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# Genetic Aspects of Autism Spectrum Disorders: From Bench to Bedside

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## 1. Introduction

Autism is a complex disorder of the immature brain, caused by different genetic and non-genetic factors and characterized by a certain behavioral phenotype. Autistic spectrum disorders (ASD) may be isolated or syndrome, in the latter case combined with other clinical symptoms, facial dysmorphism, abnormalities of the limbs or internal organs, growth retardation.

According to DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) and ICD-10 (International Classification of Diseases) autism includes symptoms of varying degrees in three categories: social interaction, communication, stereotyped behaviors. Leo Kanner defines two most typical early childhood autism disorder: 1. extreme loneliness (inability to establish normal contacts even with the closest) and 2. striving for permanence (any change in the surrounding world is of concern; sick child requires ritual immutability even in actions related to its service).

DSM-IV defines five subtypes of Pervasive Developmental Disorders (PDD):

- **Classic autism**
- **Asperger Syndrome** (develop speech in the expected age, normal mental development);
- **Desintegrative disorder** (Heller syndrome)
- **Regression in cognitive** abilities, motor skills and communication between 2 and 10 years of age, after a period of "normal" development in the first few years;
- **Autistic behavior**, not otherwise specified (individuals with autistic behavior not consistent with other subtypes);
- **Rett Syndrome**

The incidence of autism is 3-6/1000, the ratio men: women is 4:1. In recent years, the frequency of patients with autism is increasing. This is due to greater awareness of medical professionals and changing diagnostic criteria, inclusion of patients with attention deficit and hyperactive behavior in this group, rather than a real increase in incidence of autism. Clinical picture comprises lack of interest in the environment, lack of eye contact, lack of subject matter, motor and verbal stereotypes; agramatism (speak for yourself in the third person) with a peculiar intonation, singing, not asking questions. Sometimes the children develop strange passions (in numbers, equipment, etc.).

The diagnosis of "autism" is often difficult due to high variability of symptoms in different individuals and in the same patient over time. Today it is considered that 11-37% of cases of autism are within a syndrome that can be diagnosed by specific laboratory markers and / or its characteristic phenotype, chromosomal aberrations, single gene diseases (tuberous sclerosis, fragile X syndrome chromosome), environmental factors.

Despite of the organic basis of this disease, today it is diagnosed based on criteria established by consensus and not by biological markers. Family studies and those among twins show higher concordance in monozygous (60-91%) than in dizygous twins (0-6%). These studies support the existence of a genetic component in the etiology of autism. Autism is an example of high genetic heterogeneity.

## 2. Chromosomal aberrations in autism

Chromosome abnormalities have long been recognized as an important cause of learning disabilities and multiple malformation syndromes. About 0.8% of live born infants have numerical or structural chromosomal anomalies that result in an abnormal phenotype. Identification of such anomalies is important clinically and also for accurate genetic counseling. Recently, molecular-cytogenetic and array-based techniques have enabled higher resolution screens for chromosome anomalies. Since all patients with a chromosomal imbalance are dysmorphic, the association of ASD with a facial dysmorphism seems to be a good indication for chromosomal anomaly screening. Clinical features that predict an increased likelihood of finding a cytogenetic abnormality on routine testing include: congenital delay in neuro-cognitive development, one or more major malformations, prenatal onset abnormal growth pattern, craniofacial dysmorphism, unusual behavioral phenotypes, often in the autistic spectrum, and a family history of multiple miscarriages, learning disabilities or malformations. High resolution chromosome banding has been reported to have an overall detection rate of 7.5% for anomalies in patients with mental retardation/learning disabilities. It is recently reported that *de novo* balanced chromosomal rearrangements have high risk of neurodevelopmental and psychiatric disorders. Conventional cytogenetic analysis uses light microscopy to examine metaphase or prometaphase chromosomes that have been stained to produce a distinct banding pattern for each chromosome. This approach has a maximum resolution of 3-5 Mb for structural anomalies and requires mitotic cells, usually peripheral blood leucocytes, bone marrow, or fibroblasts, for analysis.

About 5% of individuals with an ASD have a microscopically identified chromosomal alteration. Cytogenetic assays have long been used to uncover chromosomal defects in patients with autism. Almost all chromosomes have been involved. The incidence of *de novo* chromosomal aberrations may be increased in groups of persons with autism, suggesting a causal relationship between certain chromosomal aberrations and the occurrence of isolated idiopathic autism.

By conventional cytogenetic and fluorescent *in situ* hybridization (FISH) methods a number of chromosomal abnormalities were found in 1.7 to 4.8% of patients with autism. The most frequent aberrations were abnormalities of 15q11-q13 locus (duplications, deletions and insertion - in 1-4% of cases), deletions of 22q and 16p, as well as partial monosomy X. Some of cytogenetic anomalies in autistic patients are presented in table 1.

Chromosomal aberration	References
inv(3)(p14;q21)	de Silva et al. (2003)
7q11.23 duplication (locus of Williams)	Somerville et al. (2005) Depienne et al. (2007)
7q inversion	Arking et al. (2008)
13q14-q22 deletion	Steele et al. (2001)
15q11-q13 duplication	Cook et al. (1997)
15q11.2 isodicentric chromosome	Wolpert et al. (2000)
15q25.2-qter trisomy	Bonati et al. (2005)
16p11.2 deletion 16p11.2 duplication	Shinawi et al. (2010) Sebat et al. (2007) Bijlsma et al. (2009)
genomic instability at 16p11.2	Eichler and Zimmerman (2008)
t(13;17)(q14;p13)	Tentler et al. (2002)
22q13 telomeric deletion	Luciani et al. (2003) Lindquist et al. (2005) Wilson et al. (2003)
22q13 interstitial deletion	Wilson et al. (2008)
Xp22.11 deletion	Marshall et al. (2008) Filges et al. (2011)

Table 1. Frequent chromosomal aberrations in patients with ASD

### 3. Autism in syndromes

- *Fragile X chromosome Syndrome*

Fragile X chromosome Syndrome (FXS) is characterized by facial dysmorphism (long face, large protruding ear mussel), large testis and various degrees of mental deficiency. This is the most common cause of inherited mental impairment, affecting 1 / 4000 males and 1 / 8000 women. It is caused by a dynamic mutation (variable number of CGG repeat) in FMR1 gene, located on the long arm of chromosome X (Xq27.3). FMR1 gene encodes a protein (FMRP) involved in the transport of RNA molecules from cell nucleus to cytoplasm.

About 90% of men with FXS have behavioral disorders that can be interpreted as abnormal social behavior, or behavior characteristic of autism spectrum - limb automatism, avoiding eye contact, signs of auto-aggression. Approximately 30% of individuals with FXS have autism.

- *Prader-Willi/Angelman Syndrome*

Angelman Syndrome (AS) and Prader-Willi Syndrome (PWS) are most often result of a deletion of 15q11-q13 locus. Abnormal imprinting or mutations are found in ~ 5% of patients with PWS and 15% of patients with AS. The loss of the father's genes in this locus leads to expression of PWS, loss or mutation of the maternal UBE3A or ATP10C gene causes AS.

AS is more often associated with autism than PWS. The diagnosis of AS should be suspected in patients with autism, severe mental deficiency and epilepsy. Between AS and autism, there is a number of common characteristics - a lack of expressive speech

automatisms, attention deficit, hyperactivity, problems with sleeping and nutrition, and delayed motor development. It is known that duplication of maternal genes in the critical locus for AS is often associated with autistic symptoms. Majority of patients with Angelman syndrome (42% -61%) meet the criteria for autism. In 25% of patients with Prader-Willi syndrome the autism diagnosis is inserted. The fact that autism occurs more often in maternal duplication of 15q11-q13 locus than in the forms with the deletion should be considered.

- *Turner Syndrome*

Turner Syndrome (TS) is caused by complete or partial absence of one X chromosome, it occurs with an incidence 1:2500 girls. Characteristics of the syndrome is the presence of gonadal dysgenesis, infertility, short stature, short neck with pterigium, facial dysmorphism, coarctation of the aorta, renal anomalies. Patients with TS have normal intelligence. Often they have reduced non-verbal skills and arithmetic skills with in a well-developed verbal intelligence. Haploinsufficiency of one or more genes in Xp22.3 region determine typical TS neurocognitive phenotype. There is an increased risk of autism in these children as 5% have classic autism, and > 25% are with autistic spectrum disorders. Girls with TS inheriting X chromosome from their mothers have poorer social skills than those inheriting X chromosome from their fathers and they are more often with autism. It is believed that on the X chromosome exist a gene determining social skills, which is expressed only when this chromosome is inherited from the father.

#### 4. Autism with known single gene defect

- *Rett syndrome*

Rett Syndrome (RS) is the only autistic spectrum disorder with a known etiology, which affects 1:12500 women (Figure 1). It is X-linked syndrome, a consequence of mutation in *MECP2* gene (Xq28), encoding methyl-CpG-binding protein-2, MECP2. Atypical forms of the syndrome, with early onset epilepsy or cramps, may be due to mutation in gene for cyclin-dependent kinase-like 5 (CDKL5).

Like the classic signs of autism, first clinical presentation of RS is between 6 and 18 months after the period of normal development. Clinical manifestations of the syndrome include regress in the neuro-psychological development, seizures, cognitive impairment, microcephaly, stereotype movements, abnormal socialization.

Many genetic and environmental factors can alter the level of *MECP2* protein in the brain and cause an effect similar to mutation in *MECP2* gene. Study the role of *MECP2* in the pathogenesis of RS and autistic spectrum disorders are considered as "Rosetta Stone" that can be used in deciphering the complex etiology of autism.

- *Tuberous sclerosis*

Tuberous sclerosis (TSC) is an autosomal dominant neurodermatosis, due to mutations in *TSC1* (9q34), which encodes the protein hamartin, or mutations in *TSC2* (16r13.3) gene for the protein tuberlin. Both proteins co-operate and participate in the control of cell growth and proliferation. Carriers of mutations in these loci are prone to tumor formation, skin changes and hamartoma in various organs (Figure 2). Brain lesions (tuberous) lead to epilepsy in more than ¾ of patients with TSC.

Given the high incidence of epilepsy in children with TSC and the frequent association between epilepsy and autism, it is not surprising that approximately 25% of patients with TSC are autistic. Among patients with autism, the incidence of TSC is 1.1 to 1.3%, this percentage is by 30% higher than the incidence of TSC in the general population.



Fig. 1. Rett Syndrome ([www.canajoharieschools.org](http://www.canajoharieschools.org))

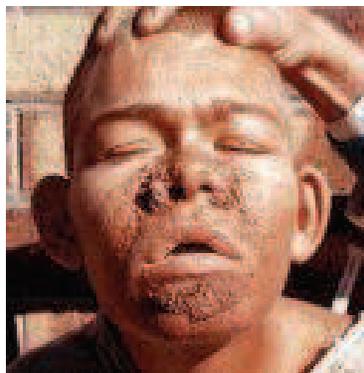


Fig. 2. Tuberous sclerosis ([www.benmoonpharma.com](http://www.benmoonpharma.com))

- *Neurofibromatosis type 1*

Neurofibromatosis (NF1) is an autosomal dominant disease characterized by the development of multiple benign tumors of nerves and skin (neurofibromas) and abnormal skin pigmentation (spots cafe-au-lait). Pigment patches are available at birth tended to increase in number and size over time. NF1 gene (17q11.2) encodes a protein called neurofibromin that functions as a tumor-suppressor. The incidence of NF1 in autistic people in different studies varies from 0.2 to 14%. Patients with NF1 have a 100-190 fold higher risk of developing autism than in the general population. Sixfold repeat of the AAAT Alu sequences in the NF1 gene is found only in patients with severe autism, and not in controls groups.

- *Metabolic diseases*

Among patients with phenylketonuria, hyper-succinyl-purinaemia, lactic acidosis, abnormal metabolism of aromatic amino acids and cholesterol, autism is more common than in the general population. Selective metabolic screening is indicated in patients with autistic behaviors and symptoms characteristic of metabolic diseases, lethargy, cyclic vomiting, seizures, mental deficiency. In some patients the early diagnosis of metabolic disorder and appropriate treatment can significantly improve their cognitive and behavioral phenotype.

In untreated patients with phenylketonuria it is very common the manifestation of auto-aggression, hyperactivity, autism. It was found that 5.71% of patients diagnosed late with pathologic metabolic condition meet criteria for autism.

- *Mitochondrial diseases*

Proportion of patients with autism have an increased lactate. It is assumed that hyperlactate-acidaemia is a consequence of impaired oxidative phosphorylation process in mitochondria of neurons. The relationship between autism and mitochondrial diseases has been demonstrated and established by decreased activity of enzymes involved in oxidative phosphorylation, changes in the structure of mitochondria and various mutations in mitochondrial DNA. In 7.2% of patients studied with autism mitochondrial disease has been proven. Mitochondrial disease as a cause of autism should be suspected in patients in which there is combination of epilepsy and signs of neurological and / or systemic dysfunction.

- *Other single gene diseases*

Elevated levels of uric acid is found in  $\frac{1}{4}$  of the patients studied with autism. The reasons for this "purine autism" remain unclear. Autism is described in association with muscular dystrophy Duchenne, Sanfilippo syndrome, Sotos, Cowden, Moebius diseases.

## 5. Genetic predisposition to autism

Identification of genes participating in the development of a disease is of paramount importance for precise diagnostics and adequate effective treatment. That is why genetic investigations are wide spread in elucidating the etiology of the disease - linkage analysis for searching of candidate-genes, association analysis of biological candidate-genes, whole genome screening.

- *SNP associations in autism*

The human genome is huge, consisting of thousands genes. This is the reason why the discovering of specific gene/genes responsible for a disease is so difficult task. Gene mapping aims in establishing the location of genes related to specific disease by using other genetic markers (Single Nucleotide Polymorphisms - SNPs) with known localization. The genes or loci, which are objects of the mapping, are these ones, which are supposed to predispose to the disease of interest - they are called disease loci. In general, there are two approaches in accomplishing the goal of mapping: linkage analysis (Linkage mapping), that is used in large families, and association studies (Linkage disequilibrium mapping) at the level of population. In linkage analysis, it is not necessary to know the pathophysiology of the disease - they detect genes with considerable effect at large distances. In contrast, association studies discover genes with little effect at small distances, as it is necessary to know the biology of the studied disease. These two approaches very often are combined in the practice.

Single Nucleotide Polymorphisms (SNPs) represent changes in single nucleotides in DNA and occur with frequency  $>1\%$ . Because of its extremely high density in the human genome, SNPs are ideal polymorphic markers for association studies in complex diseases. So far in the official database dbSNP (<http://www.ncbi.nlm.nih.gov/SNP/>, Genome build 36.3, dbSNP build 130) more than 10 millions SNPs are discovered and deposited.

Chr	Cytoband	Study	Candidate-genes	References
1	1q41-42	62 families with at least 2 individuals had autism or an autism spectrum disorder	MARK1	Buxbaum et al. (2004) Maussion et al., (2008). Bartlett et al. (2005)
2	2q31-32	411 pedigrees including 671 autistic children; 158 Irish child-parent rios (442 individuals)	cAMP-GEFII (RAPGEF4), DLX1 DLX2	Bacchelli et al. (2003) Ramos et al. (2004) Segurado et al. (2005) Liu et al. (2009) Newbury et al. (2009)
3	3q24	38 Finnish families in which a proband had autism; 18 families with autism	SLC9A9(R423X) C3ORF58 (DIA1, 'deleted in autism-1')	Morrow et al. (2008) Auranen et al. (2002)
4	4p12	470 white families with autism ; 557 non-Hispanic Caucasian families with autism; 54 African American families with autism	GABRA4 GABRB1	Ma et al. (2005) Collins et al. (2006)
5	5p14	780 families (3,101 subjects) with affected children; 1,204 affected and 6,491 control subjects; 438 Caucasian families with 1,390 individuals with autism	CDH9 CDH10	Wang et al. (2009) Ma et al. (2009)
7	7q31	219 affected sib pairs with autism; 204 families with autism; 539 additional autistic families	RAY1 (ST7) MET WNT2	Vincent et al. (2000) Lamb et al. (2005) Folstein and Mankoski (2000) Campbell et al. (2006) Wassink et al. (2001)
	7q35-36	152 families segregating autism; 635 patients and 942 controls; 539 additional autistic families	CNTNAP2 EN2 FOXP2 CNTNAP2	Vernes et al. (2008) Alarcon et al. (2008), Arking et al. (2008), Bakkaloglu et al.(2008) Molloy et al. (2005) Benayed et al. (2005) Gharani et al. (2004)
12	12q14	26 families with autism, comprising 65 affected individuals		Ma et al. (2007)

Table 2. Mapping for predisposing genes in ASD

Chr	Cytoband	Study	Candidate-genes	References
15	15q11-13	221 patients with autism	GABRB3	Shao et al. (2003) Tochigi et al. (2007)
16	16p11	859 patients of European ancestry with autism spectrum disorder and 1,409 controls		Glessner et al. (2009)
17	17q11	117 autistic trios; 115 trios consisting of a proband with autism and both parents; 84 Irish families with autism; 384 families in which at least 1 child had autism and a second sib had autism or ASD	5-HTTLPR SLC6A4 5-HTT	Abramson et al., 1989; Piven et al., 1991, Klauck et al. (1997) Kim et al. (2002) Conroy et al. (2004)
	17q21	56 sib pairs from 48 families with only affected males; 730 affected families; 281 simplex and 12 multiplex Caucasian families with autism	ITGB3	Cantor et al. (2005) Weiss et al. (2006) Napolioni et al. (2011)
19	19p13	20 Finnish families with autism	TLE2 TLE6	Kilpinen et al. (2009)
21	21p13-q11	34 families in which 1 individual had autism, a relative had either autism or ASD, and both had a definite history of developmental regression		Molloy et al. (2005)
X	Xp11	119 boys with autism	MAOA	Cohen et al. (2011)
	Xq28	141 individuals with ASD; 176 ASD patients; 38 Finnish families; 69 females with autism	RPL10 H213Q MECP2	Gong et al. (2009) Chiocchetti et al. (2011) Auranen et al. (2002) Carney et al. (2003)

Table 2. Mapping for predisposing genes in ASD. (Continuation)

By the abovementioned methods of analysis several regions are localized as associated with autism in 20 different chromosomes. Most of them are summarized in table 2. Some of the identified loci or polymorphisms showed association with specific clinical features of the autism. For example, linkage at 1q41-42 correlated to obsessive-compulsive behaviors; linkage to 2q31-32 - mild developmental delay particularly affecting speech and language, pervasive developmental disorder, attention deficit, obsessive traits, and bipolar disorder; 3q24 - Asperger syndrome or developmental dysphagia; 7q31 - specific language impairment; 7q35-36 - loss of language skills and/or loss of other socially communicative skills; Xp11 - more severe sensory behaviors, arousal regulation problems, aggression, and worse social communication skills.

In whole-genome scan of 10 000 patients with ASD, members of their families and volunteers genetic variants associated with disease have been found. They are related to CDH9 and CDH10 genes that encode cadherins. Cadherins are proteins located on the surface of cells that are pivotal for cellular interactions. Other 30 genes for cell adhesion proteins (including other cadherins and neuroligins) were also found to be strongly associated with autism. A positive association of autistic male with CNTNAP2 gene for neuroligin was revealed. In the brain of fetuses, cell adhesion proteins allow neurons to migrate to the right places and connect with other neurons. Additionally, it was found connection with rare variations in genes for the ubiquitin-proteasome system that may be included in the exchange of adhesion proteins on the cell surface. These results highlight the role of variations in genes coding proteins for intercellular adhesions to create a susceptibility to ASD.

One of the strongest candidate-gene for ASD, selected from association studies, is *EN2*, mapped to 7q36. *EN2* mouse mutants display anatomic phenotypes in the cerebellum that are similar to those reported for individuals with autism. Population-attributable risk calculations for the associated haplotype, performed by using large sample of 518 families, determined that the risk allele contributes to as many as 40% of ASD cases.

- *Copy number variations (CNV) in autism*

Literature data have showed that more than half of the variability between human genomes is due to submicroscopic copy number variations of DNA (microdeletions and microduplications), and that these CNVs are responsible for some complex diseases, even more than single nucleotide polymorphisms (Freeman et al., 2006; McCarroll and Altshuler, 2007; Redon et al., 2006). There are currently more than 6,000 known regions of CNV, and there are likely many more (Carter, 2007; Redon et al., 2006). Microarray-based Comparative Genomic Hybridization (array CGH) is currently one major technique for analyzing CNVs in a given individual (Carter, 2007). Array CGH is a sensitive, specific and rapid method for detecting unbalanced genomic changes. This method is used to detect submicroscopic aberrations, identifying critical DNA areas for a disease and clarify the genotype-phenotype correlation. Array CGH provides with direct link to genome database and potential candidate-genes, predisposing to the disease, could be revealed.

Emerged as a new molecular-genetic technique, array CGH is now used for screening the genome of affected individuals and their families and for the localization of specific genes or

chromosomal regions potentially linked to autism. Using array CGH in patients with autism, unbalanced genomic changes were found in 10-27.5% of the affected individuals. The combination of facial dysmorphism with autism is an indication for conducting screening for chromosomal reorganizations.

Using high-resolution microarray analysis, Marshall et al. (2008) found 277 unbalanced copy number variations, including deletions, duplications, translocations, and inversions, in 189 (44%) of 427 families with autism spectrum disorder. These specific changes were not present in a total of about 1,600 controls, although control individuals also carried many CNV. Although most variants were inherited among the patients, 27 cases had de novo alterations, and 3 (11%) of these individuals had 2 or more changes.

In the most recent years (see table 3) the using of array CGH in large cohorts enabled us to uncover new candidate-genes for autism with high statistical power. Most of them are responsible for normal functioning of nervous system.

Chr	Cytoband	Candidate-genes	Function	References
1	1q21	HYDIN	hydrocephalus inducing	Itsara et al. (2009)
2	2p16	NRXN1	neuronal cell adhesion	Rujescu et al. (2009)
3	3q29	FBXO45 DLG1 PAK2	synaptic transmission junction formation cytoskeleton reorganization	Quintero-Rivera et al. (2010)
	3p26 3q26 9q33	CNTN4 NLGN1 ASTN2	neuronal network formation and plasticity neuronal cell surface protein neuronal migration	Glessner et al. (2009)
11	11q13	SHANK2	molecular scaffold in the postsynaptic density	Berkel et al. (2010)
16	16p11	TBX6	regulation of developmental processes	Fernandez et al., 2010 Shinawi et al. (2010)
X	Xp22	PTCHD1	patched domain containing	Whibley et al. (2010)

Table 3. CNV in specific regions and corresponding candidate-genes for ASD

Figure 1 summarize the chromosomal locations, showing linkage with autism and containing potential candidate-genes for the disease.

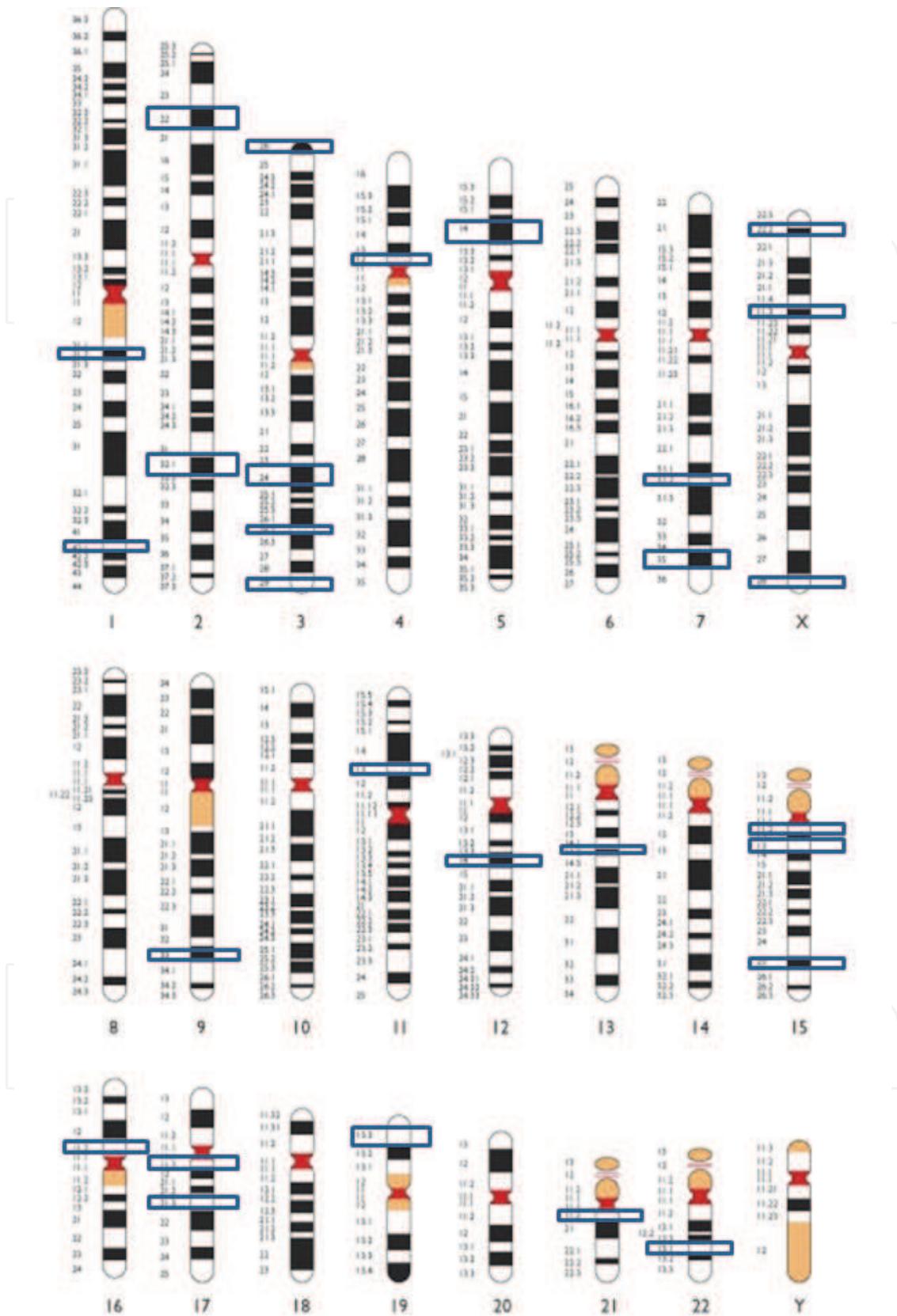


Fig. 3. Human karyogram, showing the most frequently affected chromosomes in autism and ASD.

## 6. Genetic counseling in autism

The risk for recurrence of ASD in families having children with "idiopathic" autism is 2-8%. The diagnosis of autism within malformative syndrome or metabolic conditions with known genetic defects could precise the risk for disease recurrence. It is recommended careful counseling in families with autistic patients when they plan future pregnancy.

In patients with autistic spectrum disorders the following genetic analyses are recommended:

- Karyotyping;
- Metabolic screening for phenylketonuria, hyper-succinyl-purinemia, lactic acidosis, abnormal metabolism of aromatic amino acids, monoamines and cholesterol, abnormal glycosylation (CDG);
- Screening for mutations in MECP2 and FMR1 gene;
- FISH and RT-PCR for abnormalities of 15q11-13 locus (duplications, deletions and insertion);  
Screening for mutations in mtDNK;
- Comparative genomic hybridization with microarrays (arrayCGH).

The most probable multifactorial etiology of autism suggests that interactions between multiple genes cause "idiopathic" autism but that epigenetic factors and exposure to environmental modifiers may contribute to variable expressions of autism-related traits. The extensive research in this area, consolidating clinical, genetic, metabolic and environmental data will contribute to better understanding of the disease and to better clinical management.

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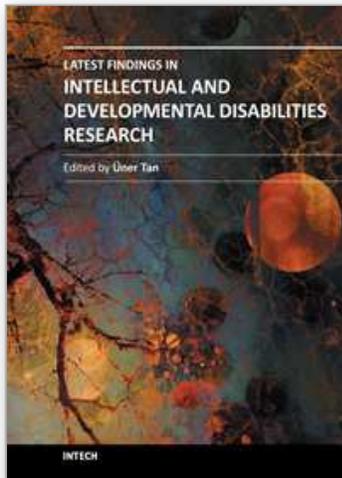
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