes 1 and Centre Hospitalier Guillaume Régnier, 154 rue de Châtillon, 35200 Rennes, France
[b] Laboratoire Psychologie de la Perception, Université Paris Descartes and CNRS UMR 8158, Paris, France
[c] Department of Child and Adolescent Psychiatry, AP-HP, GH Pitié-Salpétrière, CNRS FRE 2987, Université Pierre et Marie Curie, Paris, France
[d] Child Study Center, Yale University School of Medicine, New Haven, CT, USA
[e] Departement Hospitalo-Universitaire de Psychiatrie de l'Enfant et de l'Adolescent, Université de Bretagne Occidentale, Brest, France
[f] Division of Child and Adolescent Neuropsychiatry, University Hospital of Siena, Italy
[g] Aix Marseille Université, GMGF, Inserm, UMR_S 910, 13385, Marseille, France

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ABSTRACT

Clinical and molecular genetics have advanced current knowledge on genetic disorders associated with autism. A review of diverse genetic disorders associated with autism is presented and for the first time discussed extensively with regard to possible common underlying mechanisms leading to a similar cognitive-behavioral phenotype of autism. The possible role of interactions between genetic and environmental factors, including epigenetic mechanisms, is in particular examined. Finally, the pertinence of distinguishing non-syndromic autism (isolated autism) from syndromic autism (autism associated with genetic disorders) will be reconsidered. Given the high genetic and etiological heterogeneity of autism, autism can be viewed as a behavioral syndrome related to known genetic disorders (syndromic autism) or currently unknown disorders (apparent non-syndromic autism), rather than a specific categorical mental disorder. It highlights the need to study autism phenotype and developmental trajectory through a multidimensional, non-categorical approach with multivariate analyses within autism spectrum disorder but also across mental disorders, and to conduct systematically clinical genetic examination searching for genetic disorders in all individuals (children but also adults) with autism.

1. Introduction

The term « autism », derived from the Greek "autos" meaning "self", was introduced for the first time by the Swiss psychiatrist Eugen Bleuler (1911) to describe schizophrenic symptoms in adult patients (social withdrawal). Later, Leo Kanner (1943) borrowed the term to define a specific syndrome observed in 11 American children characterized by its early onset (the first year of life), symptomatology, and disrupted affective relationships with the social world.

Despite numerous studies conducted on autism, including studies on animal models relevant to autism (Tordjman et al., 2003, 2007), it appears that no etiological model, biomarker and specific mode of transmission have been actually identified due to discrepant or not replicated results. Autism is defined in the DSM-5 (American Psychiatric Association, 2013) and ICD-10 (World Health Organization, 1993) as impaired social communication and repetitive/restrictive behaviors or interests, with onset prior to age 3 years. The term "autism spectrum disorder (ASD)" is used in the DSM-5 to refer to a range of severity within the two relevant behavioral domains (social communication and repeated behaviors/interests), but the DSM-5 still views autism as a single categorical mental disorder and not as various autistic syndromes. The very broad DSM-5 or ICD-10 definitions of autism raise the issue of clinical heterogeneity suggesting the possible existence of subtypes or subgroups of autism. Indeed, between a child showing motor stereotyped behaviors with no language and a child showing a good level of speech production but with non-verbal communication problems and rituals, it seems that we are not facing the same pathology, even though these two children may both satisfy the autism diagnostic criteria. The heterogeneity of biological results (neuro-anatomic, biochemical or genetic) and the difficulty to replicate

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* Corresponding author at: Pôle Hospitalo-Universitaire de Psychiatrie de l'Enfant et de l'Adolescent (PHUPEA), 154 rue de Châtillon, 35000 Rennes, France.
E-mail address: s.tordjman@yahoo.fr (S. Tordjman).

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them seem again to indicate the existence of subtypes of autism which stem probably from etiological heterogeneity. Indeed, more than 200 autism susceptibility genes have been reported, and cytogenetic abnormalities have been described for almost every chromosome (for a review, see http://projects.tcag.ca/autism/).

One of the current issues in the field of genetic research on autism is therefore to work on different subtypes in order to identify the relevant genes and to get more homogeneous samples allowing the duplication of results. There are three main approaches to identifying genetic hot spots or chromosomal regions likely to contain relevant genes: (1) cytogenetic studies, (2) whole genome screens, and (3) evaluation of *a priori* selected candidate genes known to affect brain development or possibly involved in the pathogenesis of autism. Genome wide association studies (GWAS) examine associations between disease and common genetic variants. Genetic variants can be either inherited or caused by *de novo* changes (*de novo* mutations account for nearly 10% of people diagnosed with ASD; Sebat et al., 2007). Single nucleotide polymorphisms (SNPs) are small variations in the DNA sequence that occur when a single base is altered. Copy number variations (CNVs) are structural changes in DNA including deletions, inversions, insertions, duplications and repeated sequences. SNPs and CNVs have both been reported to play a major role in autism incidence (Iossifov et al., 2012; Neale et al., 2012; O'Roak et al., 2012; Sanders et al., 2012; Sebat et al., 2007; Yu et al., 2012). More precisely, common SNPs acting additively have been reported as a source of risk for ASD with heritability exceeding 60% for ASD individuals from multiplex families and approximately 40% for simplex families (Klei et al., 2012). Several CNV studies (Pinto et al., 2010; Sanders et al., 2011a; Sebat et al., 2007) identified also structural changes in DNA which contribute to the risk for ASD. Furthermore, genome-wide expression studies comparing individuals with autism to non-autistic siblings showed alterations in gene expression profile affecting neuronal development pathways (Hu et al., 2009). However, the literature on genetic variants in relation to ASD strengthens the idea of high genetic heterogeneity in ASD given that different loci and chromosomes are involved (Walsh et al., 2011; State and Levitt, 2011) and the need to discuss how such heterogeneity can lead to a common cognitive behavioral phenotype.

The emergence of the concept of "syndromic autism" (also called "complex autism": autism associated with one or more morphological signs or symptoms helping in the identification of specific genetic disorders) opposed to "non-syndromic autism" (also called "simplex autism": isolated and idiopathic autism with moderate intellectual disability to normal intellectual functioning and no associated sign or symptom except the presence of seizures) highlights also the etiological heterogeneity of "autism" (Miles et al., 2005; Cohen et al., 2005a). The concept of "syndromic autism" is important for those involved in genetic studies of autism (in order to reduce the heterogeneity of their samples), but has also practical clinical implications, in terms of diagnostic strategies, early detection or prevention of co-morbidity, therapeutic strategies with specific treatment and follow up, and genetic counselling. Progress in epidemiological, molecular and clinical genetics has led recently to new findings in the field of genetics of neuropsychiatric disorders, including genetics of autism, and has advanced current knowledge on genetic disorders associated with autism. A review of various genetic disorders associated with autistic syndrome is presented and discussed in this article with regard to possible underlying mechanisms leading to a similar clinical phenotype of autism.

2. Genetic disorders associated with autistic syndrome

Genetic disorders associated with autistic syndrome are presented in Table 1. As underlined by Abraham and Geschwind (2008), Table 1 indicates that each of the many known genes or genomic regions associated with autism accounts usually for less than 2% of autism cases (except for Fragile X syndrome), suggesting high genetic heterogeneity. Furthermore, Table 1 indicates clearly in the chromosomal disorders part that a duplication or deletion occurring at the same locus can both lead to a phenotype of autism (see for example, the 16p11.2, 1q21.1, 15q11-q13, 22q13.3, or 22q11.21 deletion/duplication), suggesting that genetic disequilibrium at certain loci might be more important than gene-dosage effects. Interestingly, these "hot spots" were also found in schizophrenia (Ikeda et al., 2010; Levinson et al., 2011), suggesting relationships between autism and schizophrenia. It is noteworthy that many CNVs (deletion/duplication) associated with autism are observed in schizophrenia but also in intellectual disability, epilepsy, learning disorder, bipolar disorder and many other disorders (see Table 2). Similar observations are reported for single gene disorders associated with autism. Indeed, deletion of the coding sequence in *MECP2* causes Rett Syndrome (Neul et al., 2008) but *MECP2* duplications have also detrimental neurodevelopmental effects given that autistic features, intellectual disability and seizures are common in boys with *MECP2* duplications (Neul, 2012; Ramocki et al., 2009; del Gaudio et al., 2006). Further research is necessary to better ascertain the underlying mechanisms of such genetic disequilibrium effects in chromosomal disorders as well as single gene disorders.

How can we explain that so many genetic disorders involving different chromosomes and genes can lead to a common phenotype of autism with, for several of these genetic disorders, apparently similar cognitive-behavioral features? In response to this question, the following hypotheses can be raised: 1) the genes involved might share some common neurodevelopemental function; 2) they might be controlled by the same "master" gene above or control other common genes with a cascade effect affecting the development of the Central Nervous System (CNS) or interact with the same gene that would modify their expression; 3) they might interact with environmental factors and share some common mechanisms, such as epigenetic mechanisms (gene X environment interactions); 4) a common bias introduced by intellectual disability cannot be ruled out and has to be discussed; 5) finally, the cognitive-behavioral phenotype may in fact differ. These five hypotheses are developed below.

2.1. Common neurodevelopmental function

The related genes might be involved in CNS development and functioning. This hypothesis is supported by several reports of autism associated with mutations of genes encoding for proteins involved in neural communication (synapse formation, adhesion, stabilisation and homeostasis, synaptic development, dendritic sprouting, neural growth, etc.), such as neuroligins NLGN3 and NLGN4 (postsynaptic cell adhesion proteins), neurexin1 (NRXN1 forming a complex with neurologin1), SHANK3 (a postsynaptic scaffolding protein), Cell adhesion molecule-1 (CADM1 driving synapse assembly), protocadherin10 (synaptic development) or contactin4 (CNTN4 involved in the formation, maintenance and plasticity of neural networks) (for more details, see Table 1, Walsh et al., 2011, and State and Levitt, 2011). Also, mutations of the related genes can provoke alterations in synaptic and neuronal signalling through impaired glutamatergic or calcium-channel signalling (Voineagu et al., 2011). It is noteworthy that molecular genetic risk factors for autism linked to alterations in calcium-channel signalling are reported by several authors (Smoller et al., 2013). It could appear interesting that genetic defects of neural communication are found in autism which involves social communication impairment. More generally, a deficit in postnatal synaptic plasticity is observed in neurodevelopmental disorders (Zoghbi, 2003).

The Geschwind laboratory findings support the hypothesis of ASD risk genes sharing common neurodevelopmental function. Indeed, their findings indicate that there are shared, convergent biology and neuropathology in post-mortem brain from individuals with ASD compared to normal brain cells involving transcriptional regulation, synaptic function (including the step-wise development of synaptic function and its modulation by neuro-inflammatory cells in ASD), and microglial regulation of neural function (Parikshak et al., 2015; Parikshak et al.,

Table 1
Main genetic disorders associated with autistic syndrome.

Genetic disorder (References)	Estimated rate (%) of the disorder in autism	Estimated rate (%) of autism in the disorder	Degree of intellectual disability (ID)	Autistic behaviors	Other behaviors	Other symptoms
CHROMOSOMAL DISORDERS						
Maternal* 15q11-q13 duplication (Cook et al., 1997; Bolton et al., 2001a; Cohen et al., 2007; Schroer et al., 1998; Wandstrat et al., 1998; Sutcliffe and Nurmi, 2003; Jacobsen et al., 1998; Steffenburg et al., 1996; Peters et al., 2004; Chamberlain et al., 2010; Rangasamy et al., 2013; Grafodatskaya et al., 2010)	1–2	80–100	Severe	Severe autistic syndrome with severe expressive language impairment	Hyperactivity and aggression	Seizures (75%), hypotonia, genitor/urinary abnormalities
Angelman syndrome* (maternal 15q11-q13 deletion, paternal uniparental disomy, mutations of *UBE3A* that encodes an ubiquitin E3 ligase) (Chamberlain et al., 2010; Huang et al., 2011; Mabb et al., 2011; Meng et al., 2012)	1	48–80	Severe	No language, stereotyped behaviors, sameness	Attention Deficit with Hyperactivity Disorder (ADHD), paroxysmal laughter, tantrums	Facial dysmorphism, microcephaly, seizures (> 1year), ataxy, walking disturbance
Prader-Willi syndrome* (maternal uniparental disomy at 15q11-q13, paternal deletions) (Chamberlain et al., 2010; Veltman et al., 2004; Descheemaeker et al., 2006; Hogart et al., 2010; Horsthemke and Wagstaff, 2008; Buiting, 2010; Cassidy et al., 2012) Paternal 15q11-q13 duplication (only four cases repoted to be associated with autism): behavioral phenotype similar to Prader-Willi syndrome (Veltman et al., 2005; Bolton et al., 2001b; Roberts et al.,2002)	Not Available (NA)	19–37	Mild to moderate	Motor and verbal stereotypies, rituals	Hyperphagia, obsessive-compulsive traits, temper tantrums	Obesity, growth delay and hypogonadism, facial dysmorphism, Hypotonia
Phelan-McDermid* syndrome (Inherited, *de novo* deletions at 22q13.3 leading to loss of *SHANK 3*) 22q13.3 duplication (Goizet et al., 2000; Manning et al., 2004; Prasad et al., 2000; Phelan et al., 2001; Soorya et al., 2013; Shcheglovitov et al., 2013; Phelan and McDermid, 2012; Peca et al., 2011; Jafri et al., 2011)	NA	75–84	Severe	Variable autistic syndrome with social communication impairments, including delayed or absent verbal language	Global developmental delay	Dysmorphic features, hypotonia, gait disturbance, recurring upper respiratory tract infections, gastroesophageal reflux and seizures
16p11.2 duplication 16p11.2 deletion (Marshall et al., 2008; Hanson et al.,2010; Weiss et al., 2008; Kumar et al., 2008; Fombonne et al., 1997)	1	33	Severe	Severe autistic syndrome with speech impairment	Gross and fine coordination difficulties, anxiety, ADHD, Schizophrenia (SCZ)	Hypotonia (Multiple congenital anomalies are possible with more distal region)
Inverted 8p21-23 (Fisch et al., 2010, 2011)	NA	30–57	Variable	Mild to moderate autistic syndrome with absent or delayed verbal language	ADHD	Minor facial dysmorphism, hypotonia, agenesis of the corpus callosum, possible heart defect

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Table 1 (*continued*)

Genetic disorder (References)	Estimated rate (%) of the disorder in autism	Estimated rate (%) of autism in the disorder	Degree of intellectual disability (ID)	Autistic behaviors	Other behaviors	Other symptoms
Down syndrome* (trisomy 21) (Bregmen and Volkmar, 1988; Mariner et al., 1986; Ghaziuddin, 1997; Moss and Howlin, 2009; Jiang et al., 2013)	2	5–10	Variable but usually severe when autism	Severe autistic syndrome	–	Facial dysmorphism, heart and intestine malformations
Smith-Magenis syndrome (17p11.2 deletion) (Smith et al. 1986; Vostanis et al., 1994; Cohen et al., 2005b)	< < 1	80–100	Variable	Self-injurious behaviors (SIB) and stereotypies, sameness	Tantrums, possible social contact, sleep disturbance	Facial dysmorphism, peripheral neuropathy, hypotonia
2q37 deletion (Ghaziuddin and Burmeister, 1999; Devillard et al., 2010; Galasso et al., 2008; Falk and Casas, 2007)	< 1	25–35	Mild to moderate	Severe communication impairment, stereotyped behaviors	Holoprosencephaly, hypotonia, hyperactivity, Obsessive-Compulsive Disorder (OCD), aggression, sleep problems	Facial dysmorphism, microcephaly, growth delay/ short stature, intestine and heart malformations, seizure
22q11.21 duplication (Lo-Castro et al., 2009a,b; Portnoï, 2009; Baker and Skuse, 2005) 22q11 deletion (DiGeorge/Vélocardio-facial syndrome)	NA	< 10	Normal to severe ID	Autistic syndrome, Pervasive Developmental Disorder-Not Otherwise Specified PDD-NOS (ICD-10 criteria)	Learning disability, anxiety, ADHD, oppositional-defiant disorder, OCD, motor problems	Facial dysmorphism, microcephaly, growth delay/ short stature, craniofacial abnormalities/cleft palate, heart defect, hypotonia
1q21.1 Copy-Number Variation (CNV) (1q21.1 deletion/duplication) (Mefford et al., 2008; Brunetti-Pierri et al., 2008)	NA	< 30	Normal to mild ID	Autistic syndrome, PDD-NOS (ICD-10 criteria)	Developmental delay, learning disability, anxiety, ADHD, aggression, SCZ and hallucination	Microcephaly (deletion) Macrocephaly (duplication)
Williams-Beuren syndrome* (7q11.23 deletion) and Reciprocal 7q11.23 duplication syndrome (Berg et al., 2007; Depienne et al., 2007; Edelmann et al., 2007; Gagliardi et al., 2003; Lincoln et al., 2007; Sanders et al., 2011b; Somerville et al., 2005; Van der Aa et al., 2009; Makeyev et al., 2012; Tordjman et al., 2012, 2013)	< 1	< 5	Mild to moderate	Autistic syndrome	Overfriendliness, overtalkativeness, visual spatial deficit, hyperacusis, feeding and sleep problems	Facial dysmorphism, short stature, heart and endocrine malformations, hypercalcemia
Turner syndrome* (most common monosomy For X chromosome) (Skuse et al., 1997; Grafodatskaya et al., 2010)	NA	3	Usually normal IQ	Females monosomic for the maternal chromosome x score significantly worse on social adjustment and verbal skills	–	Short stature, skeletal abnormalities, absence of ovarian function, webbed neck, lymphedema in hands and feet, heart defects and kidney problems
Beckwith-Wiedemann* syndrome (abnormal expression of imprinted genes on chromosome 11p15.5 such as *IGF2* and/or *CDKN1C*) (Kent et al., 2008; DeBaun et al., 2003; Smith et al., 2007; Weksberg et al., 2010)	NA	6.8 (replication needed)	Usually normal IQ	Autistic syndrome	–	Pre- and postnatal overgrowth (hemihyperplasia, macroglossia, visceromegaly) and increased risk of embryonal tumors
SINGLE GENE DISORDERS						
CHARGE syndrome* (*CHD7*, 8q21.1) (Johansson et al., 2006, 2010; Smith et al., 2005; Hartshorne et al., 2005; Patten et al., 2012; Blake and Prasad, 2006)	< 1	15–50	Variable but often normal IQ	Variable autistic syndrome	Hyperactivity, obsessive-compulsive traits, tic disorders	Coloboma of the eye, Heart defects, Atresia of the nasal choane, Retardation of growth and/or development, Genital/urinary abnormalities, Ear abnormalities/ deafness

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Table 1 (*continued*)

Genetic disorder (References)	Estimated rate (%) of the disorder in autism	Estimated rate (%) of autism in the disorder	Degree of intellectual disability (ID)	Autistic behaviors	Other behaviors	Other symptoms
Tuberous sclerosis (*TSC1*, 9q34) (*TSC2*, 16p13.3)(Bolton et al., 2002; Curatolo et al., 2008)	1–4	25–60	Variable	Severe autistic syndrome	Learning disorder	Ectodermal anomalies, renal lesions, seizures
San Filippo syndrome (*SGSH*, 17q25.3) (Nidiffer and Kelly, 1983; Wraith, 1995; Ritvo et al., 1990)	1 (replica-tion needed)	80–100	Severe	Social withdrawal, stereotyped behaviors impulsivity, language impairment, inappropriate affects	Progressive loss of acquisitions	Motor regression, hepatomegaly
Rett Syndrome* (*MECP2*, Xq28 1.1.2 MIM entry # 312750) (Amir et al., 1999; Bienvenu et al., 2000; Olsonn and Rett, 1990; Meloni et al., 2000; Smeets et al., 2005; Young et al., 2008; Martinowitch et al., 2003; Gadalla et al., 2011; Bahi-Buisson and Bienvenu, 2012; Garg et al., 2013; Neul, 2012; Neul et al., 2010; Cuddapah et al., 2014b)	< 1 in female	80–100	Severe	Autistic behaviors such as social withdrawal or eye gaze avoidance occur often during the regression stage (stage 2) in some individuals with Rett Syndrome, especially in the less severely affected children corresponding to an atypical form of Rett Syndrome, the preserved speech variant (involving also less typical hand stereotypies)	Stagnation stage (6–18 months) in girls, then regression stage (12–48 months) with total or partial loss of spoken language and volitional hand use (associated with typical stereotyped hand movements), pseudostationary stage (2–10 years), and late motor deterioration (> 10 years)	Head growth deceleration, progressive motor neuron (gait and truncal apraxia, ataxia, decreasing mobility) and respiratory (hyperventilation, breath holding, apnea) symptoms
PTEN macrocephaly syndrome (*PTEN*, 10q23.31) (McBride et al., 2010; Lintas and Persico, 2009; Buxbaum et al., 2007; Herman et al., 2007; Goffin et al., 2001)	4 in PDD with macro-cephaly	NA	Severe	Autistic syndrome and language delay	–	Progressive macrocephaly, developmental delay, macrosomy, tumors in adulthood
Smith-Lemli-Opitz syndrome (*DHCR7*, 1q12-13) (Ryan et al., 1998; Kelley and Hennekam, 2000; Tierny et al., 2001; Tierny and Nwokoro, 2001; Tint et al., 1994)	NA	50	Variable	SIB, stereotypies ("opisthokinesis") language impairment	Sensory hyper-reactivity, irritability, sleep disturbance	Facial dysmorphism, cleft palate, congenital heart disease, 2–3 toe syndactyly, hypospadias
Phenylketonuria (*PAH*, 12q22-q24.1) (Cohen et al., 2005b; Baieli et al., 2003; Miladi et al., 1992)	NA	NA	Severe	Self-injurious behavior, lack of social responsiveness	Temper tantrums, hyperactivity	Eczema, hypertonia, seizures, hypo-pigmentation
Adenylosuccinate lyase deficiency (*ASL*, 22q13.1–13.2) (Fon et al., 1995; Jaeken and Van den Berghe, 1984; Race et al., 2000; Stone et al., 1992)	< 1	80–100	Variable	Severe autistic syndrome	–	Seizures
Creatine deficiency syndrome (*GAMT*, 19p13.3) (*CRTR*, Xq28) (Nasrallah et al., 2010; Póo-Argüelles et al., 2006)	< 1	80–100	Severe	Severe autistic syndrome with poor language	–	Seizures, hypotonia
SHANK 3 (22q13.3) (Durand et al., 2007; Moessner et al., 2007)	< 1	NA	NA	Severe autistic syndrome with no language	–	–
Neurexin family: Neurexin 1 (*NRX1*, 2p16.3) (Feng et al., 2006; Ching et al., 2010)	1	NA	Variable	Autistic syndrome	Hyperactivity, depression, learning disability, but also normal behavior	Seizures, hypotonia, facial dysmorphism?

(*continued on next page*)

Table 1 (*continued*)

Genetic disorder (References)	Estimated rate (%) of the disorder in autism	Estimated rate (%) of autism in the disorder	Degree of intellectual disability (ID)	Autistic behaviors	Other behaviors	Other symptoms
Contactin Associated Protein-like 2 (*CNTNAP2*, 7q35) (Alarcon et al., 2008)	NA	NA	Variable	Autistic syndrome with verbal language impairment	–	Seizures
Contactin 4 (*CNTN4*, 3p26.2–3p26.3) (Fernandez et al., 2004a, 2008; Roohi et al., 2008)	< 1	NA	Variable	Autistic syndrome, PDD-NOS (ICD-10 criteria)	Visual spatial impairment, regression	Facial dysmorphism, developmental delay, hypotonia, ptosis.
Cell adhesion molecule-1 (*CADM1*, 11q22.3–23.2) (Zhiling et al., 2008; Fujita et al., 2012)	NA	NA	NA	Autistic syndrome with especially social communication impairment including verbal language impairment	–	–
Protocadherin 10 (*PCDH10*, 4q28) (Morrow et al., 2008)	< 1	NA	NA	Autistic syndrome	–	–
Neuroligin family: Neuroligin 3 (*NLG3*, Xq13) Neuroligin 4 (*NLG4*, Xq22.33) (Jamain et al., 2003; Laumonnier et al., 2004)	< 1	NA	Variable	Severe autistic syndrome, PDD-NOS (ICD-10 criteria)	Regression	Tic
Fragile X *[a] (*FMR1*, Xq27.3) (Fisch, 1992, 1993; Rogers et al., 2001; Bailey et al., 2001; Belmonte and Bourgeron, 2006; Kau et al., 2004; Loesch et al., 2007; Clifford et al., 2007; Harris et al., 2008; Dölen et al., 2010; McLennan et al., 2011; Bar-Nur et al., 2012; Hagerman et al., 2012; Tabolacci and Chiurazzi, 2013)	2–8	10–33	Variable	Poor eye contact, social anxiety, language impairment, stereotyped behaviors	Hyperactivity with attention deficit, sensory hyper-reactivity	Facial dysmorphism, macro-orchidism

*The asterisk indicates genetic disorders with epigenetic mechanisms associated with autistic syndrome (the list is not exhaustive).

[a] The estimated rate of FXS in individuals diagnosed with autism varies, according to Kau et al. (2004) from 2% to 8% (in fact from 0 to 8% according to the studies), and the estimated rate of autism among FXS individuals varies from 10% to 33% (Yan et al., 2005; Belmonte and Bourgeron, 2006). However, in a *meta*-analysis of published studies, Jamain et al. (2003) concluded that no evidence exists for an increased rate of autism among FXS individuals, nor is there evidence for an increased rate of FXS among individuals with autism.

Table 2
Copy number variants (CNVs) associated with autism spectrum disorder (ASD) and other disorders.

Region and CNV type (Microarray)	Candidate genes in the region	Phenotypes[a]
1q21.1 Deletion/Duplication	*HYDIN*	ASD, SCZ, ID, ADHD, IGE deficit
2q37 Deletion	*5-HTR2B*	ASD
2p16.3 Del	*NRXN1*	ASD, SCZ, ID
3q24 Deletion/Duplication	*SLC9A9*	ASD
3q29 Deletion/Duplication	*PAK2, DLG1*	ASD, SCZ, ID, ADHD, EP
3p26 Deletion	*CNTN4 and CNTN6*	ASD
3p14.1 Deletion	*SUCLG2, FAM19A4, FAM19A1*	ASD
4q13.3 Duplication	*COX18, ANKRD17*	ASD
4q33 Deletion	*AADAT and HSP90AACP*	ASD
5q23.1 Duplication	*DMXL1, TNFAIP8*	ASD
6p21.2 Deletion	*SAYSD1*	ASD
7q11.23 Deletion/Duplication		ASD,SCH, ID, EP
7q22.1 Deletion	*RELN*	ASD
7q31.2 Deletion/Duplication	*FOXP2, WNT2, MET*	ASD
7q35-q36 Deletion	*EN2, CNTNAP2*	ASD, SCH, ID, EP
8q11.23 Duplication	*RGS20, TCEA1*	ASD
10q11.22 Duplication	*OGDHL, C100rf53*	ASD
10q11.23 Duplication	*FMRPD2P1, FMRPD2*	ASD
11q13.3-q13.4 Deletion	*SHANK2*	ASD, ID
12q13.13 Deletion	*KRT76 and KRT3*	ASD
13q14.2-q14.1 Deletion	*5-HTR2A*	ASD
15q11.2 Deletion/Duplication	*CYF1P1*	ASD, SCZ, ID, DD, IGE deficit, OCD
15q11-13 Duplication	*GABRA5, GABRB3, GABG3, UBE3A, SNRPN, CHRNA7*	ASD, SCZ, ID, EP, Ataxia
15q13.3 Deletion/Duplication	*CHRNA7*	ASD, SCZ, ID, EP
16p11.2 Deletion/Duplication	*DOC2A, ERK1*	ASD, SCZ, ID, EP, DD, LD
16p13.11 Deletion/Duplication	*NDE1*	ASD, SCZ, ID, EP, ADHD, IGE deficit
17q11.2 Deletion	*SLO6A4*	ASD
17q12 Deletion/Duplication		ASD, SCZ, ID, EP
18q21.1 Deletion	*TCF4, MED1*	ASD
22q11.2 Deletion/Duplication	*PRODH, COMT, DGCR6, TBX1, CRKL, FGF8*	ASD, SCZ, ID, ADHD, EP, DD, LD
22q13.3 Deletion	*SHANK3*	ASD, SCZ, ID, DD
Xp22.31 Deletion/Duplication	*NLGN4*	ASD, SCH, ID, BD, Tourette's Disorder
Xp22.13 Duplication	*ARX*	ASD, ID, EP
Xq13.1 Deletion/Duplication	*NLGN3*	ASD, SCH, ID, BD
Xq28 Deletion	*MAGEA8, MECP2*	ASD

Adapted from Amiet et al. (2013), De Lacy and King (2013), Matsunami et al. (2013), Schaefer and Mendelsohn (2013).

[a] Abbreviations: ASD, Autism Spectrum Disorder; SCZ, Schizophrenia; ID, Intellectual Disability; EP, Epilepsy; ADHD, Attention Deficit and Hyperactivity Disorder, DD, Developmental Delay; LD, Learning Disorder; BD, Bipolar Disorder; OCD, Obsessive Compulsive Disorder.

2013; Voineagu et al., 2011).

Dendritic sprouting is also involved in neural communication, and especially in synaptic circuitry. Mutations related to dendritic sprouting might be relevant here given the dendritic abnormalities found in different genetic disorders associated with autism, such as Rett, fragile X or Down syndrome, and in their relevant animal models (Table 3). These dendritic abnormalities might lead to a similar cognitive-behavioral profile, and notably cognitive impairments. It is noteworthy that dendritic abnormalities are the most consistent anatomical correlates of intellectual disability (Kaufmann and Moser, 2000). According to Kaufman and Moser (2000), the most obvious mechanism by which dendritic pathology in general and reductions in dendritic arborizations in particular could lead to such cognitive impairments is a decrease in the cortical postsynaptic surface leading in turn to a dysfunction in the synaptic circuitry. Another mechanism has been postulated: these different genetic disorders may share a common defect in the regulation of gene expression leading to dendritic abnormalities (Kaufmann and Moser, 2000). Thus, MeCP2 (Methyl-CpG-binding Protein 2 in Rett Syndrome) is involved in transcriptional regulation whereas FMRP (Fragile-X Mental Retardation Protein) modulates protein synthesis. Interestingly, some studies demonstrate that environmental stimulation leads to increases in length and complexity of dendritic arborizations in several cortical regions, even in adult life (Greenough, 1984). This environmental effect might be related to the observed positive effects of environmental stimulation on cognitive development of children with Down syndrome (Ludlow and Allen, 1979).

It is noteworthy that a mutation of a gene involved in synaptic formation or brain development can be associated or not with autism depending on the size of the mutation or truncated protein. The *NLGN4* gene, encoding for a membrane that mediates the synapse and located towards the telomeric end of the X chromosome, offers an interesting illustration. A mutation of the *NLGN4* gene (precisely in codon 396) was associated with Asperger and Kanner autism in the same family (Jamain et al., 2003). However, another mutation of the *NLGN4* gene (precisely in codon 429) was not associated with autism but with intellectual disability (Laumonnier et al., 2004). The phenotype depends here on the size of the truncated protein. Indeed, the size of the truncated protein resulting from the mutation in codon 396 was different than the one resulting from the mutation in codon 429. In this vein, disruption of one copy of *MECP2* in typical Rett Syndrome is associated with autistic behaviors in a minority of cases but there is a classic loss of spoken language, whereas mutations of the *MECP2* gene at the end of the fourth exon (at R133C) in the preserved speech variant (atypical Rett Syndrome) are associated with autistic behaviors in a large majority of cases but spoken language is preserved (Neul, 2012; Neul et al., 2010). These findings highlight that a slight change in the mutation can be associated with important clinical changes. The severity of the phenotype has been also associated with the size of the mutation in Williams-Beuren syndrome (Tordjman et al., 2013). Finally, as suggested by Cuddapah et al. (2014a) for Rett Syndrome, the relationship between the severity of the phenotype and the type of mutation may depend on the effect of the mutation in the gene (*MECP2*) on the protein functionality (relatively preserved or severely altered functionality of MeCP2).

Table 3
Dendrite and/or neural abnormalities in genetic disorders associated with autistic syndrome.

Genetic disorder (References)	Genetic event associated with the disorder	Dendrite and/or neural abnormalities in human patients, organism models and/or neurons in vitro
Angelman Syndrome (Kishino et al., 1997; Jay et al., 1991; Sato and Stryker, 2010; Dindot et al., 2008; Lu et al., 2009)	maternal deletion at 15q11-q13, paternal uniparental disomy) disruption of the function of the maternally inherited *UBE3A*	Human patients: decrease in dendrite arborization and in the number of dendrite spines in pyramidal neurons (visual cortex) Mouse Model (*UBE3A* maternal-deficient *(m-/p +*) mouse): reduced spine density of basal dendrites (pyramidal neurons, visual cortex; UBE3A maternal-deficient mice expressing a $Ube3a^{YFP}$ fusion gene display *UBE3A*-YFP fusion gene: abnormalities in dendrite spine morphology, number and length modifications in cerebellar Purkinje cells and pyramidal neurons (hippocampus and cortex) *UBE3A*-null mutant drosophila: reduced dendrite branching of sensory neurons
Smith-Magenis Syndrome (Boddaert et al., 2004; Derwińska et al., 2012; Shelley and Robertson, 2005)	Interstitial deletion (2–9 Mb) 7p11.2	Human patients: reduced grey matter, absence of L-DOPA in cerebrospinal fluid, segmental axon demyelination and re-myelination *Pitx3(-/-)* mouse: selective loss of dopaminergic neurons
Smith-Lemli-Opitz syndrome (Elias et al., 2003; Korade et al., 2009; Jiang et al., 2010; Waage-Baudet et al., 2005)	Defect in 7-dehydrocholesterol reductase (*Dhcr7*) activity	Human patients: Post rod cell photo-response parameters (electroretinogram) impaired Mouse model: Deficient Dhcr7 cell lines: incomplete myelination; $Dhcr7^{\Delta 3-5/\Delta 3-5}$ targeted mouse: hippocampal axonal and dendrite abnormalities; *Dhcr7(-/-)* mouse: hippocampal path-finding errors
Fragile × syndrome (Irwin et al., 2001; Jacobs et al., 2010; Berman et al., 2012; Qin et al., 2011)	Extension of CGG in *FMR1*	Human patients: dendrite spines with immature morphology in cortex Mouse model: *FMRP [FVB.129P2 (B6)-Fmr1tm1Cgr]* deficient mouse: abnormal morphological features in dendrites; *CGG KI* mouse carrying an expanded CGG trinucleotide repeat on Fmr1: decrease in dendrite branches proximal to the soma, decrease total dendrite length; *FXPM KI [(CGG·CCG)n]* mouse: decrease in dendrite arborization (medial prefrontal cortex, basal lateral amygdala, and hippocampus)
Williams–Beuren syndrome (Kirov et al., 2012; Capossela et al., 2012; Proulx et al., 2010)	Hemizygous 7q11.23 deletion	deficits in NMDAR postsynaptic signalling complex and in neuronal activity-regulated cytoskeleton-associated protein Mouse model: *Eif4h(-/ +*)mouse: reduced dendrite spines; *Gtf2ird1(-/ +*) mouse: apical dendrites from layer V pyramidal cells extend to the pial surface and arborize extensively in layer II/III
San Filippo Mucopolysaccharidosis type III (MPSIII) (Takashima et al., 1985; Ferrer et al., 1988; Hocquemiller et al., 2010)	interruption of the lysosomal degradation of heparan sulfate	Human patients: long dendrites in pyramidal neurons, dendrite swellings in Purkinje cells $C57Bl/6^{NaGlu+/-}$ mouse (model of MPSIII): overgrowth of neuron trees, involving both dendrites and axons
Tuberous sclerosis (Machado-Salas, 1984; Tavazoie et al., 2005; Meikle et al., 2008; Bateup et al., 2011; Takei et al., 2004)	mutations in the *TSC1* (9.q14) or *TSC2* (16p13.3) genes	Human patients: small dendrites and few spines in pyramidal cells, distorted apical dendrites Mouse model: *Tsc1 (-/-)* or *Tsc2 (-/-)* mouse: enlargement of somas and dendrite spines; *Tsc1c-SynICre* mouse: decrease of dendrite spine density; postnatal deletion of *Tsc1* in vivo (hippocampus CA1 neurons): absence of difference in spine density In vitro mammalian model: Decrease of dendrite spine density
Contactin 4; human neuroblastoma cells (Fernandez et al., 2004b; Kaneko-Goto et al., 2008; Yoshihara et al., 1995)	deletion at 3p26.3	differentiates the human neuroblastoma cells mouse model: Isoform "BIG-2A" disease- Mouse model: BIG-2-deficient mice: altered axon guidance; in vitro mammalian cell model: CNTN4 deficiency impairs olfactory axon convergence to glomeruli
Rett's syndrome (Kaufmann et al., 2000; Marshak et al., 2012; Belichenko et al., 1994; Chen et al., 2001; Stuss et al., 2012; Vonhoff et al., 2012)	Mutations in the *MeCP2* gene (Xq.28)	Human patients: smaller umber of dendrites Xenopus model: *MeCP2* overexpression in Xenopus reduces dendrite formation, morphology and connectivity; decreased number and regional loss of dendrite spines Mouse model (*Mecp2* mutant mice: $Mecp2^{tm1.1Jae}$/Mmcd): reductions in neural cell size, dendrite branching and spine density in layer 5 motor cortical neurons associated with MeCP2 mutations Drosophila model: the heterologous expression of MECP2 in Drosophila induces moto-neuron dendrite defects (reduction of the number of dendrites)
Cowden syndrome and Duclos disease; PTEN macrocephaly syndrome (Pilarski and Eng, 2004; Amiri et al., 2012; Drinjakovic et al., 2010; Kwon et al., 2006; Perandones et al., 2004)	Phosphatase and tensin homologue gene mutations (10q23.31)	Human patients: dysplastic gangliocytoma of the cerebellum; Lhermitte- ataxia, increased intracranial pressure, and seizures Mouse model: Pten (-/-): tissue (brain) specific deleted mouse induces abnormal dendrite arborization in cerebellum and dentate gyrus; *Pten (-/-)* mouse: hippocampus hypertrophied neurons with abnormal polarity Xenopus model: Xenopus retinal ganglion cells: modulation of Pten regulate neuronal arborization

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Table 3 (*continued*)

Genetic disorder (References)	Genetic event associated with the disorder	Dendrite and/or neural abnormalities in human patients, organism models and/or neurons in vitro
Adenylosuccinate lyase deficiency (Mierzewska et al., 2009; Jurecka et al., 2012)	Adenylosuccinate lyase gene (*ADSL*) mutations (22q13.1)	Human patients: hypo-myelination, damage of oligodendroglia, axons and neural cells
Prader-Willi syndrome (Lee et al., 2005; Sharma et al., 2005; Takumi, 2011; Hashemi et al., 2007; Bonin et al., 2007)	15q11-q13 deletion and duplication Paternally expressed genes: *Mkrn3* (makorin, ring finger protein, 3), *Magel2* (melanoma antigen, family L, 2), *NDN (Necdin)*, *Snrpn* (small nuclear ribonucleoprotein N), *Snur* (upstream reading fram). Maternally expressed genes *Ube3a* (ubiquitin protein ligase E3A) and *Atp10a* (ATPase, class V, type 10A). Non-imprinted genes *Gabrb3* ($GABA_A$ receptor, subunit beta 3), *Gabra5* ($GABA_A$ receptor, subunit alpha 5), *Gabrg3* ($GABA_A$ receptor, subunit gamma 3), *Oca2* (oculocutaneous albinism II), and *Herc2* (hect (homologous to the E6-AP (UBE3A) carboxyl terminus) domain and RCC1 (CHC1)-like domain (RLD) 2)	*Magel2* −/- mouse: cytoskeletal rearrangements during neurite outgrowth; *Ndn*^{tm2Stw} necdin null mouse: morphological defects in the axonal tracts, increased neuron arborization antisense knockdown of profilin I and II isoforms inhibits neurite outgrowth and causes axonal path finding defects by disturbing the normal regulation of microfilament growth by profilins. *Ube3a see above* *Atp10a* (NI) *gabrb3* −/− mouse modulates locus coeruleus noradrenergic dendrite development *Gabra5* α5−/− mouse regulates the action potentials *Gabrg3* NI *Oca2* NI *Herc2* NI
Shank1 (Hung et al., 2008)	SH3/ankyrin domain gene 1, molecular scaffolds in the postsynaptic density protein	Mouse Model (*Shank1(−/−)*specific mouse): reduced size of dendrite spines and basal synaptic transmission
Shank2 (Schmeisser et al., 2012)	SH3/ankyrin domain gene 2, molecular scaffolds in the postsynaptic density protein	Mouse Model (*Shank2(-/-)* specific mouse): reduced dendrite spines, basal synaptic transmission, and frequency of miniature excitatory postsynaptic currents
Phelan-McDermid syndrome Shank3 (Durand et al., 2012; Bangash et al., 2011)	*SH3/ankyrin* domain gene 3, molecular scaffolds in the postsynaptic density protein	Rat model: HEK293T and COS-7 cells for transient transfection carrying mutated forms of GFP–Shank3: different targeted mutations induce abnormal dendrite spines (width and length) Mouse model: Shank3 (+/ΔC deletion of the C-terminus) mice: no change in spine density or morphology but reduced amplitude of NMDAR responses.
16p11.2 (Blaker-Lee et al., 2012)		Loss of function of the genes carried by the syntenic region generates abnormal axon tracts for 6 of the genes of the region
CHARGE syndrome (Layman et al., 2009; Hurd et al., 2010; Melicharek et al., 2010)	Hemizygous loss of function of chromosome-helicase-DNA-binding protein 7 (*CHD7*) in 2/3 of the cases	Mouse model: *Chd7Gt/+* ENU mutant mouse: olfactory neuron disorganization and loss of the orderly arrangement; *Chd7Gt/+* mutant mouse reduced neuroblasts in both epithelium and ganglion. Drosophila model: Kismet/CHD7 drosophila axon migration defects
Neurexin1 (de Wit et al., 2009)	Mutation or alternative splicing	In vitro neuron culture: Neurexin1 modulates the density of excitatory synapses and not of inhibitory synapses in interaction with leucine-rich repeat transmembrane protein
Contactin associated protein-like 2 (*CNTNAP2*) (Strauss et al., 2006; Peñagarikano et al., 2011; Bel et al., 2009)	*CNTNAP2* mutations 7q35	Human patients: neurons with abnormal dendrite structure and inappropriate orientation ion patients with CNTNAP2 Mouse Model (*Cntnap2(-/-)* mouse): abnormal neuronal migration, reduced number of interneurons, and abnormal neuronal network activity; Primary hippocampal cell culture: somatodendrite internalization of *CNTNAP2* required for normal vesicle transport
Protocadherin10 (Uemura et al., 2007)	Deletion in *PCDH10* (4q28)	Mouse Model (*Pcdh10 (-/-)* mouse): impairment of elongation of striatal axons and patterning of the putative guidance cues for thalamo-cortical projections.
Neuroligin 4 (Zhang et al., 2009)	Deletion in *NLGN4* (Xq22.33)	Mouse Model (R87W substitution in primary hippocampal mouse neurons): inactivated the synapse-formation activity of Neuroligin 4, and cancelled the effect of NL4 on synapse functioning
Neuroligin 3 (Etherton et al., 2011)	Deletion in *NLGN3* (Xq13)	*NL3 (R451C)* knock-in mouse: The mutation did not affect the brain tissues with exception for hippocampus. Increased AMPA receptor-mediated excitatory synaptic activity in hippocampal CA1, increased dendrite branching and altered structure of synapses in the stratum radiatum.
Creatine deficiency syndrome (Tachikawa et al., 2004)	Guanidinoacetate N-methyltransferase (*GAMT*) (19p13.3) Creatine transporter (*CRTR*) (Xq28)	Interaction neuron-glia
Phenylketonuria (Vermathen et al., 2007; Andolina et al., 2011)	mutations of the phenylalanine hydroxylase (*PAH*) gene (12q22-q24.1)	Human patients: indirect evidence for myelin brain alterations from white matter reduction *PahEnu2 (-/-)* mouse: smaller number of basal and apical dendrite spines, educed number of neurons with mature spines

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Table 3 (*continued*)

Genetic disorder (References)	Genetic event associated with the disorder	Dendrite and/or neural abnormalities in human patients, organism models and/or neurons in vitro
Down syndrome (Marin-Padilla, 1972, 1976; Kurt et al., 2004; Belichenko et al., 2007)	Partial or whole triplication of HSA21	Human patients: abnormal length and reduced number of dendrite spines Mouse model (Ts65Dn and Ts1Cje segmental trisomic mice): decrease in the density of dendrite spines, increase in the size of spine heads, decrease in the length of spine necks, reorganization of inhibitory
22q11.21 hemizygous deletion (Mukai et al., 2008)	hemizygous deletion from 3-Mb to 1.5-Mb deletion encompassing an area containing 27 genes.	Mouse model (mouse [*Df(16)A+/−*] with a deletion of the syntenic human 22q11.2 region): decreased density of dendrite spines and glutamatergic synapses, impaired dendrite growth

Some authors, based on the Tuberous Sclerosis model, suggest that the relationship between the type of mutation and the severity of the phenotype, including the clinical phenotype of autism, may also depend on the possible role of seizures (Amiet et al., 2013). In this model, clinical prognosis is strongly associated with the presence of severe neurodevelopmental impairments such as autism and intellectual disability. Severe neurodevelopmental impairments appear to be associated more frequently with (1) mutations in *STB2* than *STB1* gene, (2) number of tubers found in the brain and their localization (e.g., in the temporal cortex), and (3) severity of epilepsy (e.g., existence of infantile spasm and epilepticus status) and earlier age at onset of seizures (Bolton et al., 2015). Interestingly, autistic features are more predominant in the early seizure variant (an atypical form of Rett Syndrome) compared with typical Rett Syndrome (Neul, 2012).

Finally, the genes related to the different genetic disorders listed in Table 1 might not alter directly the CNS or neural communication development, but might lead to common cognitive, motor, and/or psychopathological problems that would play a major role in the development of autistic impairment. Fournier et al. (2010) conducted a meta-analysis on 51 studies and concluded that motor coordination problems constitute a core symptom of ASD. In line with these results, a model was proposed (Tordjman and Maillhes, 2009), based on the postulate that cross-modal sensory perception contributes to body-image construction and to the development of body self, which leads in turn to self/non self-differentiation and the ensuing development of social communication. The genes related to the different genetic disorders might be involved in body-image construction, motor coordination, and the development of body self. They might share a common neurodevelopmental function and their mutation would provoke a problem in the body self-representation leading to problems differentiating self/non-self, and consequently problems in the development of social communication with the appearance of autistic impairment. Thus, these genes would share some common mechanisms in terms of neurodevelopmental trajectories leading to the emergence of similar psychopathological organization.

2.2. Being controlled by the same "master control gene" or controlling/interacting with common genes (gene × gene interactions and/or protein × protein interactions)

The related genes might also be controlled by the same "master" gene above or control other common genes with a cascade effect affecting the CNS development or interact with the same gene that would modify their expression.

Indeed, we can postulate that some gene(s) playing a major role in neurodevelopment would have a double effect, one on affecting several possible genes under its control, and the other one on the expression of a same clinical phenotype. This master gene might be involved in genetic defects (such as deletion or duplication) leading to different genetic disorders. In addition, this master gene would be responsible for the expression of a similar behavioral-cognitive phenotype of autism. According to this hypothesis, the genetic abnormalities and the clinical phenotype of autism would be the consequences of the master gene effects.

The second hypothesis has been already mentioned above for the dendritic anomalies associated with genetic disorders: the genes related to the different genetic disorders would control other genes by the regulation of gene expression (transcriptional regulation, modulation of protein synthesis, etc.). They would share a defect in this regulation of gene expression involved in the expression of regulatory proteins in signalling pathways and would therefore alter common neurodevelopmental trajectories leading to a similar clinical phenotype of autism. In the same line, Roubertoux and Tordjman (2015) described a protein association network in autism. This network resulted from the STRING data base (version 9.1; Franceschini et al., 2006). The network included 51 genes associated with ASD, suggesting the existence of a unique signalling pathway associating genes involved in neural communication and synaptic homeostasis (Roubertoux and Tordjman, 2015).

Finally, we could postulate that these different genes related to the genetic disorders listed in Table 1 might interact with the same gene that would modify their expression. The promoter of the serotonin transporter gene that modifies the phenotypic expression of social communication impairment in autism is a good illustration in support of this hypothesis and could be a potential regulatory gene candidate (Anderson et al., 2002; Brune et al., 2006; Tordjman, 2008; Tordjman et al., 2001). This common regulatory gene could modify the expression of genes involved in different genetic disorders leading to a clinical phenotype of autism with similar cognitive-behavioral features.

2.3. Role of environmental factors (gene × environment interactions)

The possible prenatal, perinatal and postnatal risk factors for autism are summarized in Fig. 1 and are extensively presented in Tordjman et al. (2014) and Gardener et al. (2011).

Concerning the role of environmental factors in the development of autism associated with the genetic disorders previously reported (Table 1) and/or the protein network described by Roubertoux and Tordjman (2015), several hypotheses are currently discussed. First, "the epiphenomenon hypothesis" proposes a primary role of genetic susceptibility to autism which would increase risk for both autism and associated prenatal, perinatal and postnatal complications. A second hypothesis is to consider the genetic predisposition to autism as resulting from different chromosomal or gene disorders (Table 1). Some of the different genetic disorders might share common environmental factors or processes related to environmental factors that would contribute to the expression of a similar clinical phenotype involving social communication impairment and stereotypies. For example, oxidative stress might be a common internal environmental factor in several genetic disorders associated with autism (Damodaran and Arumugam, 2011; McGinnis, 2004; Ming et al., 2005). As underlined by Anderson (2014), the serotonin-melatonin-oxidative stress-placental intersection might be an especially fruitful area of biological investigation. Also, external environmental factors such as social and/or sensory deprivation are reported in autism with severe social communication

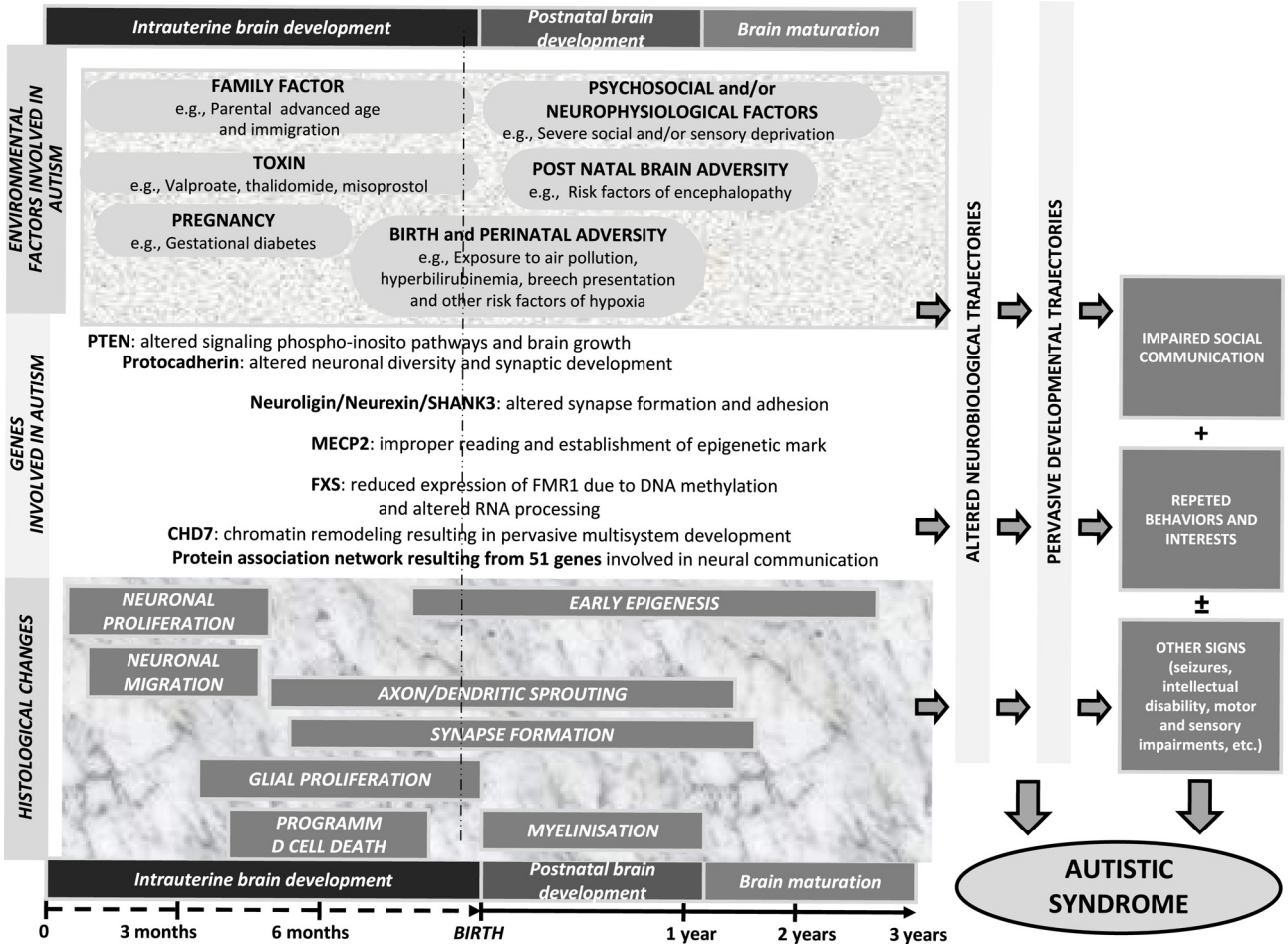

Fig. 1. Genetic and Environmental Factors associated with Autism: a Neurodevelopmental approach.
Genetic and environmental risk factors appear to influence intrauterine and early postnatal brain development, and likely alter neurobiological and neurodevelopmental trajectories resulting in the clinical core of autism (Guinchat et al., 2012; Tordjman et al., 2014). These influences may be variable depending on the period of development and the target (some examples are given putting in correspondence gene/protein function and defined stages of brain development or periods of development; Newschaffer et al., 2002).

impairment and motor stereotyped behaviors allowing self-stimulation (Steffenburg, 1991; Brown et al., 1997; Lord, 1997; Rosenhall et al., 1999; Donaldson et al., 2004; Hoksbergen et al., 2005; Rutter et al., 1999, 2007; Daneshi and Hassanzadeh, 2007; Mukaddes et al., 2007). Furthermore, epigenetics (epigenetics refers to functionally relevant modification of the genome following exposure to environmental factors during early development that influences gene expression without involving a change in nucleotide sequence) is a good illustration of common pathway related to environmental factors that might be shared by genetic disorders associated with autism. Indeed, epigenetic mechanisms are reported in many different genetic disorders associated with autism (see in Table 1: Maternal 15q11-q13 duplication, Angelman syndrome, Prader-Willi yndrome, Phelan-McDermid syndrome, Down syndrome, Williams-Beuren syndrome, Turner syndrome, Beckwith-Wiedemann syndrome, CHARGE syndrome, Rett or Fragile X syndrome); their role is discussed in Tordjman et al. (2014). Inversely, heterogeneity of environmental factors or processes related to environmental factors may lead to clinical subgroups with different cognitive-behavioral phenotypes (Fig. 1).

Finally, "the heterogeneity hypothesis" highlights possible cumulative effects mediated by environmental and/or genetic factors. The CHARGE syndrome, a genetic disorder involving multiple sensory deficits, provides an illustration of these possible cumulative genetic and environmental effects (Table 1). A positive association was reported between the severity of dysmorphic signs, cognitive impairment and effects of genetic factors (Cohen et al., 2005a; Miles and Hillman, 2000). Children with autism showing a higher number of minor physical anomalies had lower IQ and were more at risk for genetic disorder (Anderson et al., 2002; Jacquemont et al., 2006; Miles, 2011). More precisely, Miles and Hillman (2000), based on morphological examinations, distinguished the "phenotypically normal" subgroup and the "phenotypically abnormal" subgroup on the number of minor physical anomalies and the presence of systemic congenital malformations (heart defect, renal anomaly, etc.). They reported that the "phenotypically abnormal" individuals with autism were 10 times more likely to be diagnosed with a known genetic syndrome than the "phenotypically normal" individuals with autism and concluded that the "phenotypically normal" subgroup of individuals with "idiopathic autism" is causally distinct from the "phenotypically abnormal" subgroup related to an underlying genetic disorder. However, these two subgroups "phenotypically normal" and "phenotypically abnormal" bring us back to the dichotomous concept of "syndromic autism" and "non-syndromic autism", which depends on current knowledge concerning genetic disorders associated with autism. "Non-syndromic autism" might correspond in fact to unknown disorders with anomalies that will be noticed and discovered later. The search for particular minor physical anomalies or malformations is influenced by the identification and characterization of new genetic syndromes. Thus, children with autism associated with Smith-Magenis syndrome were considered in the "non-syndromic autism" category until the Smith-Magenis syndrome was identified and described with discrete facial dysmorphism including a particular shape of the mouth and relative

prognathism (Table 1).

We suggest that genetic, environmental factors and their interactions may have cumulative effects in autism, leading to a continuum from normal to pathological that replaces the dichotomous concept of "syndromic autism/non-syndromic autism". The interest of conducting research on non-dysmorphic and high functioning individuals with autism is not based on working on "pure autism" or "non-syndromic autism" which appears more and more controversial, but on understanding better the environmental and genetic mechanisms and controlling the bias of confounding factors such as intellectual disability (see next section).

2.4. The bias of intellectual disability

Level of cognitive functioning could introduce an important bias. Severe intellectual disability, often associated with the genetic disorders listed in Table 1, could mimic the clinical symptoms of autism with similar cognitive-behavioral features. Severe intellectual disability contributes probably to patients' difficulties in social communication understanding which could lead to the autism diagnosis often mistakenly made in individuals with severe intellectual disability. The genes related to the genetic disorders described previously might not be related specifically to autism but to intellectual disability.

Fragile X syndrome (FXS) is a good example of the intellectual disability bias possibly leading to a misdiagnosis of autism. Several studies report that males with FXS and autism display lower levels of cognitive functioning than males with FXS alone (Table 1), suggesting that symptoms of intellectual disability and autism overlap considerably. Hall et al. (2010) pointed out that the reference to autism in FXS is category error as it might be for other genetic disorders associated with intellectual disability.

Furthermore, the diagnosis of autism might be not valid or relevant for genetic disorders associated with severe intellectual disability, given that autism diagnostic assessments are unreliable in the context of very low IQ or mental age of less than 24 months (Lord, 1997). Major rating scales currently used for the autism diagnosis, such as the ADI-R and the ADOS (Lord, 1997), were not normed in individuals with brain disorders and/or severe intellectual disability. It is noteworthy that Kanner did not describe autism in individuals with severe intellectual disability and known brain disorders.

However, even if the bias of intellectual disability is a real issue for the misdiagnosis of autism and cannot be ruled out, some studies suggest that genetic disorders associated with autism involve genetic risk factors sharing common neurodevelopmental pathways more specific to autism than to intellectual disability. Indeed, comparison of individuals with intellectual disability but not autism and individuals with autism but not intellectual disability indicates that there are common molecular pathways more related to autism than to intellectual disability involving especially the development of glutamatergic projection neurons, possibly connecting higher order brain regions (Parikshak et al., 2013).

2.5. Non-similar cognitive-behavioral phenotype

We discussed in this article how so many genetic disorders involving different chromosomes and genes can lead to a similar clinical phenotype of autism. However, the cognitive-behavioral features may differ between these different genetic disorders and therefore the search for common mechanisms could appear irrelevant.

With regard to non-similar behavioral phenotype, as already mentioned in the introduction, a non-verbal child with motor stereotyped behaviors and a verbal-child with non-verbal communication problems and rituals might both satisfy the DSM-5 and ICD-10 diagnostic criteria for autism despite their major differences. The autism diagnostic criteria of the current classifications do not allow us to separate different subgroups. Individuals with Williams-Beuren Syndrome (WBS) might fill, for example, the DSM-5 diagnostic criteria for autism but could still appear different from "typical" individuals with autism in terms of social withdrawal (overfriendliness is often observed in WBS). However, the absence of language reported in some individuals with WBS and their non-adaptive socialization can question the possible existence of some common developmental impairment shared with other genetic disorders associated with autism (Tordjman et al., 2012, 2013).

The phenotypic similarities or differences might be more apparent and better analyzed through a dimensional and dynamic approach (adaptation of social communication, regulation of emotion, occurrence of behavioral impairments in certain situations such as stressful situations, etc.), rather than through a categorical one. This dimensional and dynamic approach can allow us to understand better the distinct or common underlying biological and psychopathological mechanisms of behavioral domain impairments. Thus, social communication impairments might be a common dimension shared by autism and schizophrenia, possibly related to genetic disequilibrium at the same loci. Inversely, social communication deficits might involve different dimensions related to different mechanisms and factors. Among them are social anxiety in FXS and severe language disorder in Cornelia de Lange syndrome. This approach can be applied to verbal communication impairments to distinguish several different dimensions such as the social dimension, productive speech or verbal stereotypies. In the same line, concerning social impairments, it is noteworthy that Bleuler used the term *autism* to refer to individuals with schizophrenia who withdraw into a world of fantasy, whereas Kanner used the term *autistic withdrawal* in the opposite sense for individuals who do not fantasize but ruminate on their thoughts. This highlights the different nuances of social communication impairments and the interest to assess better the nature of these impairments. Furthermore, a dimensional and dynamic approach can serve to differentiate disorders based on their distinct cognitive-behavioral evolutive profile. Thus, social communication impairments observed in individuals with WBS could mimic autistic features but a clear improvement in social interaction appears with time (Tordjman et al., 2012, 2013). Similarly, Rett Syndrome shares with autism common behavioral features. Indeed, despite that Rett Syndrome is considered in the DSM and ICD classifications as a differential diagnosis of autism, many children with Rett Syndrome are in fact reported to fulfil autism diagnostic criteria during the preschool years (Olsonn and Rett, 1990; Young et al., 2008). However, Rett Syndrome follows a different developmental trajectory than autism with evolutive clinical stages characteristic of Rett Syndrome (Table 1).

A dimensional and dynamic approach could help in the identification of subgroups sharing possible common psychopathological mechanisms and neurodevelopmental trajectories or inversely in the differentiation of disorders, and therefore advance research in behavior genetics such as research on genetic factors involved in social communication.

3. Conclusions and future directions

The genetic disorders associated with autism described in this article and the related discussion highlight that the concept of "syndromic autism" and "non-syndromic autism" depends, in fact, on technological progress and the actual state of knowledge. We can foresee that a "non-syndromic autism" could become few years later a "syndromic autism", if new genetic disorders are identified, allowing a better understanding and more efficient identification of discrete clinical symptoms as minor physical anomalies, malformations or associated biological anomalies. Thus, Table 1 presents a non-exhaustive list of genetic disorders associated with autism, and "non-syndromic autism" could be considered on the waiting list of "syndromic autism". Indeed, autism can be viewed as a behavioral syndrome, a "behavioral complex" found within many diagnoses (London, 2014), corresponding either to syndromic autism related to known genetic disorders or to "non-syndromic autism"

related to currently unknown disorders and on the waiting list of syndromic autism. It highlights the importance for practitioners as well as researchers to ask systematically for a clinical genetic examination, including a clinical morphology examination repeated over time given advances in knowledge with time, in all individuals (children, adolescents and adults) with autism to search for underlying genetic disorders.

There are some similarities with the field of intellectual disability in which the distinction between "syndromic intellectual disability" and "non-syndromic intellectual disability" is found. Indeed, the concept of "syndromic intellectual disability" is widely used to qualify patients with associated congenital anomalies or dysmorphism, and is helpful as a clinical step in the etiological search for an underlying genetic disorder. It could be speculated that this concept of "syndromic intellectual disability" and "non-syndromic intellectual disability" depends also, as for "syndromic autism" and "non-syndromic autism", on technological progress and the actual state of knowledge. Given the current state of knowledge, autism should be considered as a behavioral syndrome involving different dimensions and not as a separate nosographic category corresponding to a specific mental disorder. As underlined by Anderson (2008, 2014), although most research on autistic behavior has considered autism categorically, categorical approaches are unlikely to be fruitful as one should not expect to find a single or even predominant underlying cause of autism behaviors across individuals; the increasingly apparent genetic and phenotypic complexities of autism are prompting a more dimensional approach to this area. Other authors have supported recently this position (Xavier et al., 2015). Furthermore, Happé et al. (2006) presented evidence based on twin data study in the general population suggesting that domains of autistic impairments (social or communication impairments, repetitive behaviors or interests) should be fractionated and studied separately instead of searching for a single genetic, neural or cognitive explanation of a single entity of autism. To clarify further, it appears important to differentiate the descriptive level (description of autistic behavioral syndrome through a dimensional and dynamic approach studying developmental trajectory) from the etiological level (identification of underlying disorders such as genetic disorders).

Genetic studies on autism are probably restricted by clinical heterogeneity due to the use of different diagnostic classifications on one hand, and on the other hand by the possible occurrence of clinical as well as biological "subtypes" of autism. According to Newschaffer and collaborators (2002), heterogeneity within ASD is perhaps the biggest obstacle to research at all levels. It is thus necessary to determine subtypes before proceeding with genetic studies. Furthermore, the search for genetic factors involved in autism has to consider interactions between the environmental and genetic factors. A gene can be present in our genotype without ever expressing itself if it is inhibited by certain environmental factors. It would be necessary to study the effects of genetic factors integrated with those of environmental factors, whether post-or prenatal (psychosocial environment but also cytoplasmic and uterine environment, with placental exchanges and hormonal effects). Concerning Gene X Environment interactions, there is growing evidence that epigenetic mechanisms might play an important etiologic role in autism. The example of *in utero* exposure to valproate provides a good illustration of epigenetic mechanisms involved in autism (Grafodatskaya et al., 2010; Tordjman et al., 2014). Epigenetic remodeling by environmental factors opens new perspectives for a better understanding, prevention, and treatment based on the development of innovative therapeutic intervention, as already applied with the histone deacetylase inhibitor valproate treatment.

Finally, it seems important to reframe autism in a multifactorial context. Autism could be considered to result from polygenic and epistatic factors. Studies have been conducted in domains as diverse as genetics, neurochemistry, neuropharmacology, neuroendocrinology, neuroanatomy, brain imaging, and neuro-immunology. These studies, as seen in our discussion on genetic disorders associated with autism, stress increasingly that autism cannot be summed up or explained by a single biological or environmental causal factor, but rather by a multifactorial etiology related to different dimensions of impairment. George Anderson (2014) highlights the interest of network perspectives examining multiple interacting and mutually reinforcing traits and factors. Furthermore, recent findings suggest the possibility that not only single, but rather aggregate molecular genetic risk factors, linked in particular to alterations in calcium-channel signalling, are shared between autism and other psychiatric disorders (such as schizophrenia, bipolar disorder and major depressive disorder)(Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Smoller et al., 2013). However, the mechanisms underlying the role of these mutations in the development of ASD phenotypes remain to be ascertained. In addition, as indicated in Table 2, many CNVs (deletion/duplication) observed in autism are also found in other psychiatric disorders strengthening the need to develop a dimensional and transnosographic approach in ASD research. More generally, children with neurodevelopmental problems, including ASD, are often affected in more than one area of functioning of mental health to the extent that hierarchies of mutually excluding categorical diagnoses have to be considered as conflicting with scientific evidence (Anckarsäter, 2010). It suggests, according to Anckarsäter (2010), that genetic susceptibilities behind mental health problems have to be sought both in relation to specific problem types and to general dysfunction, using multivariate analyses with assessments of different types of mental disorders. Therefore, it is probably through a multidimensional, dynamic and transnosographic approach (rather than through a categorical one) with multivariate analyses conducted within ASD but also across mental disorders, involving multidisciplinary research with the participation of clinicians and neuroscientists, that advances will be made.

Conflict of interests statement

The authors declare that they have no competing financial interests.

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