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Review article

Childhood autism and associated comorbidities

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Abstract

Autism is a heterogeneous neurodevelopmental disorder with a variety of different etiologies, but with a heritability estimate of more than 90%. Although the strong correlation between autism and genetic factors has been long established, the exact genetic background of autism is still unclear. This review refers to all the genetic syndromes that have been described in children with pervasive developmental disorders (tuberous sclerosis, fragile X, Down, neurofibromatosis, Angelman, Prader-Willi, Gilles de la Tourette, Williams, etc.). Issues covered include prevalence and main characteristics of each syndrome, as well as the possible base of its association with autism in terms of contribution to the current knowledge on the etiology and genetic base of pervasive developmental disorders.

Keywords: Autism; Comorbidity; Genetic syndrome

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1. Introduction

Autism was first described in 1943 by psychiatrist Leo Kanner, who applied the term to boys socially withdrawn and preoccupied with routine, manifesting poor or no verbal communication, but not mental retardation. The term "autism", however, belongs to Bleuler (1911) and was used to describe schizophrenic patients withdrawn from social interaction and isolated to themselves ("autos" means "self" in Greek). In addition, Asperger was the first to note the tendency of the disorder to "run in families". In the following years, under the strong influence of the prevalent psychoanalytic theory, autism was considered to be of psychogenic origin, resulting from poor parenting skills. The psychogenic theory was refuted in the 1960s and 1970s [1].

British psychiatrists L. Wing and J. Gould first developed in the 1970s the concept of a range of disorders with a triad of impairments in common: impaired reciprocal social skills, impaired verbal and nonverbal communication and impaired development of imagination [2].

According to the 10th edition of the International Classification of Diseases (ICD-10) and the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), autism is currently defined as "a behaviorally defined syndrome manifested as impairment in social relatedness and communication and as repetitive routines and restricted interests" [3,4]. The term "pervasive developmental disorders" (PDDs) refers, according to DSM-IV, to five conditions: (1) autistic disorder, (2) Asperger's disorder, (3) Rett's disorder, (4) childhood disintegrative disorder, and (5) PDD not otherwise specified. The term "autistic spectrum disorder" (ASD), although not an official diagnostic term, is now in widespread use and is synonymous with the term PDD [5].

The prevalence of PDD ranges between 4.5 and 59/10,000, depending on the diagnostic criteria used in each study [2,6–9]. However, most recent studies report it to be increasing and even amounting to 110/10,000 [10]. The increasing incidence, whether it is actual or resulting from the use of broadened criteria in the recent studies, is raising the scientific interest and concern on the disorder and more specifically on its etiology.

The correlation between autism and genetic factors has been established since the 1960s, when the high concordance rate in monozygotic twins was first noted by B. Rimland [11]. Many studies on twins and siblings followed, aiming to shed light into the exact pattern of inheritance of autism [12–16].

Evidence from numerous cases involves a variety of comorbid diseases in autistic children [2,6,17–23]. Although the comorbidities of genetic origin are frequent, their rate varies widely among different studies. The number of genes involved ranges from 5–10 to 15 and maybe as many as 100 [24]. The specific factors that determine the subgroup of patients who present autism in each syndrome have not yet been fully revealed.

This review is attempting to summarize the most common "related with autism" syndromes and the possible base of this association in terms of contribution to the current knowledge on the etiology and genetic base of autism. Since for many of these conditions no epidemiological data exist, due to their rarity, the most prevalent ones will be mentioned first (Table 1) with the rest following in alphabetical order.

Table 1
Associated disorders and their rate in autism [5]

Syndrome	Number of studies	Median rate	Range (%)
Tuberous sclerosis	11	1.1	0–3.8
Fragile X	9	0.0	0–8.1
Down syndrome	12	0.7	0–16.7
Neurofibromatosis 1	6	0	0–1.4

2. Tuberous sclerosis complex

Tuberous sclerosis (TS) is a neurocutaneous autosomal dominant disorder that presents with a prevalence of 1–1.7/10,000 [25,26]. Mutations in one of two genes, *TSC1* (chromosome 9q34) and *TSC2* (chromosome 16p13) result in disrupting the normal interaction of their protein products, hamartin and tuberin, which are responsible for cellular differentiation, migration, and proliferation. This disruption leads into formation of hamartomatous growths in one or more body systems (skin, central nervous system, kidneys, heart, lungs, and retina) [27].

Skin lesions include: hypomelanotic macules, facial angiofibromas, shagreen patches, and periungual fibromata. Many of the frequent and serious complications of TSC, including epilepsy, mental retardation and a wide range of psychiatric and behavioral disorders, reflect the cerebral involvement that occurs in over 90% of cases. Structural abnormalities in the brain include cortical tubers, subendymal nodules, and migration tracts through the white matter linking subendymal and cortical lesions [27].

The prevalence of autism in TS is estimated from 16% to over 65% and, reversely, the prevalence of TS in autism at 0–4% and perhaps as high as 8–14% among the subgroup of autistic individuals with a seizure disorder [5,28,29]. Incidence of autism in TS may be even higher than those of cardiac and renal abnormalities, for which TS populations are routinely screened [30]. "The underlying reason for the association of TS and autism might be a nonspecific disruption of brain function owing to TS complex, including tuber location, seizures and their effect on brain development, cognitive impairment, a disturbance in brain development in regions associated with autism spectrum disorder, or, less likely, a linkage between a TSC gene and an autism susceptibility gene" [31].

As far as it concerns the *TSC* gene, the presence of autism may arise if the mutations occur at critical stages of neural development in neural tissue of brain regions critical in the development of autism [29]. Autistic disorder, low IQ, and infantile spasms are more common in TS patients with *TSC2* mutation [27].

The cessation of infantile spasms (with vigabatrin) in autistic children with TS is associated with significant improvement in cognition and behavior and, even, with disappearance of autistic behavior in some cases, concluding that controlling spasms in TS children is of ultimate importance for their neurodevelopmental outcome [32,33]. The above is consistent with the notion that early onset of electrophysiological disturbances within the temporal lobes (and perhaps other locations) has a deleterious effect on the development and establishment of key social cognitive skills, thereby inducing autism spectrum disorders [34]. In addition, a strong association has been reported between autism and the presence of cortical tubers in the temporal lobe and, more specifically, in specific regions of the temporal lobe, excluding the superior temporal gyrus and the right temporal lobe [35].

Conclusively, "individuals with TS are at very high risk of developing an autism spectrum disorder when temporal lobe tubers are present and, in addition, associated with temporal lobe epileptiform discharges and early-onset, persistent spasm-like seizures" [35].

3. Fragile X syndrome

Fragile X syndrome (Frax) is the most common inherited form of human mental retardation. It is caused by trinucleotide repeat expansion in the fragile X mental retardation 1 gene (*FMR1*) at the Xq27.3. The mutation prevents the expression of the encoded protein, Fragile X Mental Retardation Protein (FMRP). The prevalence of Frax is between 1/3500 and 1/9000 in males [36]. The prevalence of autism among individuals with Frax is estimated at 25–33% [37,38]. Reversely, the prevalence of Frax in autism was recently estimated at 2.1% [17]. Many authors argue that there is no association between Frax and autism in their cohorts [39,40]. It has been reported that the prevalence of autism is the same in a Frax cohort and a control group with idiopathic mental retardation [41,42].

Although the extent of association between Frax and autism is still unknown, many researchers are trying to shed light into the base of it. It has been suggested that Xq27.3 might harbor an autism susceptibility gene. One or more markers on the X chromosome have been reported to be associated with social cognition [43], but results upon association of Frax genes with autism are still highly controversial [44–49].

Another suggestion is that the association is mediated by FMRP, which is an RNA-binding protein and, therefore, its deficiency could disregulate autism related genes in different loci [50]. The absence of FMRP is probably involved in the exaggerated activation of group 1 metabotropic glutamate receptors, which modifies synaptic plasticity and synaptogenesis [51,52]. Defects of synaptogenesis have also been associated to two other X-linked genes encoding neurogilins in siblings with ASD [53]. Evidence for the association of FMRP and autism stems from the fact that FMRP is abundant in the hippocampus and cerebellum, which are often malformed

in children with autism [54,55]. In addition, it has been found that the size of the posterior cerebellar vermis in girls with Frax correlates inversely with the number of autistic features they exhibit [56]. As evidence upon the existence of a relationship between Frax and autism is highly controversial, there is still need for future multidisciplinary studies in this area [57].

4. Down syndrome

It is the most common chromosomal cause of mental retardation with a prevalence of 1/1000 live births [58]. The prevalence of Down syndrome (DS) in autism ranges from 0 to 16.7% and the rates of autism among DS individuals between 1% and 10%. It has been suggested that the comorbidity of DS and autism is not higher than expected by chance, once the affects of mental retardation, which is a risk factor for autism, are taken out [5].

However, research is focusing on the possible factors related to DS itself that may predispose to autism. One suggestion is that the association is mediated by infantile spasms, which are more common among Down infants and, also, a risk factor for autism [1]. A long duration of infantile spasms (because of late response to treatment) has been reported to be associated with more autistic features and poorer mental development [59]. It has been proposed that hypothyroidism might play a role, as it is also common among DS individuals and, in addition, a risk factor for autism [1]. Recent data link vasoactive intestinal peptide malfunction in DS brains with autism. Blockage of vasoactive intestinal peptide during development results in growth and developmental delays, neuronal dystrophy, and, in adults, cognitive dysfunction. Vasoactive intestinal peptide is elevated in the blood of both newborn children with autism and DS patients [60]. On the other hand, the level of biogenic amines has been found low in the brain of both individuals with autism and DS patients, obviously affecting the synaptic density and brain plasticity [61]. It has been proposed that disruption of serotonergic development, specifically, may be the common underlying mechanism for the two disorders [62,63].

5. Neurofibromatosis type 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant condition caused by decreased production of the protein neurofibromin, which is a tumor suppressor, associated with the *NF1* gene in the long arm of chromosome 17 at 17q11.2. It is mainly characterized by café-au-lait macules, neurofibromas, axillary or groin frecklings, optic pathway tumors, Lisch nodules and dyplastic skeletal findings (long bone bowing/pseudoarthrosis and/or sphenoid wing dysplasia). The prevalence of NF1 is estimated between 1/3000 and 1/4000 [64] and its prevalence among individuals with autism varies from 0% to 1.4% [5]. The association could be mediated by *NF1* gene (more specifically, novel *GXAlu* allele) which has been proposed as a possible candidate gene for autism [65], although reports upon this are controversial [66,67]. Given that patients with autism have a 100- to 190-fold increased risk of neurofibromatosis compared to the general population, it is obvious that the two diseases are associated, probably by sharing a common etiological background, even though it has not been yet clarified [67].

6. Angelman, Prader-Willi and isodicentric 15q chromosome syndromes

Angelman syndrome (AS) is characterized by developmental delay, mental retardation, speech impairment, gait ataxia and a "happy behavior" including laughing, smiling, and excitability. In many cases, microcephaly and seizures are also present. The prevalence of AS is estimated at 1/12,000 [68]. According to recent data, 42% of an AS population studied met criteria for autism [69]. Reversely, the estimated prevalence of Angelman in autism is 1% [70]. The syndrome is associated with silence or disruption of a maternally derived gene *UBE3A*, located on the chromosomal region 15q11.2. The inactivation of *UBE3A* is due to maternal deletions (DEL), paternal uniparental disomy (UPD), defects in an imprinting center or biparental inheritance with mutations of *UBE3A* [71].

Similarly, lack of paternal contribution within the same region (15q11–13) leads to Prader-Willi syndrome (PWS) and is mainly due either to paternal deletion or maternal uniparental disomy. Prader-Willi syndrome is characterized by hypotonia, developmental delay and mental retardation. Its birth prevalence rate is 1/29,500 [72] and the prevalence of autism in it is estimated at 25.3% [73].

It has been suggested that autism is associated with maternally derived duplications/triplications of chromosome 15q11–13 and therefore might occur more frequently in people with PWS when due to maternal uniparental disomy, than in other forms of chromosomal abnormality involving this region. Therefore, "overexpression of maternally imprinted genes in 15q11–13 confers a risk for ASD" [73]. Furthermore, the degree of cognitive impairment has been associated with the degree of genetic impairment in autistic individuals with maternally derived duplications [74].

The association of AS with autism could also be mediated by MECP2, a protein whose disruption causes Rett syndrome. It has been suggested that MECP2 has a role in the homologous pairing of imprinted 15q11–13 alleles in brain tissue, as specific deficiencies concern-

ing the organization of chromosome 15 have been observed in the developing brain of individuals with Rett, AS, and autism [75].

It was recently suggested that the *GABRB3* gene, located within chromosome 15q11–13, is a candidate for PDD. Duplication of 15q11–13 produces the isodicentric chromosome 15q syndrome, characterized by short stature, diabetes, anal and jejunal atresia, and acanthosis nigricans [76]. The additional genetic material may be interstitial, producing 46,XY karyotype or may form a separate marker chromosome. In the latter case all patients have been reported to meet criteria for PDD [77]. Duplications of the proximal long arm of chromosome 15 have also been observed in PWS. The isodicentric 15q syndrome is associated with altered behavior, developmental delay/mental retardation, and seizures/epilepsy [78].

7. Anorexia nervosa

Anorexia nervosa has been reported in cases of high-functioning autism, although some authors argue that this association is probably due to chance [79]. Twenty-three percent of a group of patients with anorexia nervosa have been reported to meet criteria for ASD [80]. The association could be mediated by mutations in serotonin transporter coding genes [81].

8. ARX syndrome

Mutations in the X-chromosome-linked Aristaless-related homeobox gene (*ARX*), located on chromosome Xp21.1 are associated with a spectrum of X-linked mental retardation disorders. These include non-specific X-linked mental retardation, Partington X-linked mental retardation syndrome, X-linked infantile spasm syndrome and X-linked lissencephaly with ambiguous genitalia [82]. Autism has often been related to *ARX* mutations [82–85]. The base of the association is not totally clear. *ARX* knockout mice manifest disruptions in overall neuroblast proliferation as well as selective abnormalities in GABA interneuron migration. The defective neural circuits that occur may predispose to ASDs. A recent suggestion associates autism with an increased ratio of excitation/inhibition in sensory, mnemonic, social and emotional systems probably caused by *ARX* [82,86,87].

9. Charge, Goldenhar and Moebius syndromes

Charge syndrome or association (coloboma, heart defect, atresia of the choanae, retarded growth and/or development, genitourinary anomalies, ear anomalies and/or deafness) is a genetically heterogeneous disorder with an incidence of 1:8500 [88]. Recently, mutations to the *CHD7* gene have been established as one cause of CHARGE [89].The prevalence of autism in Charge association varies in different studies and appears to be as high as 27.5–40% [90,91]. The autistic behavior is perhaps associated with the developmental errors in early embryogenesis of Charge patients. ASDs have been reported in other conditions resulting from early embryogenic defects, such as thalidomide embryopathy and Goldenhar and Moebius syndromes, even when the insult occured as early as week 4 to 6+ of embryogenesis [92].

Goldenhar syndrome belongs to the Oculo-Auriculo-Vertebral (OAV) Spectrum and is characterized by hemifacial microsomia, epibulbar dermoids or dermolipomas, deformity of the ears with pre-auricular appendages and malformations of the orbit, upper lid, vertebra etc. Except for the embryogenic defects, autosomal recessive and dominant, as well as multifactorial inheritance are probably involved [93,94]. The incidence of Goldenhar syndrome ranges between 1:3500 and 1:5600 in different studies [95]. In a group of 20 patients with Goldenhar syndrome, three were reported with autism and autistic like conditions [96].

Moebius syndrome is characterized by congenital palsy of mainly the 6th and 7th cranial nerves and impairment of ocular abduction, skeletal and orofacial anomalies. The condition is associated with early embryogenic disruption of vasculature. Its incidence is estimated at 2/100,000 [97]. In two groups of patients with Moebius syndrome studied, autism and autistic-like conditions were detected in 34% and 40% of the patients, respectively [96,98].

The association of embryogenic defects and autism is unclear. The homeobox genes (*HOX*) have an important role in the early stage of organization of embryonic cells. A possible disruption at that time might cause them to be activated at inappropriate times, resulting into malformation of different organs. The malformation of the brainstem observed in animal models with *HOX* genes defect is similar to that associated with autism in humans [99].

10. Chromosome 2q37 deletion syndrome

It is a newly recognized syndrome, also called "Albright hereditary osteodystrophy-like syndrome". It is mainly characterized by brachymetaphalangism and mental retardation. Autism has often been described in patients with 2q37 deletion [100–103]. Therefore, 2q37.3 is a region of interest for autism susceptibility and, more specifically, *CENTG2* has been proposed as a candidate gene for autism [103]. Absence of the corpus callosum, has also been reported in cases of 2q37 syndrome, providing a possible mechanism for the association of the syndrome with autism in those individuals [104].

11. Chromosome 13 deletion syndrome

It is characterized by a wide spectrum of abnormalities. Clinical features of the 13q deletion syndrome are difficult to define and include retinoblastoma, mental and growth retardation, craniofacial abnormalities, brain, gastrointestinal, renal and heart malformations, anal atresia, and limb and digit malformations. It is caused by a deletion of the long arm of chromosome 13 (q13–32) [105]. Deletions of 13q have been reported in cases of autism [106–108]. Disruptions of 13q are strongly related to abnormal language development, which is one of the main diagnostic criteria for autism [109].

One of the candidate genes for autism is neurobeachin, which is located at fragile site *FRA13A* and maps to 13q13.2. It encodes a protein implicated in membrane trafficking and predominantly expressed in the developing human brain [110].

In addition, serotonin 2A receptor gene (*HTR2A*) on chromosome 13q has been proposed as a primary candidate gene in autism, given that the relationship between ASDs and hyperserotonemia has been long proven [111].

12. Cohen syndrome

It is an autosomal recessive disorder with an incidence of 1/105000 births [112]. The responsible gene (*COH 1*) has been mapped to chromosome 8q22, although not all affected cases have the *COH-1* gene. The syndrome's main characteristics are ophthalmologic abnormalities, microcephaly, specific facial characteristics (short philtrum, high arched palate, thick hair and eyebrows, low hairline, protruding/crowded teeth, down slanting palpebral fissures, prominent nose), haematological abnormalities (including neutropenia), hand and feet abnormalities, truncal obesity, hypotonia, scoliosis, short stature, psychomotor delay, etc. [113,114]. Forty-eight percent of a group of patients with Cohen syndrome was reported to meet criteria for autism. As the genetics of the syndrome are not yet totally clarified, it remains to be revealed whether the subgroup with autistic features has a different genetic profile than the rest of the Cohen patients [115].

13. Cole–Hughes macrocephaly

It is a recently described syndrome characterized by macrocephaly, obesity, delayed bone age, variable developmental delay, autism and a typical face with square outline, ''dished-out'' mid-face, biparietal narrowing, and long philtrum. The syndrome is probably inherited in an autosomal dominant way and should be considered in cases of autism not fitting the diagnosis of Sotos syndrome [116–118].

14. Cowden and other hamartoma syndromes

It is an autosomal dominant disorder characterized by multiple hamartomas (occurring in the skin, breast, thyroid, gastrointestinal tract, endometrium, and brain) and macrocephaly. The ''responsible'' for the condition gene is *PTEN*, a tumor suppressor gene localized to chromosome 10q23 [119]. Mutations in *PTEN* have also been detected in other hamartoma-overgrowth syndromes presenting with autism, such as Bannayan–Riley–Ruvalcaba and Proteus and recently in a patient with VATER association and macrocephaly [120–123]. *PTEN* gene mutation was detected in 17% of a group of autistic subjects with macrocephaly, suggesting that patients with ASD and macrocephaly should be screened for *PTEN* mutation, even in the absence of other features of the hamartoma syndromes [124].

15. De Lange syndrome

It is a multiple congenital anomaly syndrome characterized by a distinctive facial appearance (long and prominent philtrum, confluent eyebrows, long eyelashes, thin downturned lips, a broad and depressed nasal bridge, and anteverted nostrils), prenatal and postnatal growth deficiency, feeding difficulties, psychomotor delay, behavioral problems, and associated malformations that mainly involve the upper extremities. Its population prevalence is 1/10,000 [125] and its etiology is the heterozygous mutation in gene *NIPBL*, located on the short arm of chromosome 5. Autism has been reported in 36% of a De Lange and its prevalence was found to be related to the degree of mental retardation, but not to the somatic phenotype [126].

16. Duchenne muscular dystrophy

It is an X-linked recessive disease with a prevalence of 5.5/100,000 [127]. Cases of autistic patients with Duchenne have been sporadically reported [128–130]. Although the hypothesis that their co-occurrence could be explained by chance has been rejected, the base for their association remains to be revealed [131].

17. Giles de la Tourette syndrome

Tourette syndrome (TS) is characterized by multiple motor and one or more vocal tics, the number, frequency and complexity of which change over time [132]. The prevalence, according to recent epidemiologic data, is between 2% and 3% [133]. Tourette syndrome is genetically determined, although perinatal factors and infections seem to play a role. The exact pattern of

inheritance is not clear [134]. The prevalence of Tourette among patients with autism is estimated at 6.5% [135]. Several suggestions have been made to explain this association. One of the hypotheses is that common genetic factors influence liability to both disorders [136]. A breakpoint in 7q31 has been recently associated with TS and is also implicated in autism and speech-language disorder [137]. It has even been proposed that children with autism could be severe cases of Tourette syndrome [138]. Another suggestion is that the comorbidity is mediated by dopamine abnormalities [139–141], which points to an involvement of the basal ganglia, as 80% of the brain's dopamine is located there [142]. It has been proposed that Tourette and autism, along with Attention Deficit/Hyperactivity Disorder and Obsessive Compulsive Disorder, are all part of a more complex disorder, called the Developmental Basal Ganglia Syndrome, which is a consequence of a wide range of genetic and/or environmental conditions that interfere with normal developmental processes of the basal ganglia and its connections [140]. Additionally, serotonin is involved in the pathology of both disorders, as one third of the individuals with PDD have elevated serum serotonin levels [143] and an inverse relationship between severity of vocal tics and serotonin binding in the midbrain and thalamus was found in GTS patients [141].

18. Hypomelanosis of Ito

Hypomelanosis of Ito is a rare neurocutaneous phenotype comprising pigmentary anomalies (patterned hypopigmented macules mainly on the trank, along the lines of Blaschko), neurological defects, structural malformations and chromosomal abnormalities [144]. The pattern of inheritance – if any – is not clear, although in some cases it is inherited as an autosomal dominant trait. The prevalence is quite low: 1/10,000 unselected patients in a children's hospital [145]. Autism is often present in the syndrome [146–150] with a prevalence of 10% [150]. Mosaic deletions of the critical for autism region 15q11q13 have been reported in hypomelanosis of Ito, providing a possible explanation for its association with autism [151].

19. Lujan–Fryns syndrome (X-linked mental retardation with marfanoid habitus)

The Lujan–Fryns syndrome or X-linked mental retardation with marfanoid habitus is characterized by tall, marfanoid stature, distinct facial dysmorphism and behavioral problems, including autism. It affects predominantly males and should be differentially diagnosed from Frax, Marfan syndrome and homocystinouria. The precise genetic cause and the prevalence of the syndrome remain to be determined [152]. In a study of 21 subjects with autism in Belgium, four of them were diagnosed with comorbid Lujan–Fryns syndrome [153], revealing that Lujan–Fryns should be considered in cases of ASD with mental retardation.

20. Mitochondrial disorders

Autism has occasionally been described in patients with mitochondrial dysfunctions such as lactic acidosis and carnitine deficiency [5]. In addition, functional neuroimaging methodologies have reported deficient energy metabolism in the autistic brain, which probably involves mitochondrial dysfunction with concomitant defects in neuronal oxidative phosphorylation within the central nervous system [154]. A study of 100 autistic children reported the detection of significantly reduced free and total carnitine, as well as pyruvate levels, along with slightly elevated lactate and significantly elevated ammonia and alanine levels [155]. However, a recent review on the association of autism and mitochondrial disorders reports that the two conditions can co-exist in only few patients, most of whom will present with multisystem abnormalities (especially neurological) associated with the autistic behavior [156].

21. Phenylketonuria

Phenylketonuria (PKU) is characterized by hyperphenylalaninemia, resulting from impaired metabolism of phenylalanine, due to deficiency of the enzyme phenylalanine hydroxylase (PAH). It is an autosomal recessive disorder caused by mutations in the *PAH* gene on chromosome 12 The untreated state, which is characterized by mental retardation, microcephaly, delayed speech, seizures etc, has nowadays been eliminated by screening of all newborn children [157].

In the past, autism has been often reported in cases of untreated PKU. Biogenic amines have been shown to facilitate formation and maintenance of synapses in the developing and adult brain [63]. The lack of biogenic amines, along with the accumulation of phenylalanine in the brain of patients with PKU is associated with the presence of mental retardation and autism [1].

Although undiagnosed PKU with comorbid autism should have become by now extinct, the present authors are aware of one more case of a 3-year-old male with autism and undiagnosed PKU in Greece. The prevalence of autism was estimated at 5.7% in a group of late diagnosed patients with PKU in 2003. In the same study none of the PKU children identified by newborn screening and on dietary treatment met criteria for autism [158].

22. Smith–Lemli Opitz syndrome

It is an autosomal recessive multiple congenital malformations syndrome, including mental retardation, failure to thrive, craniofacial abnormalities, incomplete development of male genitalia, limb anomalies and various internal organ abnormalities. It results from an inborn error in 3β-hydroxysteroid Δ7-reductase (DHCR7), the terminal enzyme required for cholesterol biosynthesis [159,160]. Its prevalence ranges from 1/20,000 to 1/40,000 live births [161] and the prevalence of autism in it is estimated at 46–53% [162,163]. Studies in mice have provided evidence that the lack of DHCR7 results into hippocampal abnormalities and hypermorphic development of serotonin neurons. Therefore, the association of the syndrome with autism seems reasonable, given the significant role of serotonin in autism [159].

23. Smith Magenis syndrome

It is a multiple congenital anomalies/mental retardation syndrome associated with a heterozygous deletion of chromosome 17p11.2. The characteristic features include mental retardation, dysmorphic facial features, minor skeletal anomalies including brachydactyly and behavioral abnormalities. Its prevalence is 1/25,000 [164]. The first systematic investigation of the association between autism and the syndrome was conducted in 1999 reporting that 93% of a Smith Magenis patients' group qualified for a diagnosis of autism [165].

24. Sotos syndrome

Sotos syndrome is an autosomal dominant disorder characterized by congenital macrocephaly, a prominent forehead with an apparently receding hairline, accelerated pre- and postnatal growth, advanced bone age and large hands and feet. Developmental delays are present in most children with Sotos. Mutations in the *NSD1* gene on chromosome 5 are responsible for a large number of Sotos cases [166]. The prevalence is not known, but is estimated to be between 1/10,000 and 1/50,000 [167]. The prevalence of the syndrome in autism was recently reported at 0.5% [17].

Although cases of autism and Sotos syndrome comorbidity have been reported [168,169], the base of the association is not clear. Macrocephaly syndromes are frequent among patients with autism (fragile X, Cole–Hughes, Sotos, etc.).

25. Steinert's myotonic dystrophy

It is an autosomal dominant disorder associated with mutations of the myotonin gene located in 19q13.3, due to expanded trinucleotid (CTG) repeats. The disease is characterized by myotonia, muscular dystrophy, cataract, hypogonadism, frontal alopecia, and ECG changes. Both infantile autism and Asperger's syndrome have been described in cases of myotonic dystrophy [170–172]. The association, if any, is yet not clear. However, it has been suggested that the same type of inheritance (trinucleotid repeats) observed in the dystrophy might play a role in autism and other neuropsychiatric disorders, such as schizophrenia and bipolar disorder. After all, the phenomenon of genetic "anticipation" (increasing severity, declining age of onset, and increasing penetrance in successive generations, due to expansion of the repeat) in "trinucleotid repeats diseases" has been observed in autism [173,174].

26. Timothy syndrome

Timothy syndrome (TS) is a multisystem disorder mainly characterized by simple syndactyly and life-threatening cardiac arrhythmias, congenital heart disease, immunodeficiency and cognitive abnormalities. It results from a cardiac L-type calcium channel (CaV1.2) mutation, *G406R* in exon 8A. In a study of 17 children with Timothy syndrome, 4 met criteria for ASDs, which may imply a role for Ca(2+) in autism [175].

27. Turner's syndrome (monosomyX)

The syndrome's birth prevalence is estimated between 1/2000 and 1/5000 female live births and its main characteristics, except for the underdevelopment of female sexual characteristics, are short stature, lymphedema of hands and feet, deep set hyperconvex nails, unusual shape and rotation of ears, narrow maxilla and dental crowding, micrognathia, low posterior hairline, broad chest with inverted or hypoplastic nipples, etc. [176]. Autism has been described in various cases of Turner's patients [177–179]. The association is probably due to an imprinted X-linked locus affecting cognitive function and not expressed from the maternally derived X chromosome. It has been reported that 45,X0 females with the maternally inherited X chromosome have reduced social cognition compared to 45,X0 females with a paternally inherited X [43]. Imprinting may actually have a similar role in the generally recognized greater vulnerability of males (who normally have maternal X chromosome only) to autism compared to females with X chromosomes from both parents [180].

28. Velocardiofacial (catch 22) or 22q11 deletion or Di George syndrome

It is the most frequent known interstitial deletion found in man and occurs in approximately 1 in 4000 live

births [181]. It is mainly characterized by a distinctive facial appearance (a long face, small ears with over-furled helices, upslanting eyes, a widened nasal bridge with a prominent nasal tip and a small mouth), cleft palate, congenital heart disease, hypoplasia of thymus with lymphocytopenia and hypoparathyroidism with hypocalcaemia. Psychiatric and behavioral disorders are often present. The prevalence of ASDs among patients with the syndrome is estimated between 20% [182] and 31% [183].

A number of genes included in the deleted region have been associated with the syndrome's phenotype. *ProSAP2* encodes a scaffold protein preferentially expressed in the cerebral cortex and cerebellum. Evidence from patient cases with autism and disruption of *ProSAP2* suggest that it may be responsible for the developmental delay and the autistic features of the syndrome [184,185].

Nevertheless the high prevalence of autism in the syndrome, Ogilvie et al. reported that no deletion was detected in a group of 103 autistic subjects investigated, showing that testing autistic patients for 22q11 deletion is unnecessary in the absence of other indications [186].

29. Williams syndrome

Williams syndrome (WS) is a rare (2–5/100,000) genetic disorder characterized by a typical facies, cardiac abnormalities, infantile hypercalcemia and growth and developmental retardation with a deficit in the visuospatial cognitive function and a relative preservation of linguistic abilities in general and spoken language in particular. The genetic base of the syndrome is a deletion at 7q11.23, where *LIM Kinase 1* gene is located among others. Neuroanatomical features of the syndrome include a reduction in brain volume, preservation of cerebellum and frontal lobes and a reduction of posterior cortical systems [187,188].

Autism has been described in several cases of Williams syndrome [189–192], although the syndrome is typically characterized by high verbal communication skills [187]. Two of the patients with autism and Williams syndrome showed elevated blood serotonin levels, although hyperserotonemia is not a common feature of the syndrome [190].

One of the suggestions for the base of the relationship between autism and Williams involves *PCLO*, which is a presynaptic cytoskeletal protein. *PCLO* has a role in synaptic plasticity and synaptogenesis. The human *PCLO* gene maps to 7q11.23–q21.3 and is, therefore, implicated as a linkage site for autism and Williams syndrome [193].

30. 47,XYY syndrome

The syndrome's prevalence is 1/1000 and the phenotype includes tall stature, speech and motor skill delays, hyperactivity and learning disabilities [194,195]. Autism has often been reported in 47,XYY males [196–201]. A study of 187 autistic subjects reported the prevalence of XYY in autism at 0.5% [17]. Obviously, the extra chromosome affects brain development and predisposes vulnerable males to PDDs [199], although the association is not clear.

31. Others

Cases of autism have been sporadically described in several other syndromes, but in most cases the comorbidity could be explained by chance alone, taking into account the fact that mental retardation is a common feature of most of the syndromes, as well as a risk factor for autism. Some of these syndromes are: Ehlers Danlos [202,203], Joubert (which was strongly associated with autism [204–206], until recent opposite evidence [207]), Leber's congenital amaurosis [208], Coffin Siris [209], Biedl Bardet [210], Kleine Levin [211], Myhre [212], Apert [213], neuroaxonal dystrophy [214], HEADD [215], Klinefelter [17,216], San Filippo syndrome [217], Noonan [218,219], 10p deletion [220], etc. Apart from phenylketonutia, several other metabolic defects are also related to autism. Among them are histidinemia, adenylosuccinate lyase deficiency, dihydropyrimidine dehydrogenase deficiency, 5′-nucleotidase superactivity, and phosphoribosylpyrophosphate synthetase deficiency [221]. In some of these disorders, the relation with autism is not by means of comorbidity, as autistic behavior is included in the main symptomatology or even the diagnostic criteria of the disorder. It has been proposed that such disorders are called ''disease entities of autism'', instead of ''comorbid with autism syndromes'' [1].

32. Environmental factors

Nevertheless the known or suspected organic causes of the syndrome, the concordance rate in monozygotic twins is 92% even for a broad autistic phenotype, suggesting that ''interactions between multiple genes cause ''idiopathic'' autism but that epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism-related traits'' [222]. These environmental triggers are probably the factor that determines the specific subgroup of patients of a genetic syndrome who will present autism. Three large epidemiological studies on autism and gene-environment interactions are already under way, associating ''autism genes'' with immune factors, toxicants, infections etc [223].

We will briefly review the most important of the already described environmental risk factors. Thalidomide [224,225] and anticonvulsants, especially sodium

valproate [226], during pregnancy are consensually associated with autism. There is also a strong association between autism and fetal alcohol syndrome [227,228]. It has been suggested that perinatal factors may play a causal role in autism. A Danish study in 2005 reported that the risk of autism was associated with breech presentation, low Apgar score at 5 min and gestational age at birth <35 weeks [229]. Maternal daily smoking in early pregnancy has also been described as a risk factor [230]. Prenatal or postnatal exposure to infections, such as rubella, herpes simplex virus, and cytomegalovirus, has been reported in several patients with ASDs [1]. Another described risk factor of PDD is lead poisoning, as the lead blood levels of autistic individuals have been reported to be significantly high [231–233]. However, the odd food preferences of the patients, along with pica and habitual mouthing, make it hard to determine whether the lead poisoning has contributed to their symptomatology or is a consequence of it [1]. It has been proposed that, until the pica disappears, all children with developmental delays or at risk for autism should have periodical lead screens [234]. Other metals have also been associated with autism. Mercury and cadmium, in addition to their neurotoxic effects, are also suspected endocrine disruptors (environmental hormones) with potential effects on thyroid function. It has been hypothesized that children with autism have a decreased detoxification capacity due to genetic polymorphism and are, therefore, vulnerable to the effects of metals. Chlorinated solvents and diesel particulate matter may also be associated with a moderately increased risk of autism [235,236].

A causal relationship between the measles, mumps, and rubella (MMR) vaccine and autism has been claimed, based on the increase of autism after introduction of the MMR vaccine. However, most recent studies have shown no effect of MMR on the incidence of ASDs [237–239].

Visual and hearing impairments often co-exist with autism. It has been suggested that the sensory deprivation could be an environmental risk factor for autism. However, it was reported in 1998 that autism was more common (56%) in individuals with retinopathy of prematurity (and severe brain damage) compared to congenitally blind children (0.1%), concluding that the association is most probably mediated by brain damage and is largely independent of the blindness per se [240]. Evidence for this also stems from a report on children with Leber's congenital amaurosis who present autism more frequently compared to blind children from other causes [208]. Similarly, most authors conclude that hearing impairment is unlikely to be an etiological factor in autism, but may be a marker for brain damage in it [241]. Autistic-like patterns have been described in deprived children in Romanian orphanages. However, their symptoms differed from autism "with respect to the improvement seen by age 6 years, to an equal sex ratio and to a normal head circumference" [242].

In general, environmental factors are not considered to be the principal cause of the disorder. "It is unlikely that one or even a few specific environmental agents are responsible for the majority of ASDs. It is more likely that some individuals have enhanced susceptibility to insults from the environment that may, in combination with their genetic predisposition, lead to autism [243]".

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