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Autism and Genetic Syndromes

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1. Introduction

Autism is a developmental disorder defined as a severe and persistent restriction in communicative skills, including lack of social and emotional reciprocity, as well as stereotyped and repetitive behaviours. Such an impairment of social interaction was already described in 1919 by the Swiss psychiatrist Eugen Bleuler within the framework of the negative symptom complex of schizophrenia. In the following decades in particularly the German language areas of Switzerland, autism was viewed by Kretschmer (1921) as a schizoid temperament whereas later, he viewed it as a special form of schizophrenia. In the late fifties, Leonhard (1957) assigned this specific disturbance in communication to the so called systematic schizophrenias. In 1943, the immigrated American child psychiatrist from Austria, Leo Kanner, originally described early infantile autism as Autistic Disturbance of Affective Contact. In a study of 11 children, four behavioural characteristics were distinguished: severe social withdrawal behavior, obsessive desire for repetitiveness, persistent fascination with specific objects or thoughts, and severe language impairments. One year later, the Austrian pediatrician Hans Asperger reported comparable findings under the title 'Die 'Autistischen Psychopathen' in Kindesalter'. Both Kanner (1943, 1971) and Asperger (1944) considered autism a communication disorder for children with severely impoverished relations with the environment (i.e., 'autistic aloneness').

Up until the beginning of the 1960s, under the influence of the then prevalent psychodynamic theories, autism was largely attributed to family and environmental factors. Rutter (1968) placed autism in a different perspective and demarcated the phenotypical presentation of both early infantile autism and schizophrenia from their biological underpinnings. Lorna Wing (1981) can be credited for bringing the descriptions of Asperger from 1944 back to our attention in the 1980s and, on the basis of extensive childhood epidemiological research, for placing autism in a broader diagnostic context and developing diagnostic criteria (Wing & Gould, 1979). Wing introduced the term 'autism spectrum disorder', which can be described on the basis of information from three domains: (a) social reciprocity, (b) verbal and non-verbal communication and imagination, and (c) a restricted, stereotyped pattern of interests and activities. These elements still constitute the diagnostic criteria from e.g. the DSM-IV category of Pervasive Developmental Disorders that include Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified (overview: Kumbier et al. 2010).

In her retrospective 'Reflections on opening Pandora's box' presented a few years back, Lorna Wing (2005) warns about stretching the boundaries of the autistic spectrum, which presently includes those who have normal to extremely high intelligence at the one end and those with a severe intellectual disability and limited social and communicative skills at the other end. In such a manner, the diagnostic label of 'autistic spectrum disorder' can possibly be misused to attain care (Volkmar et al., 2009). This is certainly not inconceivable in light of the quadrupled prevalence of pervasive developmental disorders across a period of 40 years (4.1 per 10,000 to 16.8 per 10,000), including somatic/neurological disorders that accompany autism (Fombonne, 2003; Rice, 2009). Moreover, autism and Asperger's disorder are regularly associated with other syndromes (Gillberg & Gillburg, 1989; Gillberg and Billstedt, 2000). As elegantly stated by Gillberg already in 1991 in his Emanuel Miller Memorial Lecture, researchers and clinicians, rather than allow themselves to be guided by stereotypic (sub)classifications, should be guided by a more balanced view of autism as belonging to a group of empathy disorders and thereby start the search for autism-relevant endophenotypes (Gillberg, 1992).

In the following sections, a brief overview of the current neuropsychological and genetic explanatory models will first be given. Thereafter, a selection of syndromes with a known genetic etiology that are seen to accompany autism will be discussed. To conclude, the manner in which modern genetics can be utilized in daily diagnostic practice will be elucidated.

2. Neuropsychological models

Roughly three explanatory models can be discerned for the pattern of disorders encountered in cases of autism. The *first* model is based upon the *weak central coherence* (WCC) hypothesis, which claims that patients with autism are inclined to attend to details as opposed to the whole during the processing of context-based information (i.e., strictly feature-based perception). As a consequence, the information is not understood as a meaningful whole and thus remains fragmented and confusing (Happé & Frith, 2006; Frith, 1989).

The *second* model draws upon the concept of *Theory of Mind*, which refers to the capacity to attribute thoughts, desires, and intentions to others. This capacity starts to develop around the age of three to four years and allows humans to take the perspectives of others into consideration in their own thinking. Deficiencies in this domain can easily lead to social misinterpretations and socially inadequate behavior, which form the basis of the severe communication problems that people with autism show (Baron-Cohen, 1989). In this connection, the more general notion of social cognition may be called upon and a link made to, for example, diminished activity of the amygdala and deviant perceptions of one's own emotions (Kethrapal, 2008).

In the *last* model, that of the *dysexecutive functioning* hypothesis, disturbed executive functions are assumed to play an important role. The executive functions (EF) are of major importance for the integration, steering, and control of processes required to execute purposeful behavior in new or complex situations. At a structural level, four frontal-subcortical circuits are involved in EF. The dorsolateral-prefrontal circuit has been related to executive cognitive dysfunctioning; the ventromedial circuit has been related to activation and motivation problems; and the medial- and lateral-orbitofrontal circuits have been related to disturbed affect regulation and disturbed social behavior, respectively (Chow &

Cummings, 2007; Alvarez & Emory, 2006). EF often involves the overruling of automatic responses in favour of more intentional behaviour. A capacity to flexibly switch between different behavioral repertoires (i.e., *monitoring* and *shifting*) is required for such overruling and typically found to be a problem in cases of autism. Barnes-Holmes and colleagues view EF as rule-governed behaviour and thus behaviour that stands in contrast to contingency-shaped behaviour, which has been automatized. EF thus defined, is verbal behaviour that precedes other behaviour (i.e., *verbal antecedent behavior*) and therefore distracts the individual from his usual, automatic reaction pattern. Stated differently, the probability of an alternative behavior is changed in the direction of a particular objective. In such a manner, thus, recent research on rule-governed behaviour connects EF with autism and an underlying Theory of Mind (Barnes-Holmes et al., 2004; McHugh et al, 2004).

3. Genetic models

Autism can be viewed as a classic example of a disorder with a strong genetic basis. A distinction must nevertheless be made between the Autistic disorder as originally described by Kanner and the autism spectrum disorder, which can be viewed as a component of an array of clinical pictures and syndromes that are sometimes referred to as secondary or syndromic autism (Benvenuto et al., 2009). Given the complex interplay between genes and autism, a search for at least two types of genetic factors is of importance, namely: (rare) chromosomal abnormalities or gene alterations that can be directly related to core (i.e., classic) autism and genetic copy number variants that correlate with a vulnerability to develop an autistic disorder.

In several studies from the 1980s and 1990s that use a strict definition of autism, a 69% to 95% concordance has been demonstrated in monozygotic twins, while the chance in dizygotic twins is only 0% to 24%. The contribution of the hereditary components is estimated to be 90%. The male-female ratio is between 3-4 to 1 (Brkanac et al., 2008). In order to advance the understanding of the genetic heterogeneity of autistic disorders, various techniques can be used such as (molecular) cytogenetic research, linkage studies, and association studies.

Linkage studies search for those parts of a chromosome that are found to be the same for all affected individuals in a family but different for the non-affected family members. A gene that contributes to the occurrence of a vulnerability for autism may lie in such a shared region. These studies have revealed a wide variety of loci, from which a considerable genetic heterogeneity can be concluded as well as the absence of single, specific locations for autism (Szatmari et al., 2007). Recently, in a very large-scale linkage study, two new locations have been found on chromosomes 6 and 20 (6q27 and 20p13, respectively) for which the functional significance has yet to be clarified (Weiss et al., 2009).

The same holds for candidate genes that have been implicated in a large series of association studies. These studies investigate significant genetic differences between large groups of patients, on the one hand, and groups of healthy individuals, on the other hand (Vorstman et al., 2006a). The research findings make it clear, however, that the pathophysiology of autism involves genes that code for proteins from the family of neurexins and neuroligins that play, in turn, a role in the development and functioning of synaptic and in particular glutamatergic and GABA-ergic networks (Lisé & El-Husseini, 2006; Buchsbaum, 2009). The first X-linked mutations in genes involved in the coding of neuroligin were revealed in patients with autism in two Swedish families in 2003 (Jamin et al., 2003).

When the classic microscopic cytogenetic route is followed, structural chromosomal aberrations are found in 3% to 7% of patients with autism and developmental delay. This finding concerns mainly maternal duplications on the long arm of chromosome 15 (q11-13) (Hogart et al., 2010) and deletions on the long arm of chromosome 2 (q37) (Falk & Casas, 2007), chromosome 7 (q22 and q31) (Alarcón et al., 2002) and chromosome 22 (q11) (Niklasson et al., 2009) and (q13) (overview: Kumar & Christian, 2009). The fluorescence-in-situ-hybridization (FISH) technique is used to search for specific submicroscopic deletions and is used primarily to confirm a clinical diagnosis such as the 22q11 deletion syndrome. Disadvantages of this technique are its labor intensiveness and that only one or a few chromosome regions can be examined per experiment.

More commonly used these days is the whole-genome microarray technique. Here, details more than a hundred times smaller can be perceived when compared to microscopic cytogenetic examination (de Vries et al., 2005; Veltman & de Vries, 2006). With the aid of such a 'DNA chip', the complete genome with a high resolution can be examined for the presence of microdeletions and duplications or so-called copy-number variations (CNVs). Of principal concern here are small quantitative, structural variations that are paired with a loss or gain of chromosome material. Furthermore, the 'targeted genomic array' technique can be applied to study specific regions such as the subtelomeric chromosome regions or well-known microdeletion syndrome regions (Lintas & Persico, 2009).

For various neuropsychiatric disorders including autism, CNVs possibly involved in the vulnerability for the development of a disorder within the autism spectrum have been demonstrated using the array technique (Jacquemont et al., 2006; Cook & Scherer, 2008). For some of these CNVs, a clear correlation has been demonstrated, e.g., a maternal 15q11-q13 duplication was shown for 1-3% of patients with an autistic spectrum disorder. Another frequently occurring CNV is found on the chromosome 16p11.2 which present with a deletion or duplication in approximately 1% of the patients (Weiss et al., 2008; Fernandez et al., 2010).

There are, however, also CNVs found with an, as yet, unknown significance; because, for example, the same change can be traced back to a healthy parent. A precise interpretation of the array results with the aid of bio-informatics, literature databases, data from the pedigree and clinical investigation of affected individuals, is therefore essential.

Another interesting perspective is the neuropeptide concept. It has been known for quite some time that the nonapeptide oxytocin (OXT) is involved in affiliation behaviour and social cognition via an improvement of social memory, including the recall and understanding of affective events (Hollander et al., 2007; Insel, 2010; Green & Hollander, 2010). For these reasons, research has been performed on the association between single nucleotide polymorphisms (SNPs) in the OXT gene and the OXT receptor gene (OXTr). Relative to the normal population, more SNPs were present in the OXTr for a subgroup of patients with autism, which could indicate a genetically determined vulnerability for the development of autism (Lerer et al., 2008; Lee et al., 2009). In line with these observations, Gregory et al. (2009) found that epigenetic regulation of OXTr is implicated in the development of autism.

To summarize, in linkage and association studies among patients with autistic disorders up until now, a large number of candidate genes and gene locations have been found for which it can be assumed that they may be involved in the development of functional processes of the central nervous system. In Table 1, a selective overview is presented. In the following section, the most well-known genetic disorders associated with autism will be discussed.

<i>Chromosome</i>	<i>Candidate Gene</i>	<i>Network/Function</i>
2p16.3	NRXN1	Synapse formation
2q12.3-q14.2	DPP10	Neurotransmission
3p24-26	OXTr	Neurotransmission
3p26-p25	CNTN4	Synapse formation
4p14-q21.1	GABRG/GABRA	GABA neurotransmission
7q31.1	ST7	Tumor suppression
7q35-q36	CNTNAP2	Synapse formation
8p23	DLGAP2	NMDA neurotransmission
15q11-q14	GABRA/GABRB/GABRG	GABA neurotransmission
15q13	APBA2	Neurotransmission
16p11.2	DOC2A	Neurotransmission
22q11	PRODH	Neuromodulation
22q13	SHANK3	Synapse formation
Xp22.3	NLGN4	Synapse formation
Xp11.4	TSPAN7	Neuronal growth and development
Xp22.1-p21.3	IL1RAPL1	Interleukin receptor

Table 1. Selection of genes and functions possibly involved in autism (adapted from Guilmatre et al., 2009 and El-Fishawy & State, 2010)

4. Genetic syndromes and autism

4.1 Fragile X syndrome

The fragile X syndrome (FXS; Figure 1) is the most well-known genetic disorder related to autism. Brown and colleagues (1982) were the first to report on this. Initially, FXS was described by Lubs (1969), who detected a fragile site at the end of the long arm of the X chromosome by using classical microscopic cytogenetic techniques. FXS is caused by hypermethylation of an expanded trinucleotide repeat (CGG) in the ‘fragile X mental retardation 1 (FMR1) gene’ (Xq27.3). In normal individuals, the number of CGG repeats is 5 to 45 which is stably transmitted to the next generation. In case of a FMR1 premutation, there is a small expansion of 55 to 200 repeats. In FXS, the number of repeats exceeds 200. As a result of this enlarged number of repeats, hypermethylation of the FMR1 gene occurs which leads, in turn, to a shortage or complete loss of the FMR1 protein that is essential for dendrite formation, synapse formation, and experiential learning (Marco & Skuse, 2006; Hernandez et al., 2009).

FXS is an X-linked disorder with an incidence of about 1 in 4000 newborn males. Affected males show a variable degree of developmental delay, behaviour problems, and distinctive dysmorphic features such as a long face and large, prominent ears. Female carriers with a full mutation (>200 repeats) may present with or without impaired level of intelligence. Females with FXS and normal intelligence, however, have an increased risk of mood and anxiety disorders and a schizotypal personality disorder (Franke et al., 1998).

In males with a premutation (50-200 repeats), there is an increased probability of the development of the so-called fragile-X-associated tremor/ataxia syndrome (FXTAS). Its

symptoms emerge at a later age, and the syndrome has a progressive course. The clinical picture comprises intention tremor, frequent falling, Parkinsonian symptoms, and disturbed cognitive and executive functioning (Verhoeven et al., 2008; Bourgeois et al., 2009).

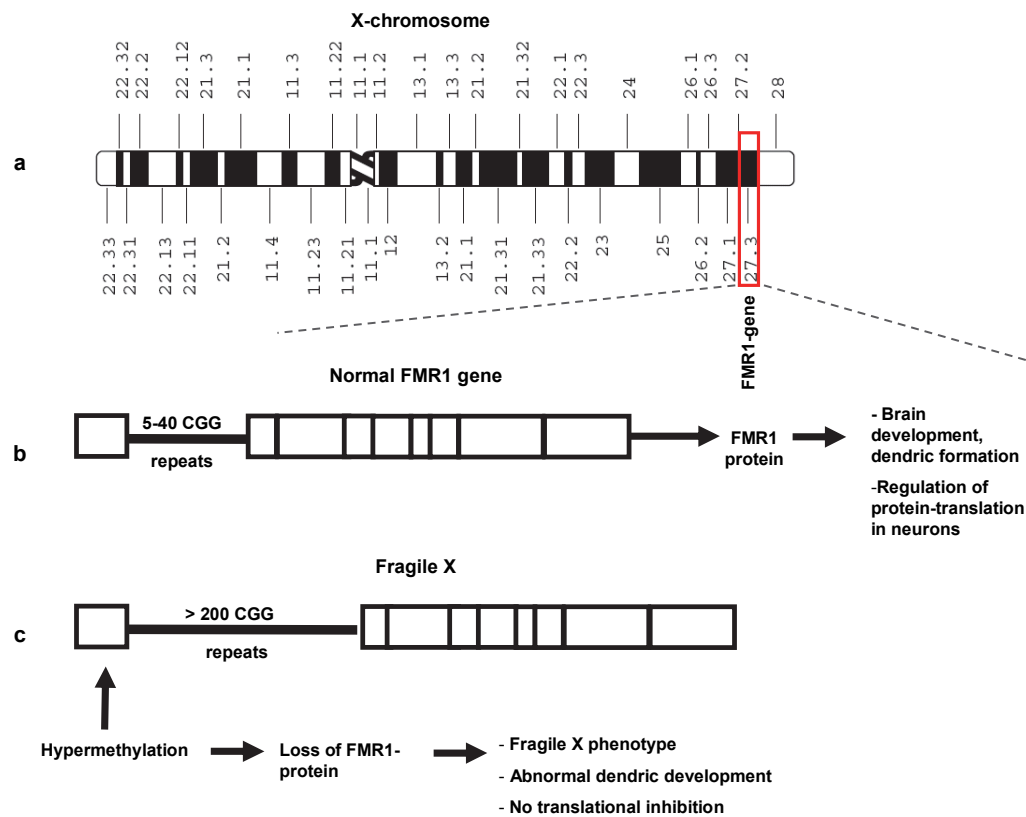


Fig. 1. Fragile X syndrome and the FMR1 gene
Schematic representation of the location of the FMR1 gene on the long arm of the X chromosome. (a) The FMR1 gene comprises a polymorph repetition of the base pairs cytosine-guanine-guanine (CGG) at the start of the gene. In healthy individuals, this number of CGG repeats varies from 5 to about 45 units. (b) Affected individuals have more than 200 CGG repeats: the full mutation. (c) The expansion to a full mutation (>200 repeats is usually associated with hypermethylation of the CGG repetition and the adjacent area, which leads to a transcription stop resulting in the absence of the FMR1 protein. This results in intellectual disability and other symptoms of the Fragile X syndrome among men, and in >50% of the women who are carriers of a full mutation. Carriers with 55 and 200 repeats are asymptomatic and are thus called premutation carriers

For decades, it has been known that the severity of intellectual disability and the intensity of related behaviour problems is proportional to the number of repeats. The psychopathological phenotype of FXS includes, in addition to the developmental delay, multiform anxiety symptoms, obsessive-compulsive characteristics, hyperactivity / impulsivity, and aggression. Epileptic phenomena are frequent. Predominant, however, are autism-related symptoms such as social anxiety and withdrawal behaviour, stereotypies like flapping or biting of the hands, perseverations, extreme sensitivity to environmental stimuli, and, in general, decreased social reciprocity with an avoidance of eye contact (Hagerman, 2005).

Using neuroimaging techniques, various structural abnormalities of the central nervous system can be demonstrated, in particular enlargement of hippocampus, amygdala, caudatus, and thalamus with a reduction of the cerebellar vermis (Hessl et al., 2004). These neuronal changes are caused by an overabundance of immature dendritic spines. In normal conditions, dendritic spines are essential for the formation of new neuronal connections that, in turn, form the basis for learning and memory. In FXS, the cognitive dysfunctions in the domains of attention, (working) memory, mathematical skills, executive functioning and social cognition largely correspond to the observed abnormalities of the central nervous system.

The treatment of patients with FXS is primarily symptomatic and aimed at the reduction of the most prominent behavioural problems or psychiatric symptoms, such as anxiety, hyperactivity, impulsivity and distractibility (Garber et al., 2008). Since the extremely heightened sensitivity to environmental stimuli is assumed to underlie the above mentioned symptoms, it is essential to reduce excessive environmental sensory activation. This can be achieved with a more structured daily program of activities, the promotion of a realistic pattern of expectations among parents/caregivers, individualized instruction and, most importantly, the dissemination of knowledge about the persistence of the FXS behavioral phenotype.

4.2 Rett syndrome

Rett syndrome (RS) was first described in 1966 by Andreas Rett. This syndrome is inherited in an X-linked manner, caused by a mutation in the Methyl-CpG-Binding Protein 2 (MECP2) gene (Xq28). In Figure 2, the location of the MECP2 gene is depicted. RS occurs almost exclusively in girls and its prevalence is estimated to be between 1/10,000 - 1/20,000. In boys, the disorder is nearly always lethal. In rare male cases, an extra X chromosome or mosaicism of the MECP2 mutation has been found.

RS is characterized by an apparently normal development in the first 6 to 18 months of life after which development stagnates, acquired skills get lost and development finally stops. This stagnation of development also becomes manifest in a retarded and disproportionate growth in head circumference, decrease of eye contact, and both cognitive and motor deterioration. Already in the first year of life, autistic behavioural elements are present such as social withdrawal, declining speech and communication, limited eye contact, grinding of the teeth, and characteristic hand stereotypies (Ben Zeev, 2007; Gonzales & LaSalle, 2010). In the majority of the patients, the syndrome is associated with severe epilepsy. The first decade is dominated by severe neurological dysfunctions and an irregular respiration pattern as a result of an immaturely developed brainstem. In addition, a prolonged QT interval is often present with, as a consequence, risk for sudden cardiac arrhythmia. From the age of 10, a developmental plateau occurs and the patient becomes severely neurologically handicapped with profound intellectual disability.

In 80% to 90% of the patients with RS, a mutation that almost always occurs *de novo*, can be demonstrated in the MECP2 gene. This gene is expressed particularly in neurons and to a lesser extent in glial cells, and involved in neuronal maturation in the postnatal period. MECP2 is involved in the expression of the gene that codes for brain derived neurotrophic factor (BDNF), which is essential for neuronal maturation and plasticity. The pathophysiology of RS thus lies conceivably in a MECP2-mediated disturbance in the regulation of BDNF. It is assumed that the severity of the disorder and the progression over time of the successive stages corresponds with a polymorphism in BDNF (Matijevic et al., 2009; Ben Zeev et al., 2009).

RS is one of the better examples of an autism-related disorder with a proven genetic pathophysiology. While there are clear differences between classical autism and the phenotypic presentation of autism in RS (i.e., characteristic stereotypy such as hand-wringing at chest level and a relative maintenance of eye contact), research in RS could nevertheless contribute to a better understanding of involvement of central nervous system dysfunctions in autism.

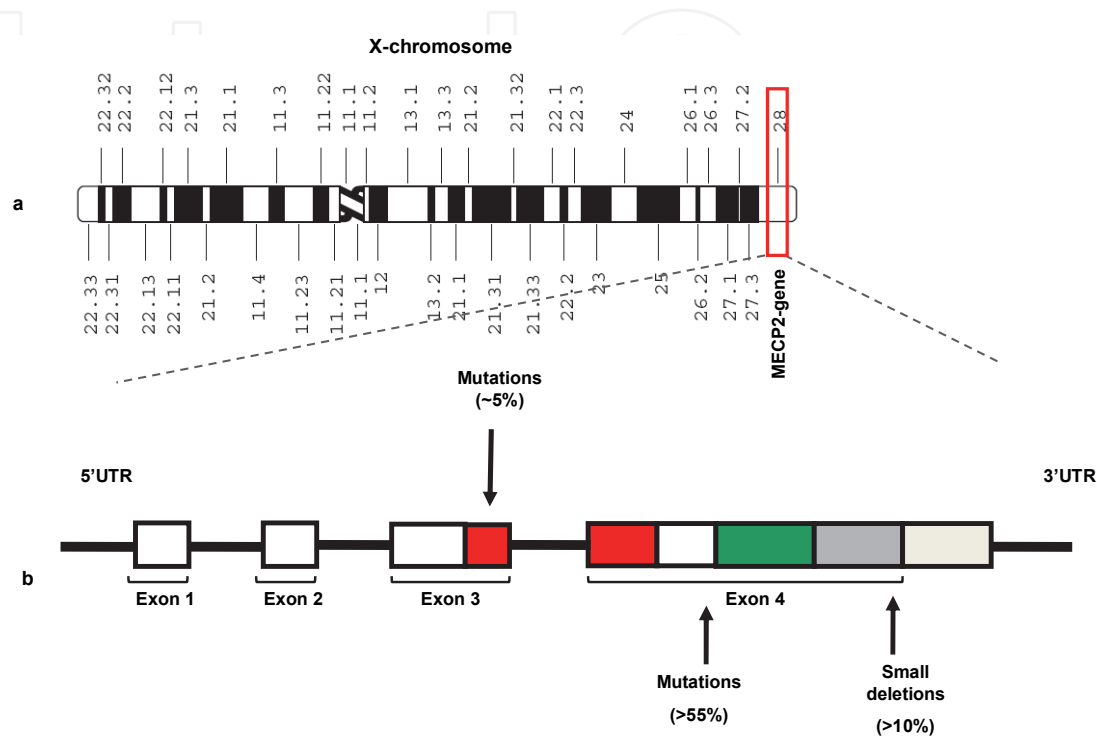


Fig. 2. Rett syndrome and the MECP2 Gene
Schematic representation of the location of the MECP2 gene on the long arm of the X chromosome. (a) The MECP2 gene is constituted by 4 coding exons. The majority of mutations among patients with Rett syndrome are found in exon 4. In addition, in more than 10% of the patients, a deletion of the last part of exon 4 is present. The terms 5' UTR (UnTranslated Region) and 3' UTR indicate the direction in which the gene is read; from 5' UTR to 3' UTR

4.3 Tuberous sclerosis

Tuberous sclerosis complex (TSC) of Bourneville-Pringle was first described in 1880 by Bourneville and is a multi-organ disorder with a autosomal dominant inheritance. The prevalence is 1 in the 6,000 - 10,000 births. TSC is caused by mutations in two genes, the TSC 1 and 2 gene. The TSC1 gene is located on chromosome 9 (9q34.3) and codes for hamartin while the TSC2 gene is located on chromosome 16 (16p13.3) and codes for tuberin. In approximately 85% of patients with a clinically confirmed diagnosis of TSC, a change in one of these two genes can be demonstrated. Usually, a *de novo* mutation is present, although 30% of the index patients has one or more affected family members. Mutations in both genes can lead to abnormal cell growth and differentiation in multiple organ systems. In the brain, this is expressed by the formation of cortical and subcortical hamartomas including tubers. In addition, various organ systems can be affected leading to the development of cystic kidneys, angiofibromas of the face, and rhabdomyomas. The structural abnormalities of the

central nervous system are associated with various forms of epilepsy, cognitive dysfunctions and symptoms of autism (Datta et al., 2008). There is, however, a great variability in the severity of the clinical characteristics across TSC patients, also within one single family.

Already in 1932 and thus *before* Kanner's publication, Critshley and Earl described the autistic characteristics associated with TSC, being decreased social contact, stereotypies, disturbed speech, and withdrawal behaviour. Research during the last few decades has shown autism to occur in about 25 to 60 percent of TSC patients, although its symptom profile differs qualitatively from that seen in classical autism. A higher level of social-cognitive functioning as well as less pronounced stereotypies are characteristic of patients with TSC. Moreover, in contrast to autism, the male-female ratio in TSC is about equal (Wiznitzer, 2004).

The neurobiological substrate for autism in TSC is still unclear. For both hamartin and tuberin, it is assumed that both proteins modulate cell function and play a role in neuronal migration, differentiation, and development and that they together form a functional complex (Asato et al., 2004). The latter can be considered as a type of 'neuronal polarity' in which over expression of the TSC1/TSC2 complex suppresses the formation of axons while an under expression is associated with the formation of tubers (Choi et al., 2008). This TSC1/TSC2 functional integration may explain that a mutation in one of the two genes can result in the same phenotype (Orlova & Crino, 2010). Finally, it has been demonstrated that the number of tubers in the brain correlates with the incidence of autism and that their localization corresponds with the type of epilepsy (Marcotte & Crino, 2006).

In sum, also for TSC, it is clear that the presence of autistic behavioural characteristics relates to a well-defined gene defect. This knowledge from TSC research may further elucidate the pathophysiology of autism.

4.4 22q11 deletion syndrome

The 22q11 deletion syndrome (22q11DS) was first described in 1978 by Shprintzen as velo-cardio-facial syndrome and is caused by an interstitial deletion of chromosome 22 (22q11.2). In Figure 3, a micro-array profile of chromosome 22 from a patient with 22q11DS is depicted.

This syndrome is associated with, among others, congenital heart and conotruncal defects, cleft palate, hypoparathyroidism, and facial dysmorphisms. The prevalence of 22q11DS is 1:4,000 with an equal male-female distribution. The deletion involved in this syndrome can encompass multiple genes, with the T-box 1 (TBX1) gene as the most important. Its encoded protein is crucial for the development of specific brain areas, heart, face, and limbs (Paylor et al., 2006). It is, however, doubtful whether this gene also plays a role in the etiology of psychiatric disorders that often accompany 22q11DS (Funke et al., 2007).

During the past decades, it has become clear that psychiatric disorders often occur in 22q11DS patients. These include psychoses in particular (Vogels et al., 2002; van Amelsvoort et al., 2004; Verhoeven et al., 2007), but also anxiety, mood, and obsessive-compulsive disorders (Shprintzen, 2000). In addition, in 15% to 30% of the patients with 22q11DS, autistic features are present such as withdrawal behaviour, impaired social interaction, reduced facial expression, and cognitive deficits, e.g., perseveration, reduced mental flexibility, and restricted problem-solving capacities (Fine et al., 2005; Vorstman et al., 2006b; Anshel et al., 2007; Niclasson et al., 2009). Closer inspection of the psychopathological profile has demonstrated that both the psychotic and the autistic symptoms evolve from a diminished comprehension of abstract and symbolic language, in addition to a limited capacity to correctly estimate the intentions, emotions, and behaviour of others (Shprintzen, 2000; Verhoeven et al., 2007).

In sum, for 22q11DS, it is obvious that detailed analysis of the cognitive, emotional, and psychiatric profile is of critical importance for the choice of an individual treatment strategy.

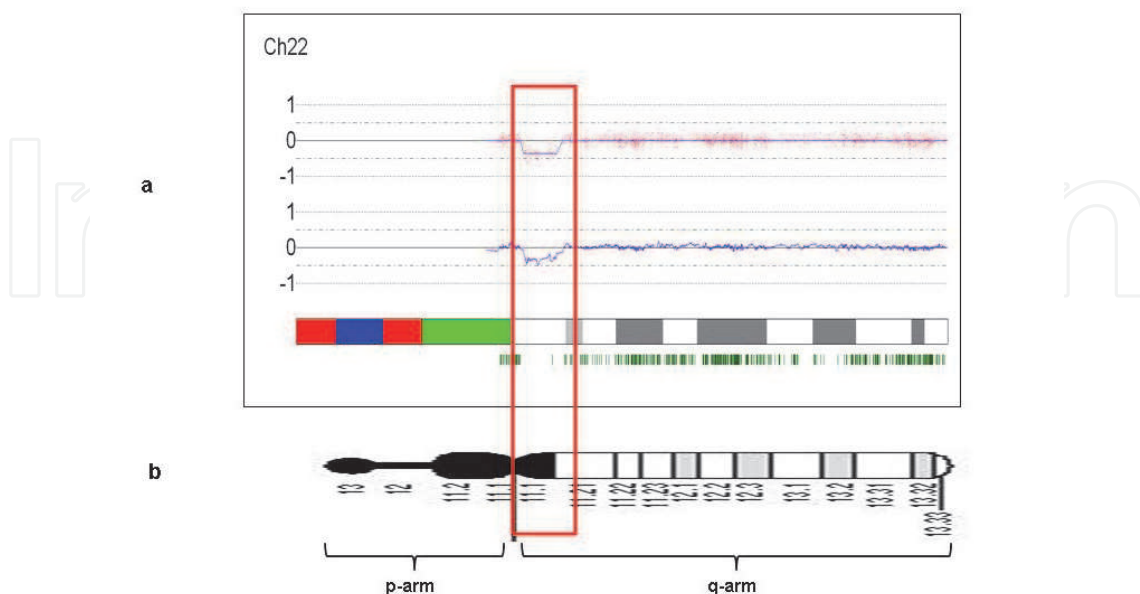


Fig. 3. Microarray profile of chromosome 22 from a patient with 22q11DS

(a) Representation of a microarray profile of chromosome 22 from a patient with a 22q11 deletion. (b) The ideogram of chromosome 22 with the indication of short p arm and the long q arm is depicted underneath.. In the upper portion, every individual clone is represented separately by a red dot on the X axis running between the end of the p arm (left) and the end of the q arm (right). On the Y axis, the amount of DNA from the patient as compared to that from control samples (CK) can be read. In case of an equal amount, the log2 ratio approximates zero. In cases of deletion, this will be -1 or lower. In cases of duplication, this will be +1 or higher. The p arm of chromosome 22 is not represented in the microarray profile because it only consists of satellites and non-coding material

4.5 Metabolic disorders

While genetically determined metabolic disorders are relatively rare, nevertheless, they often manifest with disorders along the autistic spectrum. The establishment of such a diagnosis is of importance for not only treatment and prognosis but also for gaining more insight into the pathophysiology of autism. Primarily involved are disturbances in amino acid metabolism such as phenylketonuria, disorders in purine metabolism, creatine deficiency syndromes, Smith-Lemli-Opitz syndrome (i.e., an inherited defect in the synthesis of cholesterol), urea cycle disorders, and mitochondrial disorders (Manzi et al., 2008; Zecavati & Spence, 2009; see Table 2). The latter may even have its debut with symptoms from an autism spectrum disorder (Weissman et al., 2008).

From the metabolic disorders, the creatine deficiency syndromes represent a recently recognized group of diseases that are caused by inherited defects in the biosynthesis and transport of creatine. Two defects in the biosynthesis have been reported that include deficiencies of the enzymes L-arginine-glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT). The third is a functional defect involving the creatine transporter mechanism. The latter is an X-linked syndrome caused by a defective creatine transporter and was first described by Salomons et al. (2001). It appeared to be the

result of a mutation in the creatine transporter gene called SLC6A8 that was mapped to Xq28. Its prevalence is estimated to be at least 2% of X-linked mental retardation syndromes (Rosenberg et al., 2004). Since the SLC6A8 gene is expressed in most tissues (e.g. skeletal muscle, kidney, colon, brain and heart), several organ systems can be affected.

<i>Disorder</i>	<i>First appearance</i>	<i>Characteristics</i>	<i>Treatment option</i>
Phenylketonuria	Neonatal	Intellectual disability, autism, epilepsy	Special diet
Purine metabolism disorders	From childhood	Development delay, autistic characteristics, impulsivity, epilepsy	None
Creatine deficiency syndromes	3 months – 2 years	Autistic characteristics, epilepsy/myoclonic twitches, language and developmental delays, extrapyramidal symptoms	Creatine substitution
Cholesterol synthesis defects	From childhood	Autism, psychomotor retardation	Cholesterol suppletion
Urea cycle disorders	Neonatal and postnatal	Hyperactivity, epilepsy, intellectual disability, autism	Special diet measures
Sanfilippo syndrome	Variable, depending on subtype	Loss of acquired skills, autism	None
Mitochondrial disorders	Variable, depending on subtype	Depending on organ system	None

Table 2. Metabolic disorders and autism (adapted from Zecavati & Spence, 2009 and Manzi et al., 2008)

The main organ involved in creatine deficiency syndromes is the central nervous system. Patients show severe neurodevelopmental delay and, from early infancy on, mental retardation, epilepsy, disturbances in active and comprehensible speech, autism and self-injurious behaviour become prominent (Salomons et al., 2003; Béard and Braissant, 2010). In patients with GAMT or AGAT deficiency, early oral creatine substitution treatment might effectively prevent neurological sequelae. In those with a defect in the creatine transporter gene SLC6A8, however, suppletion with L-arginine is not effective at all (Nasrallah et al., 2009).

Although metabolic syndromes should always be involved in the differential diagnosis of autism spectrum disorder, systematic screening of such patients is only mandatory in case of a suggestive actual symptomatology and/or developmental history. An example is the Sanfilippo B syndrome, a mucopolysaccharidosis caused by a mutation in the NAGLU gene, which leads to an accumulation of heparan sulfate with, as a consequence, damage to the central nervous system and various organ systems. This diagnosis was recently determined

for an older, mild intellectually disabled patient who was referred for behavior problems with a history of limited verbal and emotional communication, stereotypies, impulsivity, and anxieties (Verhoeven et al., 2010).

5. Closing remarks

The majority of patients with autism present with a mild to severe intellectual disability. In a substantial number of cases, moreover, the autistic disorder appears to be part of a genetic disorder. It is quite remarkable therefore, that *only one* genetic disorder from the array of genetic disorders associated with autism, is included in the DSM-category of autistic disorders, namely the neurodegenerative Rett syndrome. It should, however, be emphasized that the identification of autistic behaviours and the diagnosis of an autism spectrum disorder is extremely difficult in patients with severe intellectual disability in the context of a genetic syndrome (Moss & Howlin, 2009). It is also evident that in case of exceptionally high intelligence, Asperger's disorder or atypical autism are usually the autistic disorders involved. For this specific group of patients, however, no information on genetics is available as yet. These patients are often subsumed under the general DSM category 'Pervasive Developmental Disorder, Not Otherwise Specified'.

Apart from the changes of diagnostic concepts over the past decades, research on the genetic underpinnings of autism and related disorders confronts three major complexities. First, there is the large degree of genetic heterogeneity, which means that different genes can contribute in a varying way to the emergence of a disorder. A second difficulty is the polygenetic inheritance; that is, the simultaneous presence of multiple genetically-determined vulnerabilities that may be responsible for the development of a particular syndrome. A third problem lies in the well-known interaction between environmental and genetic factors during development from early conception on (Volkmar et al., 2009).

All mutations that are causative for the aforementioned disorders concern genes involved in the early development of the central nervous system. The search for susceptibility genes has made it clear that disturbed synaptic transmission in, for example, the neuroligin network is involved in the pathophysiology of a certain, albeit small, percentage of cases with autism. This kind of knowledge might be relevant for the development of putative future pharmacological treatment strategies for a subgroup of patients with autism. In this context, the earlier mentioned significance of the neuropeptide OXT could also be noteworthy.

The results from a large number of studies during the past decades lead to several conclusions. It is clear that autism, both phenotypically and genotypically, is a very heterogeneous disorder and that the quest for the grail of a single-high-impact gene will never succeed. In general, mutations or common variants in genes are thought to be involved in the neuronal domains, synaptic interaction, neurotransmission, and cell migration and growth (Freitag et al., 2010). Attention should therefore be shifted to large-scale screening for *de novo* mutations and CNVs that can influence the functioning of a gene (Sebat et al., 2007; Vissers et al., 2010).

Recently, all information available on the vulnerability genes and CNVs associated with autism has become available via the Autism Genetic Database (AGD), that can be freely accessed at <http://wren.bcf.ku.edu> (Matuszek & Talebizadeh, 2009). In addition, modern fMRI techniques may be of use to map neuronal endophenotypes that are critical for further genetic studies of autism (Losh et al., 2008; Piggot et al., 2009).

For daily clinical practice, facial dysmorphisms in patients with autism in addition to intellectual disabilities, constitute the initial indication for modern genetic investigation.

Epilepsy at young age and gradual deterioration of previously acquired skills warrant further search for a metabolic disorder. Future scientific studies may reveal to which extent sets of genes are involved in the pathophysiology of autism and autism related disorders per se, but also of neuropsychiatric disorders in general (Lichtenstein et al., 2010). In all cases it is clear that detailed information about developmental history, neuropsychiatric/neuropsychological profile as well as an elaborative inventory of family characteristics is mandatory for appropriate genetic search. This holds true for both the individual patient and for a group of well defined patients.

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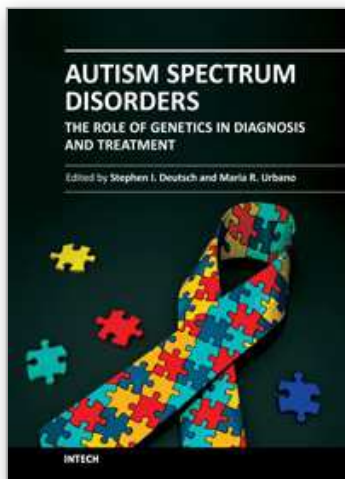
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Estimated prevalence rates of autism spectrum disorders (ASDs) have increased at an alarming rate over the past decade; current estimates stand as high as 1 in 110 persons in the population with a higher ratio of affected males to females. In addition to their emotional impact on the affected persons and their family members (in fact, the latter are often unrecognized unaffected “patients” themselves), the economic and social impacts of ASDs on society are staggering. Persons with ASDs will need interdisciplinary approaches to complex treatment and life planning, including, but not limited to, special education, speech and language therapy, vocational skills training and rehabilitation, social skills training and cognitive remediation, in addition to pharmacotherapy. The current book highlights some of the recent research on nosology, etiology, and pathophysiology. Additionally, the book touches on the implications of new research for treatment and genetic counseling. Importantly, because the field is advancing rapidly, no book can be considered the final word or finished product; thus, the availability of open access rapid publication is a mechanism that will help to assure that readers remain current and up-to-date.

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