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1. Introduction

Autism is a neurodevelopmental disorder characterized by impaired social interaction, and verbal and nonverbal communication as well as limited and repetitive behaviours. Although symptomatology of autism may be noticed around early months, diagnosis generally occurs around 24-36 months, however in some cases diagnosis may be delayed to adulthood [1]. Since behavioural symptoms and the degree of functional impairment are variable, the autistic disorder is described as a heterogenous symptom cluster of varying etiological and pathological basis [2]. Described as a multifactorial disorder created by interaction of neurologic, immunologic, environmental, and genetic factors, autistic disorder has no definite cause [3, 4]. In many cases in whom the etiology remains unclear are diagnosed as idiopathic autism or non-syndromic autism [5, 6]. Seventy percent of cases with idiopathic autism have basic symptoms without physical abnormalities whereas 30% have complex autism in which dysmorphic features are detected such as microcephaly and/or structural brain malformations [7]. Autism is associated with other syndromes such as Fragile X syndrome, Down Syndrome, and tubersclerosis in 5-25% of the cases ([8, 9]. Although phenotypic heterogeneity is the biggest challenge for research efforts directed to identify autism etiology [10], currently it is widely accepted that environmental and genetic factors play essential role in genesis of autistic disorder thanks to a recent advance in research techniques related to biological factors and widespread studies in this field [11, 12].

2. Genetics

Autistic disorder is a multifactorial genetic disorder not following classical Mendelian inheritance. Impairment in social interaction and verbal communication as well as genetic differentiation in rigid-repetitive behaviours indicates that different features in autistic disorder
may be caused by different genes associated with distinct brain regions and be related to cognitive impairment and functional abnormalities [13].

Genetic studies in the field of autistic disorder have mainly focused on molecular genetic studies, assessment of chromosomal abnormalities, twin studies and family studies. In families having an autistic child the recurrence rate has been reported as 3-8% [14, 15, 16]. The studies on twins and adopted children are important in identifying the actual importance of genetic factors. Concordance among twins enables to measure heritability, and thus to assess what percentage of the phenotype is affected by genetic factors. Monozygotic (identical) twins share 100% of the genetic material whereas dizygotic (fraternal) twins share 50% of the genetic material. Monozygotic twins’ higher rate of concordance compared to dizygotic twins may be used for calculation of heritability. Twin studies generally showed a higher concordance rate for monozygotic twins compared to dizygotic twins. The concordance rate of monozygotic twins is at least 60% when diagnostic criteria for autism (DSM-IV) are used whereas the number is as high as 71% for autism spectrum and 92% for a broader spectrum of verbal/social interaction disorders [11, 12, 16, 17]. On the other hand, the concordance rate of dizygotic twins has been reported as 1-30% [9, 17-20]. Twin studies demonstrated an average autism inheritance of 90% [21]. On the basis of these studies autism is considered to be among the most inherited psychiatric diseases [22, 23].

Although autism has a high inheritance rate, its mode of inheritance remains unclear. Multi-gene interactions and multiple loci are believed to play role in genetic susceptibility to the disease [24]. There are 3 basic approaches in this area: 1) in whole genome scanning method, it is aimed to predict the localization of a disease, about chromosomal localization of which we have no preliminary information, by starting from common genetic determinants in a community composed of multiplex families (families with more than one involved member). 2) cytogenetic studies guide molecular studies by showing inherited or de novo chromosomal anomalies in involved persons or families. 3) candidate gene studies examine the relationship of genes known to affect brain development in associated regions or alternatively, a selected precursor gene considered to hypothetically contribute to autism pathogenesis.

It has been demonstrated that structural chromosomal variations comprising also copy number variations play an important role in etiology of autism. De novo copy number variations have been identified in 7-10% of sporadic autism cases [25, 26].

In studies employing genome scanning method to reveal genetic etiology of autism, cogent evidence for an association with chromosomes 2, 7, 1, and 17, especially long arm of chromosomes 2 (2q) and 7 (7q) has been obtained. Other chromosomes less associated with autism are chromosomes 1, 9, 13, 15, 19, 22, and X chromosome [14, 16, 27]. Although a lot of genomic regions have been explored for etiology, consistent results for a limited number of regions such as 7q11, 7q31, 22q11 have been obtained [16, 28, 29]. Particularly 15q11-q13 region on chromosome 15 has been widely related to autism. It has been suggested that duplications in this region of chromosome 15 may contribute to autism development. There exist in this area a series of potential candidate genes containing gamma aminobutyric acid A (GABAA) receptor gene complex [30]. These duplications inherited maternally have been reported to be present in 1-3% of individuals with idiopathic autism [31, 32].
Another region related to autism is a deletion region located on chromosome 16p11. This region has also been demonstrated to be in relationship with Asperger Syndrome, mental retardation, and developmental abnormalities [33, 34].

It has been showed that, in individuals with autism, there is a significant increase in the frequency of allelic variations of HOXA1 gene (7p15). HOXA1 and HOXB1, which have a critical role for development of fetal caudal medullary structures, are only expressed at the third week following fertilization, a period when neural tube is formed, and they appear to be partly associated with development of superior olivary, facial and abducens nuclei. It has been suggested that HOXA1 has a role in autism tendency and is associated with early phase of brain stem development in autism etiology [16, 35]. On the other hand, there are studies where no significant association with HOXA1 gene variants and autism could be demonstrated [36, 37].

Engrailed-2 (EN-2) which is the human homologue of drosophila engrailed gene and located on the long arm of Chromosome 7 (7q36) is a homeobox gene having a critical role in mid-brain and cerebellar development. Temporal and spatial pattern of engrailed gene expression occurs simultaneously with the development of cerebellar precursor cells. Thus, it has been suggested to be important to determine correct cell number in cerebellum [38]. Petit and his colleagues (1995) reported a significant association between Pvull polymorphism at the 5' region of EN-2 gene and autism [39]. However, this association could not be confirmed in a later family study [40].

MET oncogene coding pleiotropic MET receptor thyrosine kinase is located on the long arm of Chromosome 7. MET signalization has a role in neocortex and cerebellar growth and maturation, and immune functions. MET gene and its ligand, hepatocyte growth factor (HGF), have been related to autism. Studies conducted by Campbell and his colleagues ([41,42] showed that C allele in the promoter region of MET gene decreases MET promoter activity by two fold and decreased MET gene expression is associated with autism tendency.

Another gene on Chromosome 7 is CNTNAP2 (contactin-associated-protein-like 2) gene. CNTNAP2 gene has been associated in various studies with autism, language delay, and epilepsy [43-45].

FOXP2 (forkhead box P2), a forkhead transcription factor gene, is a member of family forkhead known as the key regulators of embryogenesis; it encodes a transcription factor containing polyglutamine and is associated with development of lingual functions. In a study in Chinese society, FOXP2 gene located in the 7q31 region was linked with autism pathogenesis [46]. However, other studies did not replicate these findings [47, 48].

Another gene investigated for autism relationship is Wingless-Int (Wnt2) gene located on the long arm of Chromosome 7 (7q31-33). Wnt genes encode glycoproteins rich in cysteine, which regulate various cellular movements during the embryonic development [49]. It has been shown that Wnt has a role in regulation of activity-dependent dendritic branching in hippocampal pyramidal neurons [50]. Wnt2 gene was linked with autism in a study by Wassink and his colleagues [51].
Reelin is an important extracellular matrix glycoprotein that has an important role in development of neuronal migration, lamination, and connection during embryonic brain development and is associated with a signal pathway forming the basis of neuro-conduction, memory formation, and synaptic plasticity [52]. It is responsible for lamination in embryonic period whereas it has a role in cell signalization and synaptic plasticity in adulthood period [53]. Decrease in reelin expression has been associated with autism. RELN gene, which is located in 7q22 region and encodes reelin protein which is important in neurodevelopment, involves a polymorphic GGC repeat in 5' region. Long GGC alleles of RELN gene cause blunt gene expression; therefore, they are considered to be linked with autism [52]. There are studies reporting a significant relationship between RELN alleles with larger numbers of CGG repeats and autism [52, 54] while there are also negative studies in terms of such a relationship [55]. Besides the genetic complexity in the etiopathogenesis of this disorder, non-replication of the results of different studies should also be taken into consideration.

Neuroligins are cellular adhesion molecules located at the postsynaptic side of the synapse. Neuroligins and neuroxins, neuronal cell surface proteins, form an asymmetrical intercellular connection by adhering to each other. Interaction of neuroligins with beta neuroxins forms functional synapses [56]. Neuroligin family is composed of 5 members, i.e. NLGN1, NLGN2, NLGN3, NLGN4, and NLGN4Y. Although all of the neuroligin family is linked with autism spectrum disorder [57], the most robust evidence comes from NLGN3 (Xq13) and NLGN4 (Xp22.3) genes. Jamain and colleagues [58] found that mutations in NLGN3 and NLGN4, two X-linked neuroligin genes, are associated with autism spectrum disorders [58]. Following this, it has been demonstrated that a 2-base-pair deletion in NLGN4 gene causes premature stop codon in mental-retarded men with or without autism. This finding indicates that NLGN4 gene is not only associated with autism, but also with mental retardation [59]. Since mutations in neuroligin genes impair the functions of synaptic cell adhesion molecules, they are considered to be related with autism and neurodevelopmental defects in mental retardation [60]. Since neuroligins are abundant particularly in excitatory synapses, a defect in synaptogenesis has been suggested to result in derangement in cognitive development and communication [59]. Nonetheless, some other studies revealed negative results [61].

Genetic studies examining the relationship of neuroxins, the connection partners of neuroligins, with autism revealed that a mutation in neuroxin Ib gene results in autism susceptibility [62]. Structural variants of neuroxin I alpha gene have also been linked with autism [63].

Another protein adhering to neuroligins is SHANK3. Some forms of autism are considered to stem from a single gene, and particularly from a rare allele having a major effect. Doctor Joseph Buxbaum has reported that one of these genes is SHANK3 gene located on Chromosome 22 (22q13) which is responsible for 1% of autism and some forms of mental retardation, microcephaly, and delay in expressive language [34]. SHANK proteins are believed to be the primary regulator of postsynaptic density thanks to their ability to form multimeric complexes with postsynaptic receptors, signal molecules, and cellular skeleton proteins found in dendritic spikes. Postsynaptic density is the measurement of how synapses are linked to each other. A mutation in SHANK3 gene has been reported to be related with autism spectrum disorders [64]. Role of various mutations in Neuroligin/neuroxin/SHANK3
A large-scale study by Wang and his colleagues [65] revealed a significant relationship between a single nucleotide polymorphism located in the 5p14.1 region and autism spectrum disorders. The associated single nucleotide polymorphism is located in a region placed between cadherin 10 (CDH 10) and cadherin 9 (CDH 9) genes. CDH 9 and CDH 10 encode type II classic cadherins of the cadherin family, which are transmembrane glycoproteins responsible for calcium-dependent cell-cell adhesion. This finding shows the role of neuronal cellular adhesion molecules in autism pathogenesis [65].

Neurotrophins have many functions such as neuronal survival, target innervation, and synaptogenesis in development of peripheral and central nervous system. Neurotrophins exert their biologic functions by binding to a Trk tyrosine kinase receptor which is a high-affinity receptor. Neurotrophin family has 4 members. These are nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 and neurotrophin-4. BDNF is the most important member of neurotrophin family. BDNF has many roles in neuronal differentiation such as neuronal survival, dendritic and axonal growth/branching, synapse formation, and neuronal plasticity [66, 67]. Various studies have investigated the relationship between BDNF gene and autism. Nishimura and colleagues [68] detected an increase in BDNF expression in autistic individuals. Subsequent studies confirmed the potential role of BDNF gene mutations in autism pathogenesis [69]. A recent study in which serum BDNF levels significantly increased in autistic children found no significant impact of genetic variations of BDNF gene on autism risk; however, a significant relationship between neurotrophic tyrosine kinase receptor type 2 (NTRK2) and autism was reported [70]. A large-scale study on patients diagnosed with autism spectrum disorder and mental retardation without autism diagnoses showed that, when compared to control group, autism spectrum disorders and mental retardation had a significant increase in serum neurotrophin 4 and BDNF (both are Trk B ligands) [71, 72]. On the other hand, no changes were observed in NGF (Trk A ligand) and neurotrophin 3 (Trk C ligand) levels. In light of these findings, it has been suggested that trkB ligands may be overexpressed or secreted in central nervous system of autistic or mental retarded children during infantile period. It has also been suggested that the effect of BDNF and neurotrophin-4 on activity-dependent dendritic growth and branching [66] may be related to early and transient brain development seen in autistic infants [67, 73]. This increase in BDNF expression and/or secretion was suggested to be linked with the role of Metil-CpG-binding protein 2 (MeCP2) gene in BDNF transcription [74]. A mutation in MeCP2 gene encoding a protein functioning as a general transcriptional receptor is responsible for Rett Syndrome. It has been shown that MeCP2 selectively bind to BDNF promoter III and suppresses BDNF gene expression. MeCP2 has an important role in regulation of neuronal activity [75]. It has been suggested that MeCP2 mutations located on Xq28 locus may be a risk factor for autism by affecting BDNF expression and dendritic differentiation in cortex. In a study investigating MeCP2 gene mutation in autistic individuals for that purpose, 2 girls exhibited de novo mutations [67, 76].

Another gene linked with autism is the Fragile X mental retardation 1 (FMR1) gene encoding Fragile X mental retardation protein (FMRP). FMR1 is associated with autism secondary to
Fragile X syndrome [28]. However, fragile X mutations may be found in 7-8% idiopathic autism patients [77]. FMRP is a selective RNA-binding protein; it transports RNAs to dendrites and regulates local translation of synaptic mRNAs as a response to activation of metabotropic glutamate receptors. This protein is considered to have a role in synaptic plasticity and development of synaptic connections between neural cells. Impaired mRNA translation in the absence of FMRP leads to an alteration in protein-synthesis-dependent plasticity [28, 78].

Autism risk is higher than general population in neurofibromatosis, tuberosclerosis, or Cowden Syndrome, a rare syndrome which is characterized by multiple tumor-like growths called hamartomas and affects the intellectual abilities. These diseases develop due to dominant mutations in tumor suppressor genes NF1, TSC1/TSC2, and PTEN. Mutations in these autism-associated genes affect synaptic protein level by impairing cellular translation. Alterations in protein level results in abnormal synaptic functions [28].

Angelman syndrome and Prader-Willi syndrome mainly develop due to genetic deletions in 15q11-q13 locus or disomy (condition where two copies of a chromosome comes from a single parent) belonging to a single parent [79]. Deficiencies in paternal genes cause Prader-Willi syndrome; Angelman Syndrome which is more commonly associated with autism may be caused by deletion or mutation in maternal ubiquitin protein ligase gene UBE3A or ATP10C [80, 81]. Other rare single gene defects associated with autism are found in Williams Syndrome, Sotos Syndrome, hipomelanozis Ito, and Moebius Syndrome [82-85].

Since serotonin reuptake inhibitors have favourable effects on rituals and routines in autistic individuals and serotonin transporter gene has important role in serotonergic neurotransmission, serotonin transport gene has been investigated as candidate gene in autism. One of the polymorphisms examined in this gene is the one that is formed by long (L) and short (S) alleles owing to different number of insertion/deletion repeats of a 44-base-pair sequence in the transcriptional control region. Cook and his colleagues [86] reported a significant relationship between autism and short allele while Klauck and his colleagues [87] revealed a significant relationship between autism and long allele. A subsequent study did not duplicate these findings [88]. A different polymorphism investigated at the serotonin transport gene is the variable number of tandem repeats (VNTR) polymorphism due to repeat of a 17-base-pair region at 2nd intron of the gene 9,10, and 12 times. This polymorphism could not be related to autism [89]. Evidence has been accumulated on the relationship of many serotonin genes, notably serotonin receptor (HTR) 1B, HTR2A, HTR3A, and HTR5A, with autism [90-93].

Glutamate is the main excitatory neurotransmitter associated with cognitive functions such as memory and learning. Autism has been hypothesized as a hypoglutamatergic disorder by virtue of neuroanatomic studies and the similarities glutamate antagonists generate in healthy persons [94]. It has been demonstrated in genome scanning studies that one of the candidate regions for autism is 6q21 region [95]. This region contains glutamate receptor 6 (GluR6) gene. A study by Jamain and his colleagues [96] found a significant relationship between GluR6 gene and autism. It has been thought that GluR6 dysfunction may contribute the deterioration of communication and learning process in autism and any dysregulation of GluR expression may be related to an increase in the rate of epileptic disorder in autistic
children [96]. Other glutamatergic receptor genes associated with autism are metabotropic GluR8 and GRIN2A (glutamate receptor, ionotropic, N-methyl-D-aspartate 2A) [97, 98].

Gama aminobutyric acid (GABA) is the major inhibitor neurotransmitter in the brain. GABA\(_A\) receptors are formed by different homologous subunits. Among GABA receptor subunit genes, GABRA4 with 4p12 location has been shown to play a role in etiology of autism and increases autism risk by interaction with GABRB1 [99]. Other genes associated with autism in some other studies are GABRG3, GABRA5, GABRB3 located on 15q11-q13, and GABRA2 located on 4p [100-102]. Contrary to these findings, there are other studies with negative results in terms of the relationship between GABA receptor genes and autism in various ethnic groups [103].

Proenkephalin, prodinorphine of opioid metabolism; tyrosine hydroxylase, dopamin beta hydroxylase (DBH), D2, D3, and D5 dopamin receptors, monoaminooxidase A (MAOA) and B genes of monoaminergic system have no major role in etiology of autism shown in studies [104, 105]. However, a recent study revealed a significant relationship between MAOA gene and autism [106].

Mutations detected in autism in conjunction with all other genetic factors explored so far have been reported to explain no more than 20% of cases with autism spectrum disorder. Thus, a gene-dosage model has been proposed according to which the susceptibility for autism is determined by the sum of effects of threshold genetic and non-genetic factors [107, 108]. For autism etiology, it has been suggested that the detected chromosomal abnormalities in combination with other undetected loci cause autism. It has been considered that the inconsistencies between the results of the studies aimed to determine the role of genetic factors may be the product of genetic heterogeneity, clinical heterogeneity, and sample size and ethnic differences among different studies [109].

3. Environmental risk factors

In addition to effects of a number of genes of small effect, various environmental factors are believed to be responsible for susceptibility to autism. Development of autism seems to be dependent on interaction of susceptibility genes with each other and with the environment [110]. It has been claimed that among environmental factors related to autism are toxins (environment-polluting matters, insecticides, thimerosal in vaccines, lead), viruses (prenatal exposure to influenza, rubella, and cytomegalovirus infections), and premature birth with premature retinopathy [111-115]. Although there has been a debate regarding the relationship of autism with thimerosal in measles, rubella, and mumps vaccines; further careful evaluation of data could not support the relationship between autism and vaccines [116, 117]. The relationship between exposure to Rh immune globulin, which contained the preservative thimerosal until 2001 in the United States, and autism has also been investigated; however, no significant association has been revealed between exposure of antepartum RhIg preserved with thimerosal and an increase in risk of autistic disorder. The latter findings are in accordance with the consensus that exposure to ethymercury in thimerosal is not the cause of increased prevalence of autism [118].
Other factors related to intrauterine environment are maternal hypothyroxinemia [119], maternal influenza [120], and high levels of sex hormone exposure related to infertility treatment [121]. Thalidomide and anticonvulsant exposure in pregnancy is correlated to an increase in autism risk [122, 123]. Rasalam and his colleagues [124] showed that 8.9% of children exposed to sodium valproate in intrauterine life later develop autistic spectrum disorders such as autism or Asperger syndrome. Recently, Hadjikhani [125] have suggested that serotonin reuptake inhibitor use in pregnancy increases autism risk by causing hyperserotoninemia and indirectly affecting amygdala and oxytocin levels.

In many studies, the pre-perinatal complication rates in autistic disorder have been studied and a higher pregnancy-related complication rate has been demonstrated in autistic children [126, 127]. In a recent meta-analysis [128], the most strong risk factors for autism were advanced maternal and paternal age, maternal gestational hemorrhage, gestational diabetes, maternal prenatal drug use (particularly psychoactive drugs), and birth in a foreign country following immigration of mother. Both advanced maternal and paternal age are associated with autism. The underlying mechanism is unclear. Maternal age may be related to autism due to increased risk of chromosomal abnormalities in ova of increased age or because of unstable trinucleotide repeats [128]. The relationship between paternal age and autism is considered to result from imprinted genes (genes showing different expression patterns depending on the parent it originates), de novo spontaneous mutations that accumulate with advancing age in spermatagonia, or confounder effects of sociocultural environmental factors [129]. Another potential risk factor for autism is maternal birth abroad [130]. It has been suggested that this factor may result from absence of immunization that mother would develop against widespread infectious agents of the country in which she gives birth. Another possible explanation is about the potential role of maternal stress because of immigration [131]. A more detailed investigation on the relationship between mother immigration and autism is needed. It has been demonstrated in some studies that gestational hemorrhage increases autism risk by causing fetal hypoxia [130]. Among other factors considered to cause hypoxia and associated with increased autism risk in some studies are fetal distress, maternal hypertension, prolonged labor, cord complications, low Apgar score, and cesarean section [132]. Gestational diabetes is another risk factor, with unknown biologic mechanism [128].

Some studies demonstrated that prenatal stress increases autism risk [133, 134]. However, due to limitations that these studies are based on retrospective expressions of mothers and these mothers are generally susceptible for experiencing stressful life events outside pregnancy period, these studies need to be supported by further studies. Spontaneous abortions, pre-perinatal complications, congenital anomalies, and neurologic/immunologic abnormalities are among the negative impacts of prenatal stress. Prenatal stress also has various negative effects on brain development such as a delay in myelinization, an increase in sensitivity of amygdala to glucocorticoids, and abnormal development in dopaminergic system [135-137]. Autistic disorder is associated with a functional derangement in brain areas related to social cognitive functions in which amygdala and orbitofrontal cortex plays an important role. Orbitofrontal cortex is susceptible to effects of prenatal stress especially in the middle of gestation. Normal functioning of orbitofrontal cortex - amygdala axis is very im-
Portant for social cognitive function. Therefore, it has been suggested that damage in orbito-frontal region may cause main deficits in autism that underlies inadequate responses to other people’s mental status and that impairs self-organization of social-emotional behaviours [137, 138]. Prenatal stress may impair brain development by many mechanisms including: a) fetal hypoxia due to reducing of uterine and placental circulation, b) impairment of hypothalamus-hypophysis-adrenal axis by stimulation of secretion of maternal stress hormones that can cross placenta, c) generation of pregnancy and birth complications, d) epigenetic effects on expression of stress response-related genes [137].

It has been reported that exposure of environmental stress factors at 21-32nd weeks with a prominent peak at 25-28th weeks is associated with an increase in possibility of development of autism [134]. When data regarding progressively worsening developmental process are considered [139], it has been argued that postnatal environmental exposures in genetically susceptible children may be etiologically important [140]. Expression and the impact of many genes is influenced by environmental factors. Thus, the effect of environmental factors in etiology of autism is believed to be indirect by influencing genetic functions [140, 141].

4. Conclusion

In line with studies aimed to understand the neurobiology of autism, the presence of alterations in regional brain anatomy and functional neuronal communicative network has been currently proved. The main role among factors underlying abnormal brain development belongs to genetic factors. Evidence regarding that autism is a primarily genetic disorder is progressively increasing. Although environmental factors alone can explain a few cases, they are believed to increase autism risk by interacting with genetic susceptibility. Although data collected so far contribute to the ever-increasing body of knowledge about neurobiology of autism, they do not influence diagnosis and treatment of autism. Use of these data is aimed in future in differentiation of autism from other neurodevelopmental disorders and in diagnostic and therapeutic processes.

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