

Fragile X Syndrome and Autism: Common Developmental Pathways?

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Abstract: Identifying atypical trajectories that distinguish children with differing developmental disorders from each other and from typically developing children is a potentially powerful tool for early ascertainment and treatment of syndrome specific proficiencies and deficiencies. The past decade has seen unparalleled advances in the fields of molecular genetics, pediatrics, developmental cognitive neuroscience and brain imaging. Collaboratively, these advances have facilitated our understanding of how genes can impact upon early development, through the identification of specific patterns of cognitive and behavior processing and the deficits in these domains that are typical to a specific developmental disorder. These advances have also made early diagnoses possible for many developmental disorders, including those for which genetic etiology has yet to be determined, such as is the case for most individuals with autism, or disorders such as fragile X syndrome that result from the silencing of a single gene. This early identification necessitates thorough investigation of the impact of a condition across the lifespan beginning in early childhood when interventions are most likely to have significant benefit. This is especially relevant for disorders that at first glance appear to share overlapping behavioral and clinical symptomology. In the case of autism and fragile X syndrome, commonalities in social and communication profiles are now well documented in early childhood. However, to what degree symptom overlap implies common developmental pathways or etiologies remains unclear. The focus of this review will be to critically evaluate whether so called 'commonalities' in phenotypic outcomes actually reflect very different developmental pathways that diverge over developmental time and across syndromes. More detailed knowledge of these profiles will facilitate early timing of tailored interventions that will promote optimal development resulting in significant educational, clinical, and adaptive benefits across a child's lifespan.

Keywords: Fragile X syndrome, autism, behavioral phenotypes, atypical developmental pathways, language, social interaction.

INTRODUCTION

The past decade has seen unparalleled advances in the application of molecular genetic methods to the study of developmental disorders, including disorders with and without mental retardation. These advances include higher resolution conventional G-banded cytogenetics, the application of molecular cytogenetics in the form of Fluorescent in-Situ Hybridisation (FISH) technology, and molecular genetic analysis for specific single gene disorders, such as Fragile X syndrome. Alongside this development there has been a substantial growth in the number of pediatric studies attempting to link genomic changes (deletion, reduplication or silencing of genes) to behavioral end-states and brain function, in essence to link genotype to phenotype. The rapid growth in neuroimaging techniques, notably structural and functional imaging, including magnetic resonance, evoked related potentials, and single photon emission computed tomography, have provided a unique opportunity to further delineate the brain-behavior relationship in both typical and

atypical populations. Collaboratively, this research has made three important contributions to date: 1) that general developmental delay needs to be differentiated from syndrome specific 'signatures' that represent distinct phenotypic outcomes; 2) that similar behavioral outcomes or symptom overlap across different conditions does not necessarily imply common cognitive mechanisms or etiologies; and, 3) that awareness of the early physical, cognitive and behavioral characteristics that distinguish different neurodevelopmental disorders can promote more timely and accurate diagnosis and management that can impact at both the clinical and educational levels across developmental time. Furthermore, with these new advances comes the need to transfer this knowledge into a more meaningful context that that can help prepare affected families and professionals to respond to behavioral and cognitive challenges that are specific to their child's condition.

The focus of this review is to demonstrate the importance of these contributions towards our understanding of two neurodevelopmental syndromes that are extensively documented in the pediatric literature and which, at a first glance, appear to share common, overlapping behavioral and cognitive symptomatology: fragile X syndrome (FXS) and

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autism. We will first describe the genetic and clinical considerations and then proceed to reflect on the co-occurrences and commonalities between the two disorders across the domains of social behavior and cognition (theory of mind), language and adaptive functioning. Finally, we will outline the proposed critical differences, in a child presented to a pediatric clinic with autistic-like symptoms, the phenotypic end-states that warrant a careful and thorough examination for fragile X syndrome.

Fragile X Syndrome and Autism - Genetic and Clinical Considerations

Fragile X syndrome. FXS is the world's most common identifiable hereditary cause of developmental delay affecting 1 in 4000 male and 1 in 8000 females [1-4]. The syndrome is caused by a defect in the fragile X mental retardation 1 gene (FMR1), located near the end of the long arm of the X chromosome. The FMR1 gene carries a CGG trinucleotide repeat expansion in the 5' untranslated region. In males it is almost always associated with mental retardation. In unaffected individuals there are between 7~60 repeats, with 30 repeats found on the most common allele. In clinically affected individuals the CGG repeat region expands to over 200 repeats resulting in gene shutdown the loss of the encoded protein, FMRP. Alleles with between 55~200 repeats are called "pre-mutations" (carrier-status) and generate some FMRP. The frequency of the fragile X pre-mutation in the general population is estimated at 1 in 250 females [5] and 1 in 813 males [6] and has generally been associated with normal intellectual and cognitive functioning (but see recent studies by Aziz *et al.* [7] and Cornish *et al.* [8]). However, these pre-mutations are unstable when transmitted from carrier mother to offspring, with associated risk of giving rise to the FXS phenotype should amplification of the premutation to the full mutation range occur [9]. FMRP has been found to be involved in transcription regulation of other, so far unidentified genes [10,11]. It contains DNA sequences known to be relevant to facilitation of nucleus-cytoplasm transfer of messenger RNA, and endoplasmic reticulum messenger RNA binding. Lower than normal or absent FMRP might be affecting other gene's functioning, potentially giving rise to secondary gene effects so far unknown, but at a genetic level it is now well established that the FMR1 is the only gene involved in the pathogenesis of FXS and that the loss of FMRP and the subsequent impact of that loss on early brain development causes FXS [12] by acting on other genes that modify the exact outcome. The extent to which these discoveries explain the phenotypic outcomes in FXS, most notable at the cognitive and behavioral levels, are beginning to be revealed.

The clinical features that can characterize the syndrome include an elongated face, large prominent ears and forehead, and in males, post-pubertal macroorchidism [13]. Also present frequently are macrognathia (large jaw), conductive and sensorineural hearing loss, and visual impairments including refractory errors, strabismus (squint) and amblyopia (lazy eye) [14]. More subtle features can include narrow inter-eye distance, a highly arched palate of the mouth, and hyperextensible metacarpophalangeal joints. However, the wide variability in manifestation in both males and females makes a diagnosis based on physical features

alone almost impossible. It is precisely because of their "normal" appearance that many affected children are not identified as having FXS until relatively late in their development. Undoubtedly the most defining feature, especially in boys with the condition, is mental retardation and the resulting behavioral phenotype, most notably the autistic-like features that can accompany the syndrome from very early in development. While such features should prompt FXS DNA testing, they are also shared by many other causes of autism spectrum disorders and cannot be the sole basis for the diagnosis

Autism. Autism is a complex and severe neurodevelopmental disorder that has intrigued clinicians and scientists for decades. The disorder represents the prototypical pervasive developmental disorder (PDD), characterized by a "triad of impairments" that includes a severe disruption of social cognitive function, and impaired social interaction and communicative skills, coupled with unusually restricted and repetitive stereotyped patterns of behaviors and interests with an onset in the first 3 years of life [15]. Recent epidemiological studies indicate that the rate of autism is much higher than previously thought, with approximately 30 to 60 cases per 10,000 [16]. A dimensional approach to autism includes classification based upon cognitive measures or verbal ability, with lower functioning individuals tending to have an IQ in the lower range (<70) and demonstrating more severe symptomatology. Individuals with autism with IQs in the normal to superior range are classified as higher functioning and tend to have fewer or less severe autistic symptoms [17]. However, their functional impairments in terms of daily living, self-care and social interactional skills may still be marked.

A large number of studies confirm that autism has an important and substantial genetic component (for a review, see Rutter 2000 [18]). For example, there is a predominance in males compared to females (sex ratio M/F: 3-4 ~ 8 /1 [19]), and twin studies show concordance rates of 36 to 91% for monozygotic twins and 1 to 23% for dizygotic twins. Siblings of autistic children have a higher than expected rate of language delay [20], and parents of children with autism have been found as a group to differ from matched comparison group parents on a number of psychological criteria including executive function skills, reading measures, speech and pragmatic language deficits, friendship difficulties and being more rigid, aloof, hypersensitive to criticism and anxious [21,22]. Studies of extended families also support a strong genetic component to aetiology [23]. Thus at the *genetic level*, converging evidence indicates that autism is a very strongly heritable condition (heritability >90%) although the biological mechanisms are not well understood.

Fragile X Syndrome and Autism: Converging and Diverging Cognitive and Behavioral Pathways?

There are currently very few single gene studies for which there is a certainty of the involvement of autism; FXS is one of those disorders. Almost all affected children, and especially boys, will display autistic-like characteristics that may mimic typical autism such as language delay, echolalia, and perseverative speech alongside poor eye contact, poor social interactions and stereotypic movements [24-28]. Although still controversial, a plethora of recent studies using a

variety of “gold standard” diagnostic measures including the Autism Diagnostic Observation Schedule (ADOS-G [29]), and the Autism Diagnostic Interview-Revised (ADI-R [30]) indicate a percentage of between 20-35% of FXS individuals will fulfill criteria for a *clinical diagnosis* of autism (see Hagerman for a review [31] and Rogers *et al.* [32]). One argument is that the prevalence of autism in FXS may simply be an artifact of general cognitive delay that is inherent in many mental retardation disorders. There is some merit in this argument notably that having both autism and FXS would impact on development more severely than having autism or fragile X alone. Indeed, studies do suggest that a dual diagnosis is a significant predictor of developmental status with such children functioning at a much lower level [27, 33-38]. However, the pattern of these findings alongside other longitudinal and cross sectional studies demonstrate that children diagnosed with FXS, with and without autism, and children diagnosed with autism alone differ in subtle but fundamental and clinically important ways across developmental time and across behavioral and cognitive domains. A comprehensive review of the existing literature will be provided alongside a discussion of possible causal mechanisms that might account for why so-called commonalities in the behavioral-cognitive phenotype of FXS and autism do not imply similar etiology. We will conclude with some suggestions for clinical and educational interventions that target specific syndrome ‘signatures’ and trajectories.

Social Behavior and Cognition. Difficulties in social behavior have been well documented independently in both autism [39-41] and FXS [28,42-44]. Specifically, and at first glance, a number of similarities in the social profile emerge:

Reciprocal relationships especially in social situations (eye gaze avoidance, initiating interactions) are significantly impaired across both syndromes in comparison to the typical trajectory (*autism* [45, 46]; FXS [27, 47, 48]). The ability to perceive where another person is looking is a key component in social adapting behaviors and interactions with others. Gaze direction informs about locations of potential interest or danger in the environment, and the readiness of the individual to communicate socially. In children with autism, there is now well documented evidence of a unique style of processing gaze that differentiates them from other syndrome groups. For example, the visual preference for direct gaze over averted or closed eyes is already present in typical newborns [49-51], but has not been found among children with autism [46]. Later in life, an advantage in attentional orienting in response to eye gaze as compared to non-social cues (arrows) is seen among typically developing children but not children with autism [52]. These atypicalities in following eye gaze were further supported by findings that when viewing naturalistic social situations depicted in a movie setting, individuals with autism demonstrated atypical patterns of social visual pursuit characterized by a reduced focus on eyes and increased focus on mouths, bodies, and objects [45]. This lack of social gaze may be attributed to a lack of attention, or to distractibility, or lack of interest in interacting with others, or perhaps in dysfunctional processing of social information. They find no intrinsic importance of eye contact with other persons vs. gazing at

anything else in the room, but no specific aversion to direct eye contact either.

Although comparatively less research has examined eye gaze avoidance in children with FXS, lack of eye gaze does not appear to be motivated by a lack of understanding of the social situation or a desire to communicate, as is typically the case in autism. The majority of FXS children, although tending to avoid social interactions, will offer what is now classically termed the ‘*fragile X handshake*’, whereby an initial wish to communicate socially, with a ‘handshake’, a socially acceptable remark or even brief initial eye contact, is coupled with active and even persistent gaze avoidance. Subsequent interactions with familiar persons may be marked by the same active gaze avoidance despite the growing relationship. The gaze avoidance persists even when attempts are made to extinguish it; it may, in fact, increase in intensity. A famous photograph shows two brothers with FXS shaking hands, each with head averted to avoid eye contact [53].

Furthermore, in comparison to children with autism who struggle to maintain dyadic relationships, children with FXS tend to display relatively good social and communicative relationships, especially with parents. For example, Cohen and colleagues [54] have shown that FXS males compared to males with autism alone are sensitive to social gaze initiation by their parents but found eye contact aversive. In contrast, autistic males were insensitive to parent-initiated social gaze, and did not find eye contact aversive. However, both syndrome groups avoided eye contact with strangers. Intriguingly, age-related changes in responsive eye gaze appeared to be specific to autism alone and associated with greater communication ability. This was not the case for FXS males. Unfortunately, no studies to date have compared eye gaze behavior in children with a dual diagnosis of FXS+autism compared to children with FXS alone or autism alone; although one can speculate that a dual diagnosis will confer greater social impairment and interaction.

Thus, at first glance, although eye gaze avoidant behavior appears to unite FXS and autism, at a deeper level it serves very different purposes and are likely due to very different mechanisms underlying the disorders. In the case of FXS, hyperarousal, hypersensitivity and heightened levels of social anxiety are recognized as early prominent behavioral features and are present in affected children with and without autism, male and female [36,55-58]. Children with FXS may very quickly become overwhelmed by the demands created by social involvement, novel or unexpected situations and changes, even by the common transitions of daily life such as moving from one task to the next in a classroom environment. Generalized anxiety and/or panic disorder may occur [59], and in some rare cases even post-traumatic stress disorder [60]. In sum, although sociable and communicative, FXS children will tend to avert their eyes (so as to minimize social interactions or to avoid the sensory stimulation of eye contact) and avoid interactions. Thus, males and females with FXS will exhibit autistic-like eye gaze avoidance, but it is active rather than passive, and indeed in the presence of good understanding of social greeting behavior, symptomatic of their hyperarousal and social anxiety rather than an inherent lack of understanding of the social situation. In contrast, children with autism appear to have a more

generalized social deficit that impacts across all social situations and interactions.

Understanding the beliefs and intentions of others (theory of mind) in order to explain behavior has been extensively studied in autism and it is widely accepted that children with autism have a pervasive deficit in theory of mind ability [61, 62]. It is further speculated and that these deficits may underlie the social and communicative deficits that characterize the syndrome. In contrast, it is only recently that research has focused on identifying the extent of any such impairment in FXS [63, 64]. In their recent study, Cornish *et al.* reported that over 50% of children with FXS without autism were able to pass a ‘first-order’ false belief task (the ability to understand that others can hold false beliefs about the world and that their behaviour can be predicted on the basis of these false beliefs rather than on the bases of what is actually true) compared to only a reported third of children with autism [61, 65]. Furthermore, performance on a task that required the ability to understand one’s own mental states- in which one must distinguish between the perception of an object (its appearance) and actual knowledge of it (its real identity) showed a similar profile with FXS children relatively unimpaired compared to the percentage typically reported in autism [66]. A closer look at the error patterns also revealed quite distinct syndrome-specific ‘signatures’ that appear to reflect different cognitive mechanisms and strategies [63].

In summary, although both syndromes display theory of mind deficits, they clearly differ both quantitatively and qualitative in nature. Children with autism show a profound impairment that is not present in children with FXS who demonstrate impairment commensurate with cognitive delay, as seen in other developmental disorders that do not have a specific autism link such as children with Down syndrome.

In brief, the social/developmental contrasts between FXS and autism can be summarized as in Table 1.

Speech and Language. Delays in expressive language development, poor social use of language, and unusual speech patterns such as echolalia and dysfluences have been well established in children with autism [67-71] and in children with FXS [72-76]. However, comparatively few studies have compared language performance across both groups in the same study. Those that have report important differences in the language profiles that may help to differentiate FXS from autism.

Speech and conversational language. Studies by Sudhalter and colleagues [77-79] and others [28,80] have identified FXS specific weaknesses, most notably in affected males during conversational interactions and include tangential language, perseverative language, repetitive speech, and a tendency towards delayed echolalia. Tangential errors include off-topic questions, responses or comments that do not logically follow the preceding conversational thread; perseverative errors include the reintroduction of favorite topics over and over, even in the presence of conflicting conversational demands; and repetitive speech errors include repetition of sounds, words or phrases within an utterance or conversational turn. In all three categories, males with FXS produced significantly more errors than age matched children with autism (and children with other forms of mental retardation). This suggests that these forms of atypical language production are not the consequence of cognitive delay or of undiagnosed autism.

A possible explanation for the cause of these atypical language productions may lie in a greater increase in arousal levels in FXS males compared to autistic males. Studies have consistently demonstrated that FXS is associated with heightened anxiety which, once triggered, may take some considerable time to abate [35, 55-57, 81]. Indeed, we have argued elsewhere in this review that other aspects of the FXS signature, namely eye gaze avoidance is also likely to result from a specific anxiety deficit compared to autism that may reflect a more generalized social deficit. Thus it is very possible that the atypical language profile results from the

Table 1. Typical Social/Developmental Functioning in Fragile X Syndrome & Autism

Fragile X Syndrome	Autism
Social anxiety	Social indifference
Gaze aversion	Gaze indifference
Self-injury usually in form of hand biting in response to anxiety & excitement	Self injury variable in topography & causation
Delayed imitative & symbolic play	Permanently distorted imitative & symbolic play
Hand flapping in response to anxiety & excitement extremely common	Stereotypical & manneristic behaviours highly variable in topography & causation
Language impairments characteristically comprise delayed echolalia with repetitive, rapid & cluttered speech	Language impairments highly variable, usually affecting comprehension more than expressive language
Good understanding of facial expression	Lack of understanding of facial expression
Theory of mind may be distorted but is not absent	Absent theory of mind
Characteristically friendly & sociable, albeit often shy & socially anxious with primarily communicatory & stereotypic “autistic-like” disturbances	“Aloof”, “passive”, “active & odd” or “overpedantic & pseudomature” with primarily social & symbolic “autistic-like” disturbances

hyperarousal that social interactions cause in males and to a lesser extent females with FXS [82], resulting in speech that is rushed and consequently characterized by more perseveration and praxis errors [77]. This raises the possibility that reduction of anxiety would improve the speech of children with FXS; in fact, in clinical experience parents and teachers of children with FXS treated for Panic Disorder and Generalized Anxiety Disorder may report increase in spontaneous and accurate responsive speech.

Receptive language. Although few studies have explicitly focused on comparisons of expressive and receptive language performance across FXS and autism, three recent studies highlight the potential clinical significance in recognizing syndrome specific profiles across the sub-domains of language. Comparing performance in children with a dual diagnosis of FXS+autism and children with FXS alone and children with autism alone, Philofsky *et al.* [83] report a relative strength in receptive language compared to expressive language for children with FXS without autism. This pattern was not replicated in children with FXS+autism whose performance was much lower than children with FXS alone but similar to that of children with idiopathic autism. They speculate that low receptive language may be a marker for autism symptoms in young children with FXS. A similar receptive advantage compared to other language skills was also recently reported in an adolescent sample with FXS [72] suggesting that performance remains at a developmentally appropriate level across childhood into adolescence. In contrast, autism is strongly associated with significant receptive delays relative to other skills [84-86] suggestive of a specific 'signature' language deficit that may serve to differentiate, at a cognitive level, FXS from autism.

Adaptive behavior. Adaptive behaviors refer to goal directed behavior that is both functional and developmental and made in response to an environmental challenge. A growing body of literature has emerged to describe the nature of adaptive functioning in children with FXS compared to children with autism and those children with a dual diagnosis (FXS+autism). Although all three groups perform at a level much lower than typically developing children, recent research findings highlight important profiles of strengths and difficulties across the various domains of adaptive abilities that point to potential syndrome-specific signatures. Focusing first on overall adaptive functioning, there is a converging evidence to suggest that autistic status in children with FXS is associated with children with poorer adaptive behavior outcomes compared to children with FXS or autism alone [35,37, 42,87]. Furthermore, when adaptive functioning is teased into its component parts, children with FXS without autism appear to display a relative strength in daily living skills with weakest performance on social and motor skills [37, 88, 89]. In contrast, children with both FXS+autism display a similar developmental profile to children with autism [87] and tend to score highest on the motor domain and lowest on the communication and social domains [37]. Hatton and colleagues also provide some of the first evidence to date that suggests that differences in *rates of development* of adaptive functions may differentiate children with FXS+autism and children with FXS alone with the former diagnosis associated with slower rates of development.

Thus, the pattern of findings outlined above demonstrate an increasing understanding of how differences in the childhood end-states both across and within the domains of social, language and adaptive functioning may help to differentiate children with autism from children with FXS and from children with a dual diagnosis of FXS and autism. Recognizing these unique 'signature phenotypes' is a first step towards providing accurate diagnosis that will facilitate syndrome-specific treatments and interventions. However, surprisingly few studies have addressed the issue of whether levels of functioning change with increasing age, albeit progressing at a slower pace compared to typical developing children, or whether functioning levels actually decrease with increasing age, or even remain static across developmental time. Although published studies have consistently observed a decline in cognitive abilities from middle-late childhood onwards [90-93] in FXS, an increasing number of more recent studies have challenged this assumption. For example, both Abbeduto *et al.* [72] and Cornish and Wilding [94] found that in terms of language functioning, adolescents and young adults with FXS alone continued to increase in performance at the same rate as developmentally aged matched typical individuals. Hatton *et al.* [37] also found that children with FXS alone have faster rates of development on adaptive functions than children with a dual diagnosis of FXS+autism who demonstrate a much slower rate of development, but who nonetheless continue to develop with age. Therefore, it is possible that absolute level of performance is affected by the developmental disorder, be it FXS or autism, but the development is at a normal rate for their level of functioning. Future research using a prospective longitudinal design to chart developmental pathways from childhood into early adulthood will be needed to further define the rate of age-related changes in fragile X and autism both across and within cognitive and adaptive domains.

SUMMARY

In this review we sought to examine the extent to which behavioral overlaps in two syndromes for which there is some shared genetic variance- autism and FXS, imply common developmental pathways or 'signatures'. We have demonstrated that such a simplistic association cannot be validated given the converging evidence that significant differences, some more subtle than others, underlie these syndromes. Focusing explicitly on the domains of social, language and adaptive functioning we demonstrate quite distinct pathways between children with FXS alone and children with autism alone. In contrast, children with a dual diagnosis of FXS and autism display greater functional and cognitive impairments and a poorer prognosis than children with FXS alone. At the clinical level, early diagnosis is critical for a range of important reasons [95]. These include the right of the individual and family to know the cause and nature of the child's developmental, emotional and behavioral difficulties, relief from uncertainty, facilitation of grief resolution, focusing on the future, genetic counseling, access to information on likely strengths and needs, early instigation of appropriate interventions, and potential for linking with appropriate family and educational support networks. It is essential to be alert to the possibility of both FXS and autistic spectrum disorder in any child with developmental difficulties and, having diagnosed one, to

Table 2. Some Management Hints Relevant to Children with FXS More Than to Children with Autism

- Intellectual functioning is likely to be in the mild to moderate mental retardation range
- There is usually a clinically significant verbal-performance skill discrepancy with verbal skills exceeding non-verbal ones
- Social awareness and social understanding may be good
- However, rates and levels of social anxiety are usually high, and act as a trigger and drive for challenging behaviors
- Usually good understanding of facial expressions and emotions
- Gaze aversion rather than gaze indifference
- Often marked inattentiveness, restlessness, fidgetiness, distractibility and impulsive tendencies [96]

consider whether or not the other is also present. Greater knowledge of the signature behaviors especially of the differences between active and passive gaze avoidance, and aloofness vs. friendliness compromised by social anxiety can increase the index of suspicion, as well as being crucial in terms of how the child is to be managed subsequently.

To conclude, identifying impairments that distinguish children with differing developmental disorders from each other is a potentially powerful tool for early identification and treatment of syndrome specific strengths and difficulties, although the subtle differences between autism of unknown etiology and that associated with FXS may be as yet insufficient grounds for any course of action other than obtaining FXS DNA testing on all children who present with a pervasive developmental disorder, especially in light of the still unsettled question of secondary gene effects. In this review we emphasize the need for early identification of etiological diagnoses such as FXS, and clinical-phenomenological diagnoses such as autism, in order to institute effective, timely and individualized multi-modal intervention, support and ameliorative therapeutic care packages aimed at maximizing each individuals potential and minimizing their handicaps and challenges to family, educators, and community. Some management hints relevant to children with fragile X syndrome more than to children with autism are listed in Table 2.

REFERENCES

- [1] de Vries B B, Mohkamsing S, van den Ouweland AM, *et al.* Screening with the FMR1 protein test among mentally retarded males. *Hum Genet* 1998; 103: 520-522.
- [2] Kooy RF, Willesden R, Oostra BA. Fragile X Syndrome at the turn of the century. *Mol Med Today* 2000; 6: 193-8.
- [3] Turner G, Webb T, Wake S, Robinson H. Prevalence of fragile X syndrome. *Am J Med Genet* 1996; 64: 196-197.
- [4] Youings SA, Murray A, Dennis N, *et al.* FRAXA and FRAXE: the results of a five year survey. *J Med Genet* 2000; 37: 415-421.
- [5] Rousseau F, Rouillard P, Morel ML, Khandjian EW, Morgan K. Prevalence of carriers of premutation-size alleles of the FMR1 gene--and implications for the population genetics of the fragile X syndrome. *Am J Hum Genet* 1995; 57: 1006-1018.
- [6] Dombrowski C, Levesque S, Morel ML, Rouillard P, Morgan K, Rousseau F. Premutation and intermediate-size FMR1 alleles in 10572 males from the general population: loss of an AGG interruption is a late event in the generation of fragile X syndrome alleles. *Hum Mol Genet* 2002; 11: 371-378.
- [7] Aziz M, Stathopulu E, Callias M, *et al.* Clinical features of boys with fragile X premutations and intermediate alleles. *Am J Med Genet B Neuropsychiatr Genet* 2003; 121: 119-127.
- [8] Cornish K, Kogan C, Turk J, *et al.* The emerging fragile X premutation phenotype: evidence from the domain of social cognition. *Brain Cogn* 2005; 57: 53-60.
- [9] O'Donnell W T, Warren ST. A decade of molecular studies of fragile X syndrome. *Annu Rev Neurosci* 2002; 25: 315-338.
- [10] Bardoni B, Mandel JL, Fisch GS. FMR1 gene and fragile X syndrome. *Am J Med Genet* 2002; 97: 153-163.
- [11] Irwin SA, Patel B, Idupulapati M, *et al.* Abnormal dendritic spine characteristics in the temporal and visual cortices of patients with fragile-X syndrome: a quantitative examination. *Am J Med Genet* 2001; 98: 161-167.
- [12] Jin P, Warren ST. New insights into fragile X syndrome: from molecules to neurobehaviors. *Trends Biochem Sci* 2003; 28: 152-158.
- [13] Lachiewicz AM, Dawson DV, Spiridigliozzi GA. Physical characteristics of young boys with fragile X syndrome: reasons for difficulties in making a diagnosis in young males. *Am J Med Genet* 2002; 92: 229-236.
- [14] Turk J, Patton M. Sensory impairment & head circumference in fragile X syndrome, Down syndrome and idiopathic intellectual disability. *J Intellect Dev Disabil* 2000; 25: 59-68.
- [15] Volkmar FR, Lord, Bailey A, Schultz RT, Klin A. Autism and pervasive developmental disorders. *J Child Psychol Psychiatry* 2004; 45: 135-170.
- [16] Rutter M. Incidence of autism spectrum disorders: changes over time and their meaning. *Acta Paediatr Scand* 2005; 94: 2-15.
- [17] Szatmari P. The classification of autism, Asperger's syndrome, and pervasive developmental disorder. *Can J Psychiatry* 2000; 45: 731-738.
- [18] Rutter M. Genetic studies of autism: from the 1970s into the millennium. *J Abnorm Child Psychol* 2000; 28: 3-14.
- [19] Manning-Courtney P, Brown J, Molloy CA, *et al.* Diagnosis and treatment of autism spectrum disorders. *Curr Probl Pediatr Adolesc Health Care* 2003; 33: 283-304.
- [20] Bailey A, Phillips W, Rutter M. Autism: towards an integration of clinical, genetic, neuropsychological, and neurobiological perspectives. *J Child Psychol Psychiatr* 1996; 37: 89-126.
- [21] Piven J, Palmer P. Cognitive deficits in parents from multiple-incidence autism families. *J Child Psychol Psychiatr* 1997; 38: 1011-1021.
- [22] Piven J, Palmer P, Landa R, Santangelo S, Jacobi D, Childress D. Personality and language characteristics in parents from multiple-incidence autism families. *Am J Med Genet (Neuropsychiatric Genetics)* 1997; 74: 398-411.
- [23] Jorde LB, Mason-Brothers A, Waldmann R, *et al.* The UCLA-University of Utah epidemiological survey of autism: genealogical analysis of familial aggregation. *Am J Med Genet* 1990; 36: 85-88.
- [24] Cornish K, Sudhalter V, Turk J. Attention and language in fragile X. *Ment Retard Dev Disabil Res Rev* 2004; 10: 11-16.
- [25] Demark JL, Feldman MA, Holden JJ. Behavioral relationship between autism and fragile x syndrome. *Am J Ment Retard* 2003; 108: 314-326.
- [26] Lachiewicz AM. Abnormal behaviors of young girls with fragile X syndrome. *Am J Med Genet* 1992; 43: 72-77.
- [27] Reiss AL, Freund L. Fragile X syndrome, DSM-III-R, and autism. *J Am Acad Child Adolesc Psychiatry* 1990; 29: 885-891.
- [28] Turk J, Graham P. Fragile X Syndrome, Autism and Autistic Features. *Autism* 1997; 1: 175-197.
- [29] Lord C, Risi S, Lambrecht L, *et al.* The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord* 2000; 30: 205-223.
- [30] Lord C, Rutter M, Le Couteur A. Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 1994; 24: 659-685.

- [31] Hagerman RJ. Lessons from fragile X regarding neurobiology, autism, and neurodegeneration. *J Dev Behav Pediatr* 2006; 27: 63-74.
- [32] Rogers S J, Wehner DE, Hagerman R. The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *J Dev Behav Pediatr* 2001; 22: 409-417.
- [33] Bailey DB, Hatton DD, Skinner M, Mesibov GB. Autistic behavior, FMR1 protein, and developmental trajectories in young males with fragile X syndrome. *J Autism Dev Disord* 2001; 31: 165-174.
- [34] Bailey DBJ, Mesibov GB, Hatton DD, Clark RD, Roberts JE, Mayhew L. Autistic behavior in young boys with fragile X syndrome. *J Autism Dev Disorder* 1998; 28: 499-508.
- [35] Cohen IL. Behavioral profiles of autistic and nonautistic fragile X males. *Dev Brain Dysfunct* 1995; 8: 252-269.
- [36] Hagerman R J, Jackson AW, Levitas A, Rimland B, Braden M. An analysis of autism in fifty males with the fragile X syndrome. *Am J Med Genet* 1986; 23: 359-374.
- [37] Hatton DD, Wheeler AC, Skinner ML, *et al.* Adaptive behavior in children with fragile X syndrome. *Am J Ment Retard* 2003; 108: 373-390.
- [38] Philofsky A, Hepburn SL, Hayes A, Hagerman R, Rogers SJ. Linguistic and cognitive functioning and autism symptoms in young children with fragile X syndrome. *Am J Ment Retard* 2004; 109: 208-218.
- [39] Turk J, Graham PJ, Verhulst F. *Child & Adolescent Psychiatry: A Developmental Approach* (4th edition). Oxford: Oxford University Press. 2006.
- [40] Wing L. *The Autistic Spectrum*. Constable & Robinson: London. 2003.
- [41] Lord C, Bailey A. Autism spectrum disorders. In *Child & Adolescent Psychiatry*, ed. M. Rutter & E. Taylor, Blackwell Scientific: Oxford. 2002; 636-653.
- [42] Kau A S, Tierney E, Bukelis I, *et al.* Social behavior profile in young males with fragile X syndrome: characteristics and specificity. *Am J Med Genet A* 2004; 126: 9-17.
- [43] Kaufmann WE, Cortell R, Kau AS, *et al.* Autism spectrum disorder in fragile X syndrome: communication, social interaction & specific behaviors. *Am J Med Genet* 2004; 129: 225-234.
- [44] Reiss A L, Freund L. Behavioral phenotype of fragile X syndrome: DSM-III-R autistic behavior in male children. *Am J Med Genet* 1992; 43: 35-46.
- [45] Klin A, Jones W, Schultz R, Volkmar FR, Cohen D J. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Arch Gen Psychiatry* 2002; 59: 809-816.
- [46] Senju A, Yaguchi K, Tojo Y, Hasegawa T. Eye contact does not facilitate detection in children with autism. *Cognition* 2003; 89: B43-B51.
- [47] Garrett AS, Menon V, MacKenzie K, Reiss AL. Here's looking at you, kid: neural systems underlying face and gaze processing in fragile X syndrome. *Arch Gen Psychiatry* 2004; 61: 281-288.
- [48] Kerby DS, Dawson BL. Autistic features, personality, and adaptive behavior in males with the fragile X syndrome and no autism. *Am J Ment Retard* 1994; 98: 455-462.
- [49] von Grunau M, Anston C. The detection of gaze direction: a stare-in-the-crowd effect. *Perception* 1995; 24: 1297-313.
- [50] Batki A, Baron-Cohen S, Wheelwright S, Connellan J, Ahluwalia J. Is there an innate gaze module? Evidence from human neonates. *Infant Behav Dev* 2000; 23: 223-9.
- [51] Farroni T, Csibra G, Simion F, Johnson MH. Eye contact detection in humans from birth. *Proc Natl Acad Sci USA* 2002; 99: 9602-5.
- [52] Senju A, Tojo Y, Dairoku H, Hasegawa T. Reflexive orienting in response to eye gaze and an arrow in children with and without autism. *J Child Psychol Psychiatr* 2004; 45: 445-58.
- [53] Wolff P H, Gardner J, Paccla J, Lappen J. The greeting behavior of fragile X males. *Am J Ment Retard* 1989; 93: 406-411.
- [54] Cohen IL, Vietze PM, Sudhalter V, Jenkins EC, Brown WT. Parent-child dyadic gaze patterns in fragile X males and in non-fragile X males with autistic disorder. *J Child Psychol Psychiatr* 1989; 30: 845-856.
- [55] Belser RC, Sudhalter V. Arousal difficulties in males with fragile X syndrome: A preliminary report. *Dev Brain Dysfunct* 1995; 8: 252-269.
- [56] Miller LJ, McIntosh DN, McGrath J, *et al.* Electrodermal responses to sensory stimuli in individuals with fragile X syndrome: a preliminary report. *Am J Med Genet* 1999; 83: 268-279.
- [57] Roberts JE, Boccia ML, Bailey DB Jr, Hatton DD, Skinner M. Cardiovascular indices of physiological arousal in boys with fragile X syndrome. *Dev Psychobiol* 2001; 38: 107-123.
- [58] Symons FJ, Clark RD, Hatton DD, Skinner M, Bailey DB Jr. Self-injurious behavior in young boys with fragile X syndrome. *Am J Med Genet A* 2003; 118: 115-121.
- [59] Hagerman RJ, Fulton MJ, Leaman A, Riddle J, Hagerman K, Sobesky W. A survey of fluoxetine therapy in fragile X syndrome. *Dev Brain Dysfunct* 1994; 7: 155-164.
- [60] Turk J, Robbins I, Woodhead M. Post-traumatic stress disorder in young people with intellectual disability. *Journal of Intellectual Disability Research* 2005; 49 Part II: 872-875.
- [61] Baron-Cohen S. Theory of mind and autism: a 15-year review. In S. Baron-Cohen, D. Cohen, & H. Tager-Flusberg (Eds.), *Understanding other minds: perspectives from autism and developmental cognitive neuroscience* (2nd Ed), Oxford: Oxford University Press. 1999; 3-20.
- [62] Baron-Cohen S, Leslie AM, Frith U. Does the autistic child have a "theory of mind?" *Cognition* 1985; 21: 37-46.
- [63] Cornish K, Burack JA, Rahman A, Munir F, Russo N, Grant C. Theory of mind deficits in children with fragile X syndrome. *J Intellect Disabil Res* 2005; 49(Pt 5): 372-378.
- [64] Garner C, Callias M, Turk J. Executive function and theory of mind performance of boys with fragile-X syndrome. *J Intellect Disabil Res* 1999; 43(Pt 6): 466-474.
- [65] Yirmiya N, Solomonica-Levi D, Shulman C. The ability to manipulate behaviour and to understand manipulation of beliefs: A comparison of individuals with autism mental retardation, and normal development. *Dev Psychol* 1996; 32: 62-69.
- [66] Baron-Cohen S. Are autistic children behaviourists? An examination of their mental-physical and appearance-reality distinctions. *J Autism Dev Disord* 1989; 19: 579-600.
- [67] McCleery JP, Tully L, Slevc LR, Schreiber L. Consonant production patterns of young severely language-delayed children with autism. *J Commun Disorder* 2006; 39: 217-231.
- [68] Pry R, Petersen A, Baghdadli A. The relationship between expressive language level and psychological development in children with autism 5 years of age. *Autism* 2005; 9: 179-189.
- [69] Ghaziuddin M, Gerstein L. Pedantic speaking style differentiates Asperger syndrome from high-functioning autism. *J Autism Dev Disord* 1996; 26: 585-595.
- [70] Rapin I, Dunn M. Language disorders in children with autism. *Semin Pediatr Neurol* 1997; 4: 86-92.
- [71] Zwaigenbaum L, Bryson S, Rogers T, Roberts W, Brian J, Szatmari P. Behavioral manifestations of autism in the first year of life. *Int J Dev Neurosci* 2004; 23: 143-152.
- [72] Abbeduto L, Murphy MM, Cawthon SW, *et al.* Receptive language skills of adolescents and young adults with down or fragile X syndrome. *Am J Ment Retard* 2003; 108: 149-160.
- [73] Roberts JE, Mirrett P, Burchinal M. Receptive and expressive communication development of young males with fragile X syndrome. *Am J Ment Retard* 2001; 106: 216-230.
- [74] Sudhalter V, Scarborough HS, Cohen IL. Syntactic delay and pragmatic deviance in the language of fragile X males. *Am J Med Genet* 1991; 38: 493-497.
- [75] Sudhalter V, Belser RC. Atypical language production in males with fragile X syndrome. In: *Educating children with fragile X syndrome* (ed: Dew-Hughes, D.) Routledge Taylor: London, New York. 2004; pp. 25-31.
- [76] Taylor, C. Speech & language therapy. In: *Educating children with fragile X syndrome* (ed: Dew-Hughes, D.) Routledge Taylor: London, New York. 2004; 106-114.
- [77] Belser RC, Sudhalter V. Conversational characteristics of children with fragile X syndrome: repetitive speech. *Am J Ment Retard* 2001; 106: 28-38.
- [78] Sudhalter V, Belser RC. Conversational characteristics of children with fragile X syndrome: tangential language. *Am J Ment Retard* 2001; 106: 389-400.
- [79] Sudhalter V, Cohen IL, Silverman W, Wolf-Schein EG. Conversational analyses of males with fragile X, Down syndrome, and autism: comparison of the emergence of deviant language. *Am J Ment Retard* 1990; 94: 431-44.

- [80] Ferrier LJ, Bashir AS, Meryash DL, Johnston J, Wolff P. Conversational skills of individuals with fragile-X syndrome: a comparison with autism and Down syndrome. *Dev Med Child Neurol* 1991; 33: 776-788.
- [81] Keysor C S, Mazzocco MM, McLeod DR, Hoehn-Saric R. Physiological arousal in females with fragile X or Turner syndrome. *Dev Psychobiol* 2002; 41: 133-146.
- [82] Lesniak-Karpiak K, Mazzocco MM, Ross JL. Behavioral assessment of social anxiety in females with Turner or fragile X syndrome. *J Autism Dev Disorder* 2003; 33: 55-67.
- [83] Philofsky A, Hepburn SL, Hayes A, Hagerman R, Rogers SJ. Linguistic and cognitive functioning and autism symptoms in young children with fragile X syndrome. *Am J Ment Retard* 2004; 109: 208-218.
- [84] Jarrold C, Boucher J, Russell J. Language profiles in children with autism. *Autism* 1997; 1: 57-76.
- [85] Rapin I. *Preschool Children with Inadequate Communication*. London; McKeth Press 1996.
- [86] Tager-Flusberg H, Sullivan K. Early language development in children with mental retardation. In J.A. Burack., R.M. Hidapp., Zigler, E. (Eds) *Handbook of Mental Retardation and Development*. New York; Cambridge University 1998.
- [87] Rogers SJ, Wehner DE, Hagerman R. The behavioral phenotype in fragile X: symptoms of autism in very young children with fragile X syndrome, idiopathic autism, and other developmental disorders. *J Dev Behav Pediatr* 2001; 22: 409-17.
- [88] Dykens EM, Hodapp RM, Ort SI, Leckman JF. Trajectory of adaptive behavior in males with fragile X syndrome. *J Autism Dev Disord* 1993; 23(1): 135-145.
- [89] Dykens E, Ort S, Cohen I, *et al.* Trajectories and profiles of adaptive behavior in males with fragile X syndrome: multicenter studies. *J Autism Dev Disorder* 1996; 26: 287-301.
- [90] Fisch G S, Simensen RJ, Schroer RJ. Longitudinal changes in cognitive and adaptive behavior scores in children and adolescents with the fragile X mutation or autism. *J Autism Dev Disorder* 2002; 32: 107-114.
- [91] Fisch G S, Carpenter NJ, Holden JJ, *et al.* Longitudinal assessment of adaptive and maladaptive behaviors in fragile X males: growth, development, and profiles. *Am J Med Genet* 1999; 83: 257-263.
- [92] Fisch G S, Carpenter N, Holden JJ, *et al.* Longitudinal changes in cognitive and adaptive behavior in fragile X females: a prospective multicenter analysis. *Am J Med Genet* 1999; 83: 308-312.
- [93] Fisch G S, Shapiro LR, Simensen R, *et al.* Longitudinal changes in IQ among fragile X males: clinical evidence of more than one mutation? *Am J Med Genet* 1992; 43: 28-34.
- [94] Cornish K M, Wilding J. Does cognitive performance increase or decrease across development in fragile X syndrome: Impact of verbal mental age and gender. In J. Malard (Ed.), *Advances in fragile X Research*. New York: Nova Publishing. In press.
- [95] Turk J. The importance of diagnosis. In: *Educating children with fragile X syndrome* (ed: Dew-Hughes, D.) Routledge Taylor: London, New York 2004; pp. 15-19.
- [96] Turk J. Fragile X syndrome and attentional deficits. *J Applied Research Intellect Disabil* 1998; 11: 175-191.