Chapter 4
Autism in Genetic Intellectual Disability

Insights into Idiopathic Autism

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Abstract Despite early controversy, it is currently accepted that a substantial proportion of children with intellectual disability of genetic origin meet criteria for autism spectrum disorders (ASD). This has led to an increased interest in studying conditions such as Fragile X syndrome (FXS) as genetic models of idiopathic ASD. Here, largely based on our own studies, we expand this notion to propose that the study of ASD in genetic intellectual disability can provide important clues about many aspects of idiopathic ASD including its core behavioral features. Thus, FXS could reveal a molecular–neurobiological–behavioral continuum for deficits in complex social interactions in ASD. Down syndrome (DS) could disclose similar bases for repetitive and stereotypic behaviors in ASD, while DS and Rett syndrome are likely to share commonly affected molecular–neurobiological–behavioral pathways with individuals with idiopathic ASD who experience developmental regression. Consequently, the in-depth characterization of ASD in genetic intellectual disability could be doubly rewarding by improving the clinical management of severely affected individuals with these disorders and by shedding light into key aspects of idiopathic ASD.

Keywords Autism · genetics · intellectual disability · fragile X · down · Rett

Introduction

Autistic features have long been recognized in multiple genetic disorders associated with intellectual disability. However, autism has only recently been characterized in a comprehensive manner in these disorders. The comorbidity of intellectual disability and autism raises significant methodological and clinical issues. The first is whether severe cognitive impairment, present in a substantial proportion of patients with disorders such as Down syndrome (DS), precludes a confident diagnosis of autism. This is an issue of relevance not only to genetic

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A.W. Zimmerman (ed.), *Autism*, DOI: 10.1007/978-1-60327-489-0_4,

intellectual disability, but also to other severely impaired individuals who fulfill Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) [1] criteria for autism without a recognizable etiology. A second, overlapping, issue is the contribution of delayed or impaired communication, a frequent feature of genetic disorders associated with intellectual disability, to the diagnosis of autism or autism spectrum disorders (ASD). Despite these concerns, studies in the last decade have reported that a significant proportion of patients with Fragile X syndrome (FXS), DS, and Velocardiofacial syndrome (VCFS) meet DSM-IV criteria for ASD and demonstrate behavioral profiles consistent with the DSM-IV label [2, 3]. Other disorders that display features overlapping with those of idiopathic ASD or social impairments of relevance to autism include Rett syndrome (RTT), Angelman syndrome, Prader–Willi syndrome, Smith–Magenis syndrome, Williams syndrome, Turner syndrome, tuberous sclerosis, San Filippo syndrome, phenylketonuria, adenylosuccinate lyase deficiency, Cohen syndrome, and Smith–Lemli–Opitz syndrome [2, 3].

General Issues

The study of genetic disorders associated with ASD has several implications. In addition to addressing the particular diagnostic and therapeutic issues affecting a subset of individuals with severe phenotypes and complex medical and educational needs within FXS [4], DS [5], VCFS [6], and other conditions, this line of research could identify important genetic and neurobiological mechanisms in idiopathic ASD. A second, less well-recognized rationale is that the aforementioned genetic disorders may lead to a more complete characterization of the heterogeneous behavioral features of idiopathic autism. The latter issue is in line with the recent interest in subdividing idiopathic ASD into discrete clinical groups or endophenotypes [7, 8]. This approach is already demonstrating its value in the characterization of genetic abnormalities underlying idiopathic autism. It is our opinion that detailed phenotyping in idiopathic ASD and genetic disorders associated with ASD will also be essential for the development of specific clinical guidelines and novel treatment trials for all autistic disorders. The following sections describe the current and potential contributions of genetic disorders associated with intellectual disability to the behavioral and clinical features, the neurobiology, and finally the genetics and molecular biology of idiopathic ASD. This chapter will focus on our and others' work on FXS, DS, and RTT.

Background on Genetic Disorders Associated with Idiopathic Autism

Fragile X Syndrome

Fragile X syndrome is the most prevalent form of inherited intellectual disability, and the second most common genetic etiology of intellectual disability,

Table 4.1 Characteristic features of Fragile X syndrome

Physical features	Neurobehavioral features
Large ears	Mild to moderate mental retardation
Thick nasal bridge	Language delay, predominantly expressive
Prominent jaw	Rapid/burst-like speech
High-arched/narrow palate	Attentional-organizational dysfunction
Pale blue irises	Visuospatial impairment
Strabismus	Hyperactivity
Pectus excavatum	Hyperarousal
Kyphoscoliosis	Anxiety, particularly social
Lax joints	Autistic-like features
Single palmar crease	Aggressive behavior
Flat feet	Stereotypic/preservative behavior
Cutis laxa	Hypotonia
Mitral valve prolapse	Nystagmus
	Seizures

From: Adapted from Kaufmann WE, Reiss AL. Molecular and cellular genetics of Fragile X syndrome. *Am J Med Genet* 1999; 88: 11–24 [10].

affecting 1:4000 males and 1:6000 females [9]. The disorder is linked to the expansion of a CGG polymorphism in the (5′UTR) regulatory region of the *FMR1* gene. When the normal number (∼30) of CGG repeats increases to >200 (full mutation), *FMR1* promoter hypermethylation, *FMR1* transcriptional silencing [i.e., no production of Fragile X mental retardation protein (Fmrp), an RNA-binding protein and translational regulator], and the FXS phenotype occur. Intermediate level expansions (60–200 CGG repeats), which are termed permutations, are not associated with FXS [10] but with a carrier status or other clinical phenotypes (e.g., mild cognitive/behavioral problems, Fragile X Tremor Ataxia Syndrome or FXTAS) [11]. In addition to mild to moderate mental retardation (MR), FXS is characterized by dysmorphic features, connective tissue abnormalities (e.g., lax joints), and other non-CNS phenotypical anomalies (e.g., macroorchidism after puberty) (Table 4.1). However, variable cognitive and language impairments and associated neurobehavioral problems, including attentional difficulties, hyperactivity, anxiety, and autistic disorder, constitute the major medical and educational concerns for patients with FXS [10, 4]. Similar to other genetic disorders, because of ascertainment bias and variable diagnostic approaches, the exact proportion of individuals with certain phenotypical features in FXS is unclear [4]. Nonetheless, as expected in an X-linked condition, the characteristic features of FXS are more prominent in affected males, and ASD is almost exclusively a clinical issue in the latter group.

Down Syndrome

Down syndrome is the most common genetic cause of intellectual disability, occurring in an estimated 1:1740 live births [12, 13]. The DS phenotype

Table 4.2 Characteristic features of Down syndrome

Physical features (variable)	Neurobehavioral features (variable)
Flat facial profile	**Early development**
Poor primitive and deep tendon reflexes	Intellectual speech impairment
Hypotonia	Hypotonia-motor delay
Hyperlaxity of joints	Infantile seizures
Excessive skin on neck	**Childhood**
Slanted palpebral fissures	Inattention-hyperactivity
Pelvic dysplasia	Aggressive–disruptive behaviors
Anomalous auricles	Stereotypies–autistic features
Dysplastic midphalanx 5th finger	Unusual sensory preferences-responding
Single palmar crease	**Adolescence and adulthood**
Adolescence and adulthood	Depression
Down syndrome newborns demonstrating more than four features (100%)	Anxiety
Down syndrome newborns demonstrating more than six features (90%)	Obsessive–compulsive features
	Late adulthood
	Alzheimer-type pathology and dementia
	Seizures
	Parkinsonian features

From: Adapted from Roizen NJ, Patterson D. Down's syndrome. *Lancet* 2003; 361: 1281–1289 [13] & Capone GT, Roizen NJ, Rogers PT. Down Syndrome. In: Accardo PJ and Johnston MV (Eds). *Developmental Disabilities in Infancy and Childhood*. Baltimore: Paul H. Brookes Publishing Co, 2007: 285–308 [15].
From: Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002; 8:61–65 [17]. Reprinted by permission.

results from trisomy 21. In addition to characteristic dysmorphic features, anatomical abnormalities include cardiac and gastrointestinal malformations. Neurological abnormalities include cognitive impairment, neuromusclar hypotonia, and occasionally seizures [13]. Although most children with DS are described as sociable and affectionate [14], a relatively significant proportion (10–15%) manifest atypical neurobehavioral symptoms. These include hyperactivity and impulsivity, oppositional and disruptive behavior, stereotypic movement and autistic features. In contrast to FXS, emphasis on behavioral syndromes is a relatively new development in DS. Nevertheless, the complex management issues involving care of individuals with DS and abnormal behavior and the diagnostic challenges represented by the similarities between SMD and ASD highlight the importance of this research area in DS. Table 4.2 summarizes the most salient features of the DS phenotype.

Rett Syndrome

Rett syndrome is an X-linked condition that affects predominantly females, with an incidence of approximately 1:9000 girls by age 12 years. Rett syndrome is a severe disorder, lethal in most male cases [16] and the second leading cause

of global developmental delay and severe intellectual disability in females, after DS [17]. The majority of RTT cases are associated with mutations in the coding region of *MECP2*, a gene located on Xq28, which encodes the transcriptional repressor methyl-CpG-binding protein 2 (Mecp2) [18, 19]. Rett syndrome is a complex condition because of its dynamic evolution (Table 4.3), particularly from the neurological viewpoint, and range of clinical presentations (i.e., classic vs. atypical RTT) [17]. Depending on the clinical stage (for stages, see Table 4.3), females with RTT could appear normal, although cognitive impairment typically becomes evident by 18 months of age. In addition to language delay or loss and frequent deceleration of head growth, individuals with RTT present with loss of motor skills and hand use as well as characteristic stereotypic hand-wringing movements. Additional manifestations include respiratory irregularities,

Table 4.3 Characteristic features and stages of Rett syndrome

Original staging system	Later additions
Stage I: Early-onset stagnation	
Onset age: 6 months to 1.5 year	Onset from 5 months of age
Developmental progress delayed	Early postural delay
Developmental pattern still not significantly abnormal	Dissociated Development "Bottom-shufflers"
Duration: weeks to months	
Stage II: developmental regression	
Onset age: 1–3 or 4 year	
Loss of acquired skills/communication	Loss of acquired skills: fine finger, babble/ words, active playing
Mental deficiency appears	Occasionally "in another world"
	Eye contact preserved
	Breathing problems still modest
	Seizures in only 15%
Duration: weeks to months, possibly 1 year	
Stage III: psuedostationary period	
Onset age: after passing Stage II	"Wake-up" period
Some communicative restitution	Prominent hand apraxia/dyspraxia
Apparently preserved ambulent ability	
Unapparent, slow neuromotor regression	
Duration: years to decades	
Stage IV: late motor deterioration	
Onset age: when Stage III ambulation ceases	Subgrouping introduced:
	Stage IV A: previous walkers, now nonambulent
Complete wheelchair dependency	Stage IV B: never ambulent
Severe disability: wasting and distal distortion	
Duration: decades	

From: Hagberg B. Clinical manifestations and stages of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 2002, 8: 61–65 [17]. Reprinted by permission.

seizures, and notably impaired social interaction. The latter led to the unique inclusion of RTT in the DSM-IV-TR [1] as the only etiologically defined condition among ASD. Additional links between RTT and idiopathic ASD, to be discussed below, include the identification of individuals with RTT-like *MECP2* mutations and other neurological phenotypes such as nonspecific intellectual disability, Angelman syndrome, and ASD [17, 19]. Consistent with the widespread distribution of *Mecp2*, non-CNS features of RTT include disturbed gastrointestinal motility and abnormal autonomic vascular regulation, all apparently related to peripheral neuronal dysfunction. Table 4.3 depicts the most salient features of RTT.

Clinical and Behavioral Features of Genetic Disorders Associated With Autism: Implications for Idiopathic Autism or Autism Spectrum Disorders

With the exception of FXS, the characterization of autistic features in genetic disorders associated with intellectual disability is at an early stage. Despite this, available data suggest that each major genetic disorder presenting with ASD has a distinctive profile. Interestingly, these profiles highlight specific aspects of the autistic disorder in such a way that their study, as a whole, provides complementary insights into most key features of idiopathic ASD.

Autism in Fragile X syndrome: Deficit in Complex Social Interaction and Adaptive Socialization, with Severe Social Withdrawal but no Regression

Of all genetic disorders associated with ASD, the best characterized is FXS [2]. Despite initial controversy [20, 21], it is now accepted that a relatively large proportion (~20–45%) of boys with FXS meet DSM-IV criteria for a nonregressive type of ASD [4, 22, 23]. Concern about the validity of ASD diagnosis in FXS originates from the fact that most males with FXS display some autistic features (e.g., gaze avoidance, hand flapping) [4]. Nonetheless, we [24, 25] and others [26, 27] have demonstrated that it is possible to identify a group of boys with FXS who exhibit a core social interaction impairment in accordance with the DSM-IV definition of ASD. Indeed, these individuals show a neurobehavioral profile similar to that of their counterparts with idiopathic ASD [28, 29, 30]: severe social indifference [31]; a spectrum of social interaction deficits [23, 25] that is relatively independent of cognitive function [25, 27]; greater receptive than expressive language delay [27, 31, 32]; persistence of gaze avoidance during continuous social challenge [32]; and a fairly stable diagnosis over time [33, 31, 27]. Furthermore, the profile of autistic features on the

Autism Diagnostic Interview-Revised (ADI-R) [34] of boys with FXS indicates that diagnosis and severity of ASD are driven by impairment in complex socioemotional aspects and not in simple social behaviors [25]. Emphasizing the core social disturbance in males with FXS and ASD, we have shown that in statistical models including several measures of communication skills and adaptive socialization, the latter is the only significant predictor of ASD [25] (Fig. 4.1). The relevance of this central impairment in socialization skills is highlighted by the fact that adaptive socialization is considered a key reference measure for resolving diagnostic discrepancies between the two gold standard instruments in idiopathic ASD [34], the ADI-R [33] and the Autism Diagnostic Observation Schedule-Generic [36].

Extending the abovementioned findings, an examination of the role of dimensions of social behavior in diagnosis and severity of ASD in boys with FXS demonstrated that delay in adaptive socialization skills is the primary correlate and severity of social withdrawal is a close secondary factor [31]. It is important to note that among boys with FXS, the most severe ASD phenotype is linked to both impaired adaptive socialization and prominent social withdrawal [31]. An in-depth study of these two behavioral dimensions has led to an initial understanding of the relationship between ASD and social anxiety, the other major social disorder in FXS [4]. We have observed that social withdrawal behaviors, which include both avoidance and indifference, are distributed in a continuum of severity in boys with FXS [31]. As described years ago, a large proportion of boys with FXS display excessive shyness without apparent functional or clinical consequences; however, the rest show either marked avoidance or a more severe combination of severe avoidance and indifference. In line with severe avoidance, the intermediate social withdrawal phenotype is linked to the diagnosis of social anxiety, while the most affected group presents an extremely high frequency of severe ASD diagnosis. These clinical observations suggest that social anxiety and ASD have a common behavioral root in FXS, namely social withdrawal, and that the interaction between social withdrawal and impaired adaptive socialization and its cognitive

Fig. 4.1 Diagram of the relationship between skills and ASD in FXS. Note that delay in socialization skills is a selective contributor to the diagnosis and severity (measure as ADI-R/ADOS-G scores) of ASD in FXS. Abbreviations: Rec, receptive; Exp, expressive; lang, language skills; ADI-R, Autism Diagnostic Interview-Revised; ADOS-G, Autism Diagnostic Observation Schedule-Generic

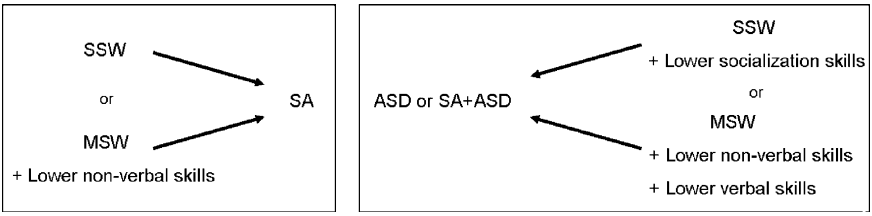

Fig. 4.2 Model of the relationships among social withdrawal, cognitive impairment, social anxiety, and ASD in FXS. Left panel: Note that either severe social withdrawal (SSW) per se or mild social withdrawal (MSW) in conjunction with lower nonverbal skills would lead to social anxiety (SA). Right panel: A more complex combination of deficits, specifically the addition of lower socialization or verbal skills, is required for ASD alone or comorbid with social anxiety. Abbreviations: SSW, severe social withdrawal; MSW, mild social withdrawal; SA, social anxiety

correlates (e.g., deficit in verbal reasoning) [31] will ultimately determine the ASD phenotype (Fig. 4.2). At the neurobiological level, we postulate that ASD in FXS has an obligatory cortical component, involving prefrontal and temporal regions, which when combined with limbic dysfunction leads to a severe ASD phenotype. Other cognitive deficits (e.g., severe nonverbal delay/parietal lobe dysfunction) would constitute variable components of ASD in FXS. In summary, the study of ASD in FXS could provide important clues about both core elements of impaired reciprocal social interaction and limbic (i.e., amygdalar) components of the social cognition system disrupted in idiopathic ASD [37, 38].

Autism in Down Syndrome: Complex and Simple Stereotypic Behaviors and High Prevalence of Regression

Depending upon the diagnostic criteria used and the method of ascertainment, the prevalence of ASD in individuals with DS is estimated to be between 5–10% [39, 40], which represents a 25-fold increase in risk for ASD compared to the general population. As with FXS in the 1990s, pediatricians and mental health providers have been reluctant to recognize or diagnose ASD in children with DS, resulting in uncertain educational placement, a missed opportunity for rational pharmacotherapy, and unnecessary hardship for parents [39, 41]. The controversy of DS + ASD has been influenced by stereotyped notions about DS, ASD, or severe cognitive impairment, as well as by the unique challenges of evaluating children with particularly low cognitive and adaptive skills and associated maladaptive behaviors. For these reasons, there has been considerably less research interest in DS + ASD when compared to other neurogenetic syndromes with severe intellectual disability. While young children with DS often have marked delay in speech production, this is well compensated for

by the use of sign or gesture [42]). In contrast, individuals with DS at risk for developing ASD may display atypical behaviors during infancy or the toddler years [43]. Social indifference, lack of sustained joint attention, and disinterest in gesture or functional communication may also be noted. Other behaviors seen prior to 36 months may include stereotypies, irritability head banging or self-injury, fascination with lights or ceiling fans, episodic deviation of eye gaze, extreme food refusal, and unusual stereotyped play with toys or other objects. Associated auditory processing impairments may cause the child to act as if deaf. Children with DS and a history of infantile spasms or myoclonic seizures are at particularly high risk for developing ASD [44, 45].

Formal analyses of behavioral profiles of children with DS and ASD have confirmed clinical impressions that stereotypic behaviors are prominent [46, 47] (Table 4.4). These stereotypies include both simple motor and more complex behaviors [47]. Considering that stereotypic movement disorder (SMD) is an important comorbidity in DS, in our studies we have compared children with DS + ASD, not only in those with typical behavior but also in children with DS + SMD [46, 47]. Children with DS + ASD typically satisfied —three to four criteria under social impairment, compared to only—one to two criteria for the DS + SMD group. Using the highly informative Aberrant Behavior Checklist (ABC), we also demonstrated that ABC's lethargy/social withdrawal behavior, specifically items representing avoidance and indifference, better differentiated the DS + ASD and DS + SMD groups [47]) (Table 4.4). Analyses with the corresponding Relating scale of the Autism Behavior Checklist further support the distinction between DS + ASD and DS + SMD [47]. Notably, atypical social behaviors displayed by children with DS + SMD or disruptive behavior disorder (DB), though reminiscent of ASD, do not significantly impair social function.

To date, only one study has specifically employed the prelinguistic ADOS-G and the ADI-R, in addition to DSM-IV criteria "gold standard" instruments, in children with DS. In individuals with DS and severe-profound intellectual disability, ASD could be identified, but discordance between the two instruments

Table 4.4 Behavioral characteristics of DS + ASD, DS + SMD, and typical DS (ABC profiles)

Subscale	ASD	SMD	Typical	ANOVA	*t* -tests
Irritability	13.2 ± 9.3	7.4 ± 6.4	4.4 ± 4.4	$F < 0.0001$	a
Lethargy	18.1 ± 9.4	6.6 ± 5.5	2.5 ± 3.6	$F < 0.0001$	a,b,d
Stereotypy	12.5 ± 4.1	7.2 ± 3.1	0.5 ± 1.5	$F < 0.0001$	a,b,c
Hyperactivity	20.8 ± 10	15.4 ± 7.1	8.5 ± 8.7	$F < 0.0001$	a,e
Inappropriate speech	2.5 ± 3.0	2.3 ± 2.6	1.0 ± 1.7	$F = 0.01$	ns

ASD versus Typical: (a) $P < 0.0001$; ASD versus SMD: (b) $P < 0.0001$; SMD versus Typical: (c) $P < 0.0001$, (d) $P < 0.0001$, (e) $P = 0.0002$. Post-hoc pairwise *t*-test statistically significant <0.003 after correcting for multiple comparisons using the Bonferroni procedure.

From: Capone GT, Grados M, Kaufmann WE, Bernad-Ripoll S, Jewell A. Down syndrome and comorbid autism-specturm disorder: characterization using the Aberrant Behavior Checklist. *Am J Med Genet* 134A: 373–380 [46]. Reprinted by permission.

raised both methodological and conceptual issues [48]. This investigation emphasized that although lower cognitive performance is an important correlate of ASD (i.e., lower than typical DS or DS associated with SMD [46]), it is not an obligatory component, as we have recently verified in our own data. Nonetheless, we acknowledge that the relationship between profound cognitive impairment (IQ < 25), maladaptive behavior, ASD risk and severity remains controversial and additional studies on the subject are needed [49, 50, 51]. It is plausible that these complete neuro behavioral clusters reflect "overlapping-yet-distinct functional outcomes" resulting from underlying neurobiological impairment determined by the approximately 350 genes mapping to chromosome 21. Thus, the "severe developmental delay" explanation becomes proxy for a "genetically neurobiologically mediated impairment in brain organization and function," which results in severe intellectual disability with variable expression of ASD.

In terms of temporal evolution, a large proportion of children with DS symptoms of ASD have a slow and insidious onset, progressing over many months or years (G.T. Capone, personal observation). However, in approximately one-third of our cohort with DS + ASD, there is a history given of deterioration in cognitive-speech-language-social skills without motor deterioration, clinical seizures, or prior atypical (for DS) development (unpublished data). Many display loss of skills between 3 and 6 years when stereotypy, irritability, sensory aversions and maladaptive behaviors may appear or intensify (personal observation), leading to the diagnosis of late-onset autism or childhood disintegrative disorder (CDD) [46]. Interestingly, in terms of the behavioral profiles described below, there are no differences between children with DS and typical autism and those with CDD [47]) (Table 4.5). Clearly, descriptive studies and methods of investigation employing well-defined diagnostic criteria are needed to better understand the phenomenon of regression in DS + ASD.

We conclude that ASD in DS is a good model for understanding the behavioral and neurobiological relationship between stereotypic behavior and

Table 4.5 Aberrant behavior checklist in down syndrome and autism spectrum disorders by DSM-IV Type

Subscale	Autism = 38	PDD = 8	CDD = 12	ANOVA	*t*-Tests
Irritability	14.2 ± 10.1	8.5 ± 6.7	13.3 ± 7.7	F = 0.30	ns
Lethargy	18.6 ± 9.4	8.6 ± 5.8	22.8 ± 7.4	F = 0.002	a,b
Stereotypy	12.3 ± 4.2	11.2 ± 4.0	14.7 ± 3.4	F = 0.12	ns
Hyperactivity	20.7 ± 10.8	20.8 ± 10.0	21.3 ± 8.0	F = 0.98	ns
Inappropriate speech	2.0 ± 2.4	4.4 ± 5.0	2.4 ± 2.9	F = 0.12	ns

PDD versus CDD: (a) $P < 0.001$; Autism versus PDD: (b) $P = 0.005$.
Post-hoc pairwise *t-test* statistical significance < 0.003 after correcting for multiple comparisons using the Bonferroni procedure.
From: Capone GT, Grados M, Kaufmann WE, Bernad-Ripoll S, Jewell A. Down syndrome and comorbid autism-spectrum disorder: characterization using the Aberrant Behavior Checklist. *Am J Med Genet* 134A: 373–380 [46]. Reprinted by permission.

social reciprocity in idiopathic ASD, as well as for studying early and late regression phenomena. Finally, DS + ASD will provide unique insights into core social interaction impairments in individuals with severe cognitive impairment.

Autism in Rett Syndrome: Preserved Communication and Motor Function With Regression

The study of autistic features in RTT has focused on two different aspects: the differential diagnosis from idiopathic ASD in young females and the RTT + ASD comorbidity in higher functioning RTT patients. The issue of differentiating RTT from idiopathic ASD has been central to this genetic disorder since its initial descriptions emphasized the combination of "autism, dementia, ataxia, and loss of purposeful hand use" as key features of RTT [52]. Subsequent refinements of the RTT phenotype highlighted the diversity and severity of the motor and communication deficits, which contrasted with the relative preservation of cognitive and motor function in idiopathic ASD [53, 54, 55]. Another important distinction is that autistic features in RTT follow the dynamic course of the disorder (see Table 4.3 for clinical stages in RTT), in contrast to the relative stability of idiopathic ASD. Recognition of autistic manifestations in RTT typically coincides with the regressive phase (Stage II), between 1 and 4 years, in the most common "classic" form of the disorder [55, 56] that also includes loss of language and fine motor skills and is followed by clinical improvement to virtual disappearance of social interaction deficits by late childhood (see Table 4.3) [17]. In spite of the clinical differences between RTT and idiopathic ASD, it is clear that autistic symptomatology is more prevalent in RTT than in comparable samples of females with idiopathic severe intellectual disability [57] and that many young girls with RTT meet DSM-IV criteria for ASD [58]. Our recent large-scale study of 313 RTT patients concluded that even after several years following the identification of *MECP2* as the "RTT gene," a significant proportion of patients is diagnosed as having (idiopathic) ASD in early life (i.e., ~18%). A profile emerged for the girls with RTT and misdiagnosis; they tended to have a milder phenotype, particularly in terms of motor function, with relatively late appearance of typical RTT features (Table 4.6; [59]). Interestingly, R306C, a mutation typically associated with a milder RTT phenotype, and T158M, a mutation linked to a wide range of phenotypical outcomes [60], were overrepresented in girls with RTT and ASD misdiagnosis [61].

A more controversial issue is the possibility of RTT + ASD comorbidity beyond the regressive phase of the disorder. The strongest evidence comes from the study of a milder (atypical) RTT phenotype, the so-called preserved speech variant (PSV), which, similar to other milder forms of RTT, is commonly associated with the R133C mutation [61, 62]. Although girls with PSV have better communication skills, they also tend to have more severe autistic

Table 4.6 Early Clinical features in RTT patients with and without initial diagnosis of autism.

Early clinical symptoms	No autism diagnosis mean score	Autism diagnosis mean score	*P* value for autism diagnosis	Odds ratio (OR) for autism diagnosis	95% confidence interval (CI)	
					LCI	UCI
Age at diagnosis of Rett syndrome in years	4.72	6.08	0.09	1.05	0.99	1.10
Age at loss of hand function in months	23.25	29.74	0.02	1.02	1.00	1.04
Age at loss of communication in months	20.25	25.69	0.04	1.02	1.00	1.04
Age at onset of hand stereotypies in months	26.02	31.83	0.05	1.02	1.00	1.03

From: Young DJ, Bebbington A, Anderson A, Ravine D, Ellaway C, Kulkarni A, de Klerk N, Kaufmann WE, Leonard H. The diagnosis of autism in a female: could it be Rett syndrome? *Eur J Pediatr* 2007: in press [59]. Reprinted by permission.

features; nonetheless, the autistic symptoms appear to regress by early adolescence [62]. These observations, in conjunction with several surveys demonstrating a low frequency of *MECP2* mutations among individuals with ASD [63, 64, 65, 66], lead to the conclusion that disruptions of the *MECP2* gene are a rare cause of a stable autistic phenotype. Overall, the study of the relationship between RTT and ASD is informative in that it emphasizes that the expression of autistic symptoms requires minimally preserved motor and communication systems (i.e., uncommon misdiagnosis in girls with severe RTT phenotype), a critical point for the diagnosis of ASD in individuals with severe intellectual disability. The close association of the emergence of autistic features and the loss of cognitive and fine motor skills in RTT indicates that this genetic disorder may be a good model of regression in ASD. It is interesting to notice that regardless of the specific phenotype (e.g., RTT, Angelman syndrome-like), individuals with *MECP2* mutations almost invariably present with loss of developmental skills [19]. Finally, although *MECP2* mutations per se may not be a common etiology of ASD, the association of RTT and ASD diagnosis signifies the potential role of imbalances in Mecp2 (*MECP2* product) in the pathogenesis of idiopathic autism.

Insights into the Neurobiology of Idiopathic Autism

Despite the detailed analyses of autistic features in FXS, DS, and other disorders with relatively well-understood neuroanatomy, the neurobiological correlates of ASD in these conditions have only been occasionally explored. This is due to a number of difficulties inherent to this type of research. First, a

major source of information on the neurobiology of genetic intellectual disability is the study of mouse models that reproduce only to a limited extent the behavioral features, including autistic manifestations, of the disorder. Other experimental strategies, such as in vitro models, could disclose relevant data only if the cellular model is already linked to a genetic correlate of ASD (e.g., R133C *MECP2* mutation in some girls with RTT and autism). For all these reasons, most of the neurobiology of genetic intellectual disability and ASD has to rely on neuroimaging and neurophysiological investigations of affected subjects.

Neurobiology of Fragile X Syndrome and Autism Spectrum Disorder: Anomalies of the Cerebellar Vermis and Limbic Dysfunction

To our knowledge, only one study has directly examined affected neural systems in individuals with FXS who meet DSM-IV criteria for ASD. As shown in Fig. 4.3, we found that boys with FXS and autism proper (as opposed to milder forms of ASD) have, on MRI scans, relatively larger posterior–superior cerebellar vermi than their counterparts without autism, although they are smaller than in typically developing controls [67]. Interestingly, the abnormal region (i.e., lobules VI–VII) is the same one previously described as relatively smaller in individuals with idiopathic ASD [68], a finding confirmed in our study [67]. Despite these observations about the cerebellum, the profile of ASD in FXS, as in idiopathic ASD, suggests a major disturbance in limbic and adjacent temporal regions [38]. Although mild MRI volumetric increases in the hippocampus have been reported in subjects with FXS [69], so far no study has evaluated the relationship between these morphometric changes and ASD status [70]. Moreover, cortisol reactivity (i.e., variability in cortisol levels) to a social challenge, a measure of limbic–hypothalamic function, has been found to

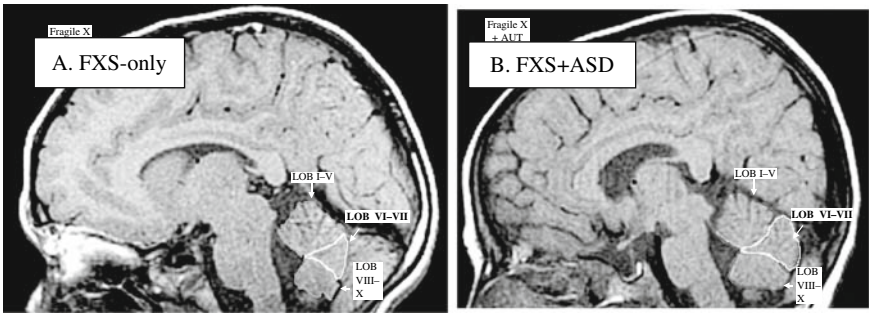

Fig. 4.3 Cerebellar vermis abnormality in FXS and ASD. Representative midsagittal MRIs of subjects with FXS with (FXS + ASD) and without (FXS-only) autism. The posterior–superior cerebellar vermis (lobules VI–VII) is delineated in white. Note in B the larger and protruding outline of this vermian region

be decreased in children with FXS and severe autistic behavior [71]. The opposite seems to be true for FXS subjects with prominent social avoidance [71, 72]. Although intuitively, decreased hormonal and behavioral responses to social stimuli are compatible with ASD, the precise mechanism of these cortisol changes in FXS is unknown. We have reported a higher frequency of acetylation of the glucocorticoid-negative regulator annexin-1 in males with FXS [73], particularly in those with severe social withdrawal [74]. However, annexin-1 is involved in the acute phase of cortisol modulation [75], and it is therefore unclear whether it has any role in the reported slow return to baseline observed in boys after a cognitive/social challenge [72]. Another candidate for abnormal cortisol regulation in FXS is the glucocorticoid receptor alpha; the synthesis of this low-affinity cortisol receptor is directly regulated by the deficient Fmrp [76], and its levels are decreased in dendrites of hippocampal neurons in a mouse model of FXS [77]. These animals also show increased cortisol levels after a stressful situation [78]; however, no behaviors of relevance to ASD appear to correlate with these cortisol anomalies.

Two general neuronal abnormalities have been described in FXS and/or corresponding mouse models: aberrant configuration of dendritic spines (i.e., long, tortuous, immature appearance; [79]) and enhanced activity of class I metabotropic glutamate receptors leading to increased long-term depression [80]. The latter is linked to the postulated negative regulatory role of Fmrp in protein synthesis triggered by metabotropic glutamate receptor activation [79, 80]. Although these anomalies involve brain regions implicated in idiopathic ASD, their ubiquitous nature and lack of formal comparisons involving individuals with FXS and ASD preclude the establishment of meaningful relationships. Nonetheless, the fact that one study showed reduced class I metabotropic glutamate receptor-dependent long-term potentiation in the lateral amygdala [81] (an area linked to both anxiety and ASD [38, 82]) in mice deficient in Fmrp, and that class I metabotropic glutamate receptor antagonists will be available for clinical use relatively soon [83] has increased the interest in metabotropic glutamate receptors as potential targets in ASD. In conclusion, the best-characterized neurobiological correlate of ASD in FXS is a relative enlargement of the posterior–superior vermis. However, data on FXS subjects and experimental models suggest that several limbic regions may also be functionally abnormal. Considering the close relationship between social anxiety and ASD in FXS, careful work will be required for differentiating limbic anomalies linked to either disorder.

Neurobiology of Down Syndrome and Autism Spectrum Disorders: Cerebellar Enlargement and Stereotypies

The neuroanatomical features of DS include microcephaly and decreased brain size, selective volumetric reduction of the frontal lobe, hippocampus and cerebellum, immature gyral patterns, abnormal neocortical lamination, and delayed cortical fiber myelination [13, 67, 70, 79], many of them confirmed

Table 4.7 Bilateral increase of WM volumes in the brainstem and cerebellum in DS + ASD

	DS only ($N = 15$)	DS + ASD ($N = 15$)
Brain	1022.7 ± 106.9	1041.6 ± 157.4
GM	641.8 ± 62.2	661.4 ± 105.8
WM	380.9 ± 55.0	380.2 ± 56.5
Brainstem	31.7 ± 4.0	32.1 ± 4.9
GM	19.6 ± 3.3	18.4 ± 4.3
WM	12.1 ± 2.0	13.7 ± 1.6*
Cerebellum	84.6 ± 9.5	88.5 ± 12.0
GM	67.1 ± 8.1	66.6 ± 11.9
WM	17.5 ± 2.4	21.8 ± 3.0*

*$p < 0.05$

by MRI morphometric studies [67, 70, 84, 85, 86, 87, 88]. However, little is known about the neuroanatomy of DS and comorbid ASD. In a recent study [89], we examined regional brain volume changes in children with DS and typical behavior (DS-only), DS + ASD, and controls. We found that when compared to the DS-only group, children with DS + ASD show significant bilateral increases in WM volumes in the brainstem and cerebellum (Table 4.7). Although still smaller than in age-matched controls, the relatively larger cerebellar volumes in DS + ASD correlated positively and selectively with severity of stereotypies (specifically with item number 11 on the ABC, "*stereotyped, repetitive movements*"). In addition, initial assessments of brain growth show that individuals with DS + ASD display an accelerated pattern between the ages of 2 and 5 years, when compared with controls. The preferential enlargement of cerebellar WM and the pattern of brain growth in subjects with DS + ASD mimic those observed in children with idiopathic ASD [90]. These results indicate that ASD in DS follows a similar pathogenetic course to idiopathic ASD, specifically pointing to cerebellar WM hyperplasia as a trademark of ASD against different genetic backgrounds [89].

Mice with segmental trisomy (Ts65Dn) have a dosage imbalance for genes corresponding to those on human chromosome 21q21–22.3 [91]. Although there are no reports of behavioral abnormalities resembling ASD in these mice, they exhibit cognitive deficits found in idiopathic ASD and postulated in DS + ASD (i.e., working memory and long-term memory; [92]). Additional characterizations of the Ts65Dn mice, including the synaptic bases of their neurobehavioral abnormalities [93,94], may contribute to better understanding and clinical approaches to ASD in DS [95].

MeCP2Deficiency and the Neurobiology of Autism Spectrum Disorders

There is no direct information on the neurobiology of RTT and autistic features. Nevertheless, postmortem and neuroimaging (magnetic resonance spectroscopy,

MRS) data relevant to the regressive stage of RTT (see Table 4.3), when autistic features are noticed, indicate that the basic process is glutamate-dependent toxicity. Both increases in glutamate concentration [96] and in the density of NMDA receptors [97, 98] in the cerebral cortex provide a solid basis for an excitotoxic phenomenon [99]. We recently showed increased glutamate concentrations in the frontal white matter [100], an area where reductions in axonal markers and elevations in astrocytic markers have also been described [101, 102]. These data suggest that the period of regression in RTT, with its associated emergence of autistic features, could also be linked to white matter disturbances, which have been recently implicated in idiopathic ASD [103]. Although to date no study has characterized patients with RTT and autistic features by neuroimaging or other methods, our recent work indicate that girls with RTT and *MECP2* mutations associated with either ASD misdiagnosis or comorbidity tend to have relatively greater preservation of anterior frontal cortex volumes [104].

Behavioral characterizations of mice deficient in Mecp2 indicate that features of relevance to ASD, especially anxiety, correlate with severity of Mecp2 (*MECP2* product) deficit and with volumetric reductions of the amygdala and hippocampus [105]. The same group reported that choline supplementation to nursing dams attenuated motor function but not fear conditioning (i.e., anxiety) in these Mecp2-deficient mice [106], suggesting that abnormal social behavior associated with Mecp2 deficit may have unique underlying mechanisms. Another study in mice carrying an RTT-like *MECP2* mutation demonstrated increased anxiety-like behavior and elevated serum glucocorticoid levels, which were associated with increased limbic expression of corticotropin-releasing hormone [107]. The same animals displayed deficits in contextual fear and social memories and different paradigms of social interaction [108, 109]. Altogether, the study of the neurobiology of *MECP2* mutations and RTT suggests that Mecp2 deficit leads to autistic features in the context of an excitotoxic process that could involve several forebrain structures. As in FXS, *MECP2* mutations could be associated with both anxiety- and ASD-like behaviors and disturbances in the hypothalamic–pituitary–adrenocortical (HPA) axis.

Genetic and Molecular Pathways Common to Autistic Disorders

This is probably the area in which most significant advances have been made toward understanding the bases of ASD. As expected of a heterogeneous condition, multiple molecular pathways have been implicated in the genesis of autistic manifestations. Despite these accomplishments, major methodological obstacles still remain. Although analyses of samples and cell lines of affected patients can lead to straightforward results, the links between in vitro measures

in peripheral cells and ASD neurobiology are tenuous and, at present, require a combination of experimental approaches and/or analyses of postmortem brain samples.

Molecular Basis of Fragile X Syndrome and Autism Spectrum Disorders: Cytoplasmic FMR1-Interacting Protein 1 and Other Downstream Fmrp Targets

Since 1991, it has been known that mutations in *FMR1* are the cause of the vast majority of FXS cases and that the phenotypic manifestations of FXS are the result of a marked reduction in the levels of *FMR1*'s product, the Fragile X mental retardation protein (Fmrp) [10]. In contrast with consistent reports on correlations between magnitude of Fmrp decrease and severity of physical and cognitive phenotype [4, 110], lymphocytic Fmrp levels do not seem to predict behavioral abnormalities in FXS [111]. Only recently, large-scale studies have demonstrated a modest relationship between Fmrp deficit and severity of autistic behavior [112, 113]. These findings are not surprising considering that Fmrp is an RNA-binding protein that regulates the synthesis, particularly at synaptic sites, of a relatively large number of proteins (5–8% total mRNA; [10, 113, 114, 115]). Therefore, specific neurobehavioral features in FXS are more likely to depend on a relatively greater involvement of certain Fmrp targets and neuronal circuits that are not reflected in general measures of Fmrp. A recent publication by Nishimura and colleagues [116] examined gene expression profiles in lymphoblasts from boys with FXS and ASD, comparing them with typically developing controls and boys with duplication of chromosome 15 and ASD (dup15q; a recognized genetic abnormality associated with ASD; [2]). Of 120 differentially expressed genes, including 15 previously identified in neuronal [77]) and "phenotypically generic" lymphoblast [76] FXS/Fmrp-deficient samples, 68 were also dysregulated in the dup15q group (Table 4.8). Among them there was G protein-coupled receptor 155 (*GPR155*), a gene regulated by the cytoplasmic *FMR1*-interacting protein 1 (*CYFIP1*), an antagonist and binding partner of Fmrp that is a member of the Rac GTPase system involved in neurite development [79, 117]. Since *CYFIP1* and another one of its targets, [the janus kinase and microtubule-interacting protein 1 (*JAKMIP1* or *MARLIN-1*)], were also dysregulated in patients with dup15q; Jakmip1 was reduced in brains of *FMR1* knockout mice; and *JAKMIP1* and *GPR155* were differentially expressed in male sib pairs discordant for idiopathic ASD; it can be concluded that the *CYFP1* signaling pathway is implicated in different genetic forms of ASD. Although the abovementioned study [116] did not formally compare subjects with FXS with and without ASD, the comprehensive and comparative nature of the assays suggests that the study of peripheral cells from individuals with FXS and ASD may be highly informative for understanding mechanisms underlying idiopathic ASD. Additional analyses

Table 4.8 Genes dysregulated in lymphoblasts from patients with FXS and ASD

Gene name	Gene abbreviation	Levels
Nuclear receptor subfamily 3 group C member 1	*NR3C1* (*)	Upregulated
Vimentin	*VIM* (*)	Downregulated
Iduronate 2-sulfatase	*IDS* (**)	Upregulated
Hairy and enhancer of split 1	*HES1* (**[&])	Upregulated
Immunoglobulin superfamily, member 3	*IGSF3* (**)	Upregulated
CDK2-associated protein 2	*CDK2AP2* (**)	Downregulated
Ubiquitin specific peptidase 8	*USP8* (**)	Downregulated
MAX-like protein X	*MLX* (**)	Downregulated
Ribosomal protein S5	*RPS5* (**)	Downregulated
C-terminal binding protein 1	*CTBP1* (**)	Downregulated
Spleen tyrosine kinase	*SYK* (**)	Downregulated
F-box protein 6	*FBXO6* (**)	Downregulated
Mitogen-activated protein kinase kinase kinase 11	*MAP3K11* (**)	Downregulated
Sorting nexin 15	*SNX15* (**)	Downregulated
CD44 antigen	*CD44* (**)	Downregulated
G protein-coupled receptor 155	*GPR155* ([@])	Downregulated

(*) Reported by Miyashiro et al. [77]).
(**) Reported by Brown et al. [76].
([&]) Associated with attention-deficit hyperactivity disorder (Brookes et al. [118]).
([@]) Also found in patients with chromosome 15 duplication and ASD (Nishimura et al.; [116])

will have to determine whether the specific neural pathways affected by this gene expression dysregulation are those implicated in ASD of unknown cause.

Molecular Basis of Down Syndrome and Autism Spectrum Disorders: Genes Involved in Early Brain Development

The characteristic cognitive–behavioral profile of DS + ASD suggests that this phenotype is distinct. Although the DS critical region of chromosome 21 includes 360 unique genes [119], little is known about the dosage of these genes and phenotypical variability in DS (congenital heart defects; [120]). However, a recent study of 34 idiopathic autism-affected relative pairs with the regressive phenotype demonstrated genetic linkage to chromosome 21q between markers DS21S1432 and DS21S1899 [121]. Of the seven known genes that map to this region, two (*BTG3* and *CXADR*) are expressed in fetal brain and a third one maps just outside this region and is also involved in early brain development (*NCAM2*). Of particular interest is *BTG3* (also termed *APRO4/ANA*) since balanced expression of this gene appears to be critical for neuronal differentiation in the forebrain [122, 123], a fundamental process linked to both intellectual disability and ASD [124]. In conclusion, although no specific molecular data are available on ASD in DS, studies of idiopathic ASD indicate that genes in chromosome 21 may play a critical role in the pathogenesis of ASD.

Mecp2 Levels are Dysregulated in Idiopathic Autism Spectrum Disorders

In preceding sections, we have discussed the relationship between RTT, *MECP2* mutations, and the diagnosis of ASD. Although mutations in the coding region of *MECP2* are infrequently associated with ASD [63, 64, 65], reduced levels of Mecp2 secondary to either mutations in regulatory regions of the gene [125, 66] or as yet unknown physiological signals [126, 127] have been reported in both male and female subjects with ASD. Of particular interest is the demonstration of abnormal Mecp2 levels, particularly reductions, associated with aberrant promoter methylation in frontal cortex of subjects with ASD [127]. Although changes in brain Mecp2 levels are not specific to ASD, since they are also observed in other developmental disorders (e.g., Angelman syndrome), they may significantly contribute to neurological disturbances in ASD. For instance, reports suggest that Mecp2 abnormalities lead to allelic dysregulation and decreased expression of GABAA receptor gene subunits and reduced expression of UBE3A [128, 129]. As stated with regard to molecular abnormalities in FXS and ASD, the link between aberrant Mecp2 expression and affected neural pathways in ASD is yet unknown.

Data on the neuronal phenotype [130] and levels of Mecp2 [131] in the brain from subjects with RTT and other developmental disorders allowed us to propose a model for phenotypes secondary to Mecp2 deficit (Fig. 4.4). If mild reductions in Mecp2 levels (due to disrupted regulatory signals) occur during the early postnatal period when synaptic activity plays a critical role in modulating neuronal and synaptic development, the outcome is most likely ASD or Angelman syndrome. If the Mecp2 deficit is severe or persistent into late postnatal life, as expected from *MECP2* mutations, the most probable outcome would be a RTT phenotype.

Concluding Remarks

We have presented published and preliminary data, as well as some hypothetical models, supporting the notion that the study of genetic disorders associated with intellectual disability and ASD, namely FXS, DS, and RTT, has important implications not only for the individuals affected by these severe comorbidities, but also for the entity termed "idiopathic ASD." The behavioral features of ASD in genetic disorders are varied, and therefore informative of several key aspects of ASD, such as core social interaction impairment, stereotypic behaviors, and developmental regression. They also represent a contribution to the evaluation of the role of severe cognitive and motor impairment in the expression of autistic features. The emerging knowledge on neuroimaging of ASD in FXS, DS, and RTT emphasizes the involvement of brain areas already implicated in idiopathic ASD, in particular the cerebellum and limbic regions. These MRI morphometric approaches may eventually identify additional

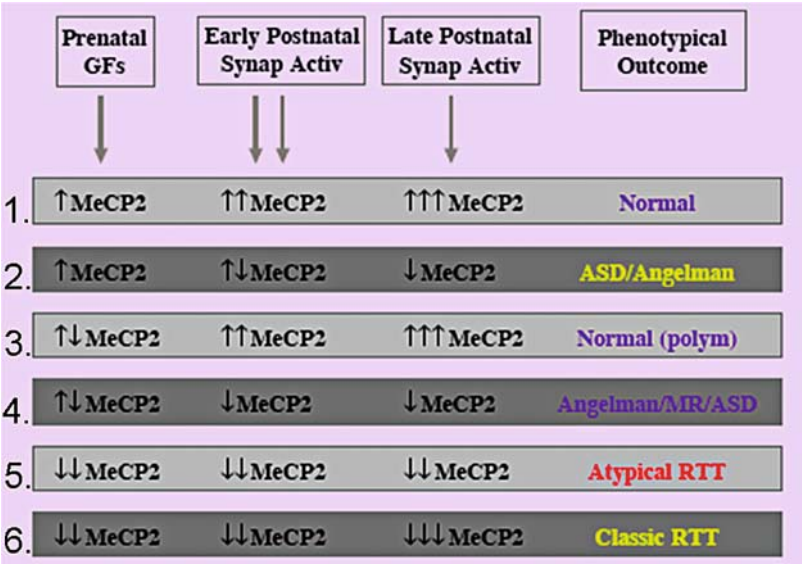

Fig. 4.4 Model of phenotypical outcomes secondary to Mecp2 deficiency.
(1) During normal development, onset of Mecp2 expression (↑) coincides with early neuronal differentiation directed by specific signals [i.e., growth factors (GFs)]. Levels of Mecp2 expression/function increase (↑↑), for most cortical and limbic regions, in early postnatal life and are strongly modulated by synaptic activity during the critical period of synaptic maturation. In the same regions, Mecp2 levels continue to increase (↑↑↑) into adulthood.
(2) If developmental synaptic activity or other factors (e.g., 15q11–13 abnormality) regulating Mecp2 expression in early postnatal life are disturbed, levels of Mecp2 could decrease and a phenotype of Angelman syndrome or ASD may develop.
(3) If Mecp2 polymorphisms or mild prenatal Mecp2 deficits (↑↓) occur, depending on the genetic compensatory capacity of the subject or X inactivation skewing, no phenotype (polymorphism [polym]) or (4) a non-RTT disorder with mild Mecp2 deficiency (↓) may arise. This situation will explain the majority of non-RTT phenotypes associated with MECP2 mutations, including Angelman syndrome, ASD, and nonsyndromic MR.
(5) If Mecp2 dysfunction takes place early and is severe (↓↓), as in most patients with pathogenic *MECP2* mutations, development of subcortical pathways will be affected. These secondary/compensatory neurotransmitter changes, in combination with insufficient Mecp2-dependent response to synaptic signals during the critical postnatal period, will perpetuate Mecp2 deficiency.
(6) If 'facilitating' factors (e.g., genetic polymorphisms, unfavorable X inactivation skewing) are also present, a more severe classic RTT phenotype with severe MeCP2 deficit (↓↓↓) will emerge. Otherwise, MeCP2 function will remain at a moderately low level (↓↓) and an atypical/variant RTT phenotype will develop.
Note that this model does not distinguish between RTT patients with or without *MECP2* mutations, since the postulates are based on Mecp2 function that could be impaired by other genes functionally associated with Mecp2. Abbreviations: GFs, growth factors; Synap Activ, synaptic activity. The intensity of the gray shading symbolizes the presence (darker) or absence (lighter) of negative or 'facilitating' factors that lead to a more severe phenotype

neural circuits involved in both genetic and idiopathic ASD. It remains to be seen to what extent animal models of these genetic disorders will provide valuable data for idiopathic ASD. Nonetheless, recent progress on mouse models of autism [132] suggests that better tools will ultimately be available for the characterization of these experimental paradigms. Data on the molecular correlates of ASD in genetic disorders have recently been quite revealing. Undoubtedly, abnormalities in Mecp2 expression play a role in the development of ASD. The issue to be determined is at which level of the pathogenetic process they do so. Furthermore, gene expression analyses place Fmrp targets at the center of pathways common to several genetic forms of autism. Data are also suggestive of an important role for genes in the DS critical region of chromosome 21. The integration of all these pieces of data is a major challenge, to be better addressed when additional data become available.

The first goal in the field of ASD associated with genetic intellectual disability is, of course, to acquire more data on the aforementioned areas. However, it is also necessary to introduce new approaches. In terms of behavioral studies, experimental paradigms should complement findings derived from clinical measures. Our recent work on identifying dynamic behavioral features of ASD in FXS by the social approach scale is a good example [133]. Naturalistic observations may also be informative as revealed by our study of RTT's neurological and behavioral phenotype through video recordings by parents [134]. In terms of neuroimaging, there is the need for applying the entire spectrum of techniques. Given the close association of severe cognitive impairment and ASD in these disorders, functional MRI remains an elusive approach. Most likely, the study of gene expression profiles in lymphoid and postmortem samples from affected individuals will continue providing promising leads. The challenge here is the integration of molecular and neurobiological data; the comprehensive evaluation of *CYFIP1* and its targets in ASD associated with FXS and chromosome 15 duplication by Nishimura and colleagues [116] illustrates that such work is feasible.

The present review was based on our work; consequently, we did not intend for it to be comprehensive. The study of other genetic disorders associated with ASD (e.g., VCFS, tuberous sclerosis) could also be extremely valuable. The increasing number of genetic abnormalities reported in individuals with "idiopathic" ASD [135] will most likely change the view of the relationship between genetic disorders and autism and, perhaps also, the criteria for diagnosing ASD. Regardless, in our opinion, our sketchy knowledge on the molecular, neurobiological, and behavioral correlates of ASD in FXS, DS, and RTT already demonstrates that these disorders are valuable models for autism research.

Acknowledgments This work was partially supported by NIH grants HD33175, MH67092, HD24448, HD24061, RR00052, and by awards from FRAXA and IRSA to W.E.K. We are grateful to the families who have participated in our research projects at the Center for Genetic Disorders of Cognition & Behavior, Kennedy Krieger Institute, Baltimore, Maryland.

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