Genetic and molecular biology of autism spectrum disorder among Middle East population: a review

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Abstract

Background: Autism spectrum disorder (ASD) is a neurodevelopmental disease, characterized by impaired social communication, executive dysfunction, and abnormal perceptual processing. It is more frequent among males. All of these clinical manifestations are associated with atypical neural development. Various genetic and environmental risk factors are involved in the etiology of autism. Genetic assessment is essential for the early detection and intervention which can improve social communications and reduce abnormal behaviors. Although, there is a noticeable ASD incidence in Middle East countries, there is still a lack of knowledge about the genetic and molecular biology of ASD among this population to introduce efficient diagnostic and prognostic methods.

Main body: In the present review, we have summarized all of the genes which have been associated with ASD progression among Middle East population. We have also categorized the reported genes based on their cell and molecular functions.

Conclusions: This review clarifies the genetic and molecular biology of ASD among Middle East population and paves the way of introducing an efficient population based panel of genetic markers for the early detection and management of ASD in Middle East countries.

Keywords: Autism, Genetic, Risk factor, Diagnosis, Prognosis, Middle East

Background

Autism spectrum disorder (ASD) is a neurodevelopmental disease with disrupted social and emotional communication, learning problems, anxiety, epilepsy, language defect, and restrictive behaviors [1, 2]. All of these clinical manifestations can be related to the reduced size of cells in the hippocampus and limbic system and elevated number prefrontal cortex neurons [3]. ASD patients have also unusual temporal and frontal lobe development and less amygdala volume and gray matter in MRI results which indicated limited brain development in these patients [4]. The prevalence of ASD is approximately 2.47%, 0.06%, and 0.36% in the USA, Iran, and Asia, respectively [1, 5]. The range of ASD prevalence has been reported between 0.14 and 2.9 percentages in Persian gulf populations [6]. Various genetic and environmental factors are involved in ASD progression. Maternal fever and infections, zinc deficiency, folate prenatal intake, and air pollution are among the important environmental risk factors of ASD [7]. The high maternal and paternal age and mitochondrial dysfunction are also the risk factors of ASD [8, 9]. About 800 genes involved in synapse function, chromatin modification, and cortical development are associated with autism.
[10]. NL3, HOXA1, ANK2 MECP2, and ITGB3 mutations were associated with brain morphology and function. CNTNAP2 has a key role in enhanced frontal lobe connectivity and activation of AKT/mTOR pathway [1]. Moreover, 10% of all ASD cases are related with other genetic disorders such as fragile X, Noonan, and Rett syndromes [11]. Single nucleotide polymorphisms (SNP), copy number variations, and epigenetic modifications are the most frequent genetic alterations in ASD patients [12, 13]. The most significant susceptibility locus associated with ASD is located on chromosome 7, especially 7q31, which includes FOXP2, RAY1/ST7, and IMMP2L genes [14]. Moreover, epigenetic deregulations such as DNA methylation and histone modification have pivotal role during ASD progression [11]. Since the recurrence rate of ASD is higher in families with one affected child, genetic counseling plays an important role in prevention of other affected child birth. Early diagnosis can also improve the quality of life in ASD children. Because of heterogeneity of ASD, whole exome sequencing, ASD/ID panel, and chromosomal microarray analysis have been suggested for ASD diagnosis [9]. Behavioral therapy techniques such as peer feedback and video modeling are suggested to improve the quality of life and learning and social relationship in these patients [15]. Psychiatrists routinely use medications such as anticonvulsants, alpha-2 agonists, antidepressants, and antipsychotics for treatment of patients with autism spectrum [16]. Regarding the rising trend of ASD incidences in Middle East countries, it is required to assess the molecular biology of ASD in this area. In present review, we have summarized all of the significant genetic variations associated with ASD in Middle East population for the first time in the world (Fig. 1, Table 1). PubMed, Scopus, Embase, and Web of Science were used for the data collection. The search strategy in PubMed was based on MeSH: “Autism Spectrum Disorder and Genetic” in Middle East countries until the November of 2020. This review clarifies the genetic and molecular biology of ASD and paves the way of introducing a population-based panel of genetic markers for the early detection and better management of ASD among Middle Eastern population.

Receptors and neurotransmitters

Dopamine D3 receptor (DRD3) is localized in limbic areas and cortical brain, which are involved in locomotion and emotional and cognitive processes, as well as endocrine functions. The rs6280 (C>T) SNP of the first DRD3 exon results in a serine to glycine substitution (ser9Gly) in mental disorder [58]. The glycine allele carriers in hypercortisolemia cases might be more susceptible for developing hyperdopaminergic responses to stress [59]. It has been reported that the Ser9Gly (rs6280) Gly allele or Gly/Gly, Ser/Gly genotypes had significantly better responses to antipsychotics like risperidone in Iranian autistic patients [17]. Glutamate metabotropic receptor 7 (GRM7) is a G-protein coupled glutamate receptor which has spatiotemporal expression in the cerebral cortex, cerebellum, and hippocampus [18]. The rs779867 (T> G) is an intronic polymorphism of GRM7 that is significantly associated with ASD in Chinese children [60]. Another study has demonstrated a correlation between rs779867 polymorphism and ASD in Iranian patients. The rs779867 G/G genotype and G allele were significantly more frequent in ASD patients compared to control group [18]. HTR2A encodes

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**Fig. 1** All of the genetic aberrations involved in ASD progression among Middle East population. Blue, green, and black colors refer to the aberrant expression, promoter methylation, and polymorphisms, respectively.

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Rahmani et al. Human Genomics (2021) 15:17
| Study | Year | Gene | Country | Population | Results |
|-------|------|------|---------|------------|---------|
| Reception and neurotransmitters | 2017 | DRD3 | Iran | 56 patients, 56 controls | Polymorphisms were correlated with response to risperidone in autism patients. |
| Noroozi et al. [18] | 2016 | GRM7 | Iran | 518 patients, 472 controls | Polymorphisms were correlated with the risk of ASD. |
| Elhawary et al. [19] | 2019 | HTR2A, HTR2C, SLC6A4, BDNF | Saudi Arabia | 110 patients, 102 controls | Polymorphisms were correlated with sex in ASD. HTR2C and BDNF polymorphisms were correlated with severity. |
| Sener et al. [20] | 2016 | CC2D1A, HTR1A | Turkey | 44 patients, 27 controls | Expression was associated with ASD patients. |
| Hamza et al. [21] | 2016 | GABRB3 | Iraq | 40 patients, 25 controls | Polymorphisms were correlated with sex in ASD. |
| Hosseinpour et al. [22] | 2017 | NRP2 | Iran | 50 patients, 70 controls | Polymorphisms were correlated with the risk of ASD. |
| Yuksel et al. [23] | 2016 | OXTR | Turkey | 27 patients, 39 controls | OXTR promoter methylation was associated with ASD patients. |
| Ocakoglu et al. [24] | 2018 | OXTR | Turkey | 100 patients, 90 controls | Polymorphisms were correlated with severity of autism spectrum disorder. |
| Salem et al. [25] | 2013 | MAOB | Egypt | 53 patients, 30 controls | Polymorphisms were correlated with sex in ASD. |

| Synaptic/neuronal activity | 2018 | CYFIP1/2 | Iran | 30 patients, 41 controls | Expression was associated with ASD patients. |
| Safari et al. [27] | 2017 | SNAP25 | Iran | 472 patients, 524 controls | Polymorphisms were correlated with the risk of ASD. |
| Zare et al. [28] | 2017 | CNTNAP2 | Iran | 200 patients, 260 controls | Polymorphisms were correlated with the risk of ASD. |
| Firouzabadi et al. [29] | 2016 | ACE | Iran | 120 patients, 120 controls | Polymorphisms were correlated with the risk of ASD. |
| Ghafouri-Fard et al. [30] | 2020 | BDNF, BACE1, BDNF-AS, BACE1-AS | Iran | 50 patients, 50 controls | Expression was associated with ASD. BACE1-AS and BDNF expression were correlated with age in female participants. |

| Inflammatory factors | 2018 | TNF-α, IL-6, IL-17, and IL-2 | Iran | 30 patients, 41 controls | Polymorphisms were correlated with autism. |
| Fallah et al. [32] | 2020 | IFNG, IFNG-AS1 | Iran | 50 patients, 50 controls | Expression was associated with ASD patients. |
| Safari et al. [33] | 2020 | HOTAIR | Iran | 427 patients, 430 controls | Polymorphisms were correlated with the risk of ASD. |
| Safari et al. [34] | 2017 | FOXP3 | Iran | 523 patients, 472 controls | Polymorphisms were correlated with the risk of ASD. |
| Mostafa et al. [35] | 2012 | HLA-DRB1 | Egypt | 100 patients, 100 controls | Polymorphisms were correlated with sex in ASD. |

| Amino acid metabolism | 2017 | MTRR | Iran | 142 patients, 214 controls | Polymorphism was correlated with risk of autism. |
| Haghiri et al. [37] | 2016 | MTR | Iran | 108 patients, 130 controls | Polymorphism was correlated with increased risk of autism. |
| Jabbar et al. [38] | 2018 | MTR | Iraq | 70 patients, 30 controls | Polymorphisms were correlated with sex in ASD. |
| Behiry [39] | 2017 | CBS | Egypt | 40 patients, 40 controls | Polymorphisms were correlated with ASD. |
serotonin receptor 5-HT2A that can be epigenetically regulated through DNA methylation and regulate fetal brain development and adult cognitive function. HTR2A SNPs are associated with a number of psychiatric disorders [61]. HTR2A rs7997012 A > G intronic SNP is correlated with social adjustment in depressed [62]. The HTR2C is a G protein-coupled receptor (GPCR) that responds to signaling through the serotonin. The serotonin transporter encoded by SLC6A4 transports the serotonin from synaptic spaces into presynaptic neurons. Functional SLC6A4 rs3813034 (G2563T) polymorphism is located in the miR-16–binding site and affects the SLC6A4 expression and function. It has been reported that there were significant associations between SLC6A4 rs3813034, HTR2A rs7997012, BDNF rs6265, and HTR2C rs6318 polymorphisms and autism susceptibility among a subpopulation of Saudi subjects. Heterozygosity was significantly associated with the risk of ASD for the HTR2C rs6318 and SLC6A4 rs3813034 variants. The HTR2C rs6318 and BDNF rs6265 SNPs were correlated with autism. HTR2A rs7997012 A > G intronic SNP is correlated with social adjustment in depressed [62]. The

| Study                | Year | Gene | Country | Population | Results                                                                 |
|---------------------|------|------|---------|------------|-------------------------------------------------------------------------|
| Taheri et al. [40]  | 2019 | MOCOS| Iran    | 406 patients | 411 controls Polymorphisms were correlated with the risk of ASD.         |
| Mobasheri et al. [41]| 2019 | VDR  | Iran    | 81 patients  | 108 controls Polymorphism was correlated with reduced risk of autism.    |
| Coskun et al. [42]  | 2016 | VDR  | Turkey  | 237 patients | 243 controls Polymorphisms were correlated with ASD.                     |
| Sayad et al. [43]   | 2017 | RORA | Iran    | 518 patients | 472 controls Polymorphisms were correlated with autism risk in dominant inheritance model. |
| Emamalizadeh et al. [44]| 2017| RIT2 | Iran    | 470 patients | 470 controls Polymorphisms were correlated with the risk of ASD.         |
| Hamedani et al. [45]| 2017 | RIT2 | Iran    | 532 patients | 472 controls Polymorphisms were correlated with the risk of ASD.         |
| Noroozi et al. [46] | 2017 | VMAT1| Iran    | 495 patients | 484 controls Polymorphism was correlated with autism.                    |
| Kamal et al. [47]   | 2015 | DRD4 | Egypt   | 178 patients | 128 controls Polymorphisms were correlated with ASD.                     |
| Azzam et al. [48]   | 2018 | SLC6A3| Egypt   | 50 patients  | 50 controls SLC6A3 polymorphisms were correlated with mother’s age. DRD1 polymorphisms were correlated with age in ASD. |
| El-Tarras et al. [49]| 2012| SLC6A3| Saudi Arabia| 50 patients | 50 controls Polymorphisms were correlated with sex in ASD. |
| Meguid [50]         | 2015 | MTHFR| Egypt   | 24 patients  | 20 of their mothers. 30 control and 42 healthy control mothers. MTHFR polymorphisms were correlated with ASD and higher in autism children mothers. |
| El-Baz et al. [51]  | 2017 | MTHFR| Egypt   | 31 patients  | 39 controls Polymorphisms were correlated with sex in ASD.              |
| Shawky et al. [52]  | 2014 | MTHFR| Egypt   | 20 patients  | 20 controls Polymorphisms were correlated with sex in ASD.              |
| Arab and Elhawary [53]| 2019| MTHFR| Saudi Arabia| 112 patients | 104 controls Polymorphisms were correlated with sex in ASD.             |
| Muftri et al. [54]  | 2020 | MTHFR| Iraq    | 38 patients  | 22 controls Polymorphisms were correlated with sex in ASD.              |
| Beiranvandi et al. [55]| 2020| EN2  | Iran    | 67 patients  | 100 controls Polymorphisms were correlated with the risk of ASD.       |
| Eftekharian et al. [56]| 2018| PIAS | Iran    | 30 patients  | 41 controls Expression was associated with age in ASD patients.         |
| Dasdemir et al. [57]| 2016 | XRCC4| Turkey  | 100 patients | 96 controls Polymorphisms were correlated with ASD.                     |
significantly correlated with severe cases. There were significant associations between HTR2A rs7997012 and rs6265A variants of BDNF and ASD [19]. Coiled-coil and C2 domain containing 1A (CC2D1A) regulates 5-hydroxytryptamine receptor 1A (HTR1A) expression in neuronal cells via binding to 14-bp 5′-repressor element upstream of the promoter of HTR1A [63]. Mutations in the CC2D1A signaling results in non-syndromic intellectual disability, ASD, and seizures [64]. It has been shown that there was a significant inverse association between CC2D1A and HTR1A gene expressions in blood sample of ASD patients compared to control subjects among a group of Turkish patients [20]. Gamma-aminobutyric acid receptor subunit beta-3 (GABRB3) is involved in pathogenesis of some diseases such as Angelman syndrome, Prader-Willi syndrome, epilepsy, and autism [65]. It has been reported that the GABRB3 gene polymorphism was significantly associated with autism among Iraqi patients [21]. Neurexins (NRPs) are non-tyrosine kinase cell surface glycoproteins which function in various types of signaling pathways. NRPs identified as coreceptors for vascular endothelial growth factor (VEGF) and class III semaphorins. Many physiological processes such as cardiovascular, neuronal development, angiogenesis, and lymphangiogenesis are associated with neurexin glycoproteins [66]. It has been suggested that the rs849563 (T>G) polymorphism located at exon 10 of neurexin-2 can be as risk factor for ASD among Iranian patients [22]. The OXTR is a GPCR of oxytocin that activates a set of signaling cascades, including the MAPK, PKC, PLC, or CaMK pathways [67]. OXTR and the oxytocin signaling pathway have important roles in the etiology of autism [68]. It has been reported that there was a high frequency of OXTR promoter hypomethylation in ASD compared with healthy control in a sample of Turkish autistic children [23]. Another study also reported a significant correlation between OXTR rs237902 polymorphism and severity of autism in a subpopulation of Turkish subjects. The GA and AA genotype (GA/AA) carriers of rs237902 had more severe pathological symptoms compared with GG genotype carriers in males [24]. MAOB belonged to the monoamine oxidases involved in dopamine and serotonin oxidation. It is located in the mitochondrial outer membrane which has critical roles in neuroactive and vasoactive amine metabolisms in peripheral tissues and central nervous system [69]. It has been observed that there was a correlation between MAOB rs1799836 and autism among a group of Egyptian cases in which the G allele frequency was significantly more frequent in patients compared with healthy controls. Plasma MAOB activity was also significantly reduced in males with G allele compared with A allele carriers [25].

**Synaptic/neuronal activity**

Cytoplasmic FMR1-interacting proteins 1/2 (CYFIP1/ CYFIP2) are components of the WAVE regulatory complex (WRC) which are critical regulators of actin polymerization that is involved in spinal morphology and presynaptic activity. CYFIP1/CYFIP2 abnormalities have been observed in neurodevelopmental disorders [70, 71]. There were significant CYFIP1/2 upregulations in autism patients compared with healthy subjects among a subpopulation of Iranian patients. These genes might be potential biomarkers for ASD diagnosis [26]. Synaptosomal-associated protein 25 (SNAP-25) has an important role in nerve terminal plasticity [27]. The rs3746544 G>A is located in the 3′-untranslated region (3′-UTR) of SNAP-25 associated with attention-deficit hyperactivity disorder [72]. It has been found that there was a correlation between the rs3746544 SNAP25 and ASD patients in a sample of Iranian cases [27]. Contactin-associated protein 2 (CNTNAP2) as a member of the neurexin superfamily is a presynaptic cell adhesion protein involved in neuron connections at synapses. It is mainly expressed in the brain and spinal cord. CNTNAP2 can be a genetic risk factor of ASD and related neurodevelopmental disorders [73]. It has been observed that rs7794745 CNTNAP2 was correlated with ASD susceptibility in Iranian population [28]. Angiotensin-converting enzyme (ACE) is an enzyme involved in regulation of blood pressure through conversion of the inactive angiotensin I to the active peptide angiotensin II. Angiotensin II has a pivotal role in blood pressure regulation and fluid-electrolyte balance [74]. ACE has an important function in neurokinin de-generation which is a family of neurotransmitters involved in regulation of behavior and memory [29]. It has been reported that the rs4343, rs4291, and also ACE I/D polymorphism affected the activity of this enzyme and the level of Ang II [75, 76]. The rs4343 (G > A) ACE polymorphism is involved in hypertension, left ventricular hypertrophy, migraine, and coronary artery diseases [77]. Insertion/deletion (I/D) ACE polymorphism was associated with cardiovascular disease in which the D allele increased risk of cardiovascular disease. I/D polymorphism were also linked with blood pressure [78]. It has been reported that the ACE genetic variants were associated with autism in a group of Iranian subjects in which G allele of rs4343 was associated with ASD risk. Both DD genotype of ACE I/D and the D allele were also significantly correlated with ASD. Moreover, there was an association between rs4291 and autism among Iranian autistic patients [29]. The BACE1 is a transmembrane protease involved in amyloid precursor protein (APP) cleavage which is a regulator of synapse formation. Amyloid beta peptides constitute the amyloid beta plaques in Alzheimer’s disease (AD) pathogenesis [79, 80].
The neurotrophin brain-derived neurotrophic factor (BDNF) belongs to the nerve growth factor family that functions in development and maintenance of normal brain. It controls the survival and maturation of neurons through tropomyosin receptor kinase B (TrkB) activation. BDNF–TrkB binding triggers the PI3K/AKT signaling pathway that affects various phases of synaptic development. It has been reported that there was an association between BDNF and pathogenesis of psychiatric disorders [81]. The BDNF, BACE1, and their antisenses were significantly upregulated in Iranian autistic patients compared with matched healthy subjects. Therefore, the BDNF, BACE1, and their antisenses may have role in the pathogenesis of ASD and might be as putative markers for ASD [30]. The PI3K/AKT is reported as a critical pathway in regulation of polarity acquisition and axon branching. It is also involved in regulation of nerve cell migration to the cortical plate [82]. PTEN is a negative regulator of PI3K/AKT pathway through PI3K suppression that can also be regulated by various factors. WWP1 is an E3 ubiquitin-protein ligase involved in de-activation of PTEN that results in activation of PI3K/AKT signaling pathway. It has been observed that there was a correlation between the WWP1 germline variations and normocephalic ASD [12]. Therefore, it seems that the PI3K/AKT signaling has a pivotal role during ASD progression via aberrant WWP1/PTEN and BDNF/TrkB axis [12, 30].

**Inflammatory factors**

Tumor necrosis factor (TNF-α) is an inflammatory cytokine produced by macrophages and monocytes. It binds to its receptors during acute inflammation to mediate cell proliferation, differentiation, and apoptosis [78]. IL-6 is produced in response to infectious lesion leading to inflammatory response, hematopoiesis, and immune reactions. IL-6 also functions in the maturation of B cells [83]. IL-17 is secreted by CD4 Th17 and CD8 Tc17 cells to induce G-CSF, CXCL1, and CXCL2 productions [84]. IL-2 is a critical cytokine for proliferation of T and B lymphocytes. It has been observed that there were significant increased levels of TNF-α, IL-6, and IL-17 and decrease levels of IL-2 in ASD patients compared with healthy subjects among a subpopulation of Iranian autism patients [31]. Th17 cells are proinflammatory cells that involve in immunity against several extracellular pathogens. They require IL-6, TGF-β, and IL-21 for their differentiation [85]. Regulatory T cells (Tregs) and suppressor T cells belonged to a distinct T cell subset that regulates immune response. CD4, FOXP3, and CD25 are biomarkers of Tregs [86]. Interferon-γ is a soluble cytokine that functions in the immune response. It is a predominant inducer of indoleamine dioxygenase (IDO) that converts tryptophan to kynurenine in kynurenine pathway [87]. IFNG-ASI plays an important role in regulation of IFNG expression in human CD4+ T cells [88]. It has been shown that there was significant IFNG up-regulation and IFNG-ASI downregulation in Iranian children with ASD compared with controls. The male autism children had also higher levels of IFNG expression compared with healthy subjects. Moreover, there was a significant direct association between IFNG-ASI expression level and age in ASD group [32]. The HOTAIR is a lncRNA associated with immune responses through downregulation of the NF-κB-related cytokines in macrophages [89]. The rs12826786 C>T as functional polymorphism is located in the promoter region of HOTAIR that is associated with breast cancer among Turkish patient [90]. It has been demonstrated that there was a significant association between rs12826786 in HOTAIR and risk of ASD in Iranian children autism patients [33]. FOXP3 is a pivotal regulator of T reg cell development and function [91]. The rs2233265 polymorphism in the promoter sequence of FOXP3 is associated with multiple sclerosis [92], acute coronary syndrome [91], and recurrent spontaneous abortion [93]. It has been observed that there was a significant association between FOXP3 rs2233265-G allele and ASD risk among Iranian subjects [34]. HLA-DRB1 belongs to HC class II that plays a critical role in the immune system. It has been reported that there were significant associations between HLA-DRB1*03 and HLA-DRB1*11 variants and autism among Saudi cases [35].

**Amino acid metabolism**

Methionine synthase reductase (MTRR) is a family of electron transferases and plays a role in folate-dependent homocysteine/methionine metabolism which regenerate methionine synthase (MTR) to active form. Other enzymes of the homocysteine metabolic pathway are Methylene tetrahydrofolate Reductase (MTHFR) and Thymidylate Synthase (TS). MTRR is involved in reduction of MTR-cob (II) alamin to MTR-cob (I) alamin, and transform 5-methyltetrahydrofolate to tetrahydrofolate [94, 95]. The MTRR 66A > G (rs1801394) polymorphism changes an isoleucine into a methionine (Ile22Met) leading to the reduced enzyme activity [96]. It has been found that the rs1801394 was a risk factor in some cancers [36]. Association between rs1801394 and drug response has been also reported in some disease such as rheumatoid arthritis [97] and childhood acute lymphoblastic leukemia [98]. It has been demonstrated that there was a correlation between MTRR A66G polymorphism and autism in a sub population of Iranian patients. GG was higher in autistic children than controls. The result showed that the G allele might increase risk of autism [36]. Methionine synthase is involved in methyl transfer from N5-methyl-5,6,7,8-tetrahydrofolate to
l-homocysteine in the final step of methionine regeneration [99]. The MTR A2756G (rs1805087) polymorphism changes an aspartic acid to glycine (D919G) that results in reduced enzyme activity. There was a correlation between rs1805087 SNP and DNMTI methylation levels in cancer cells [100]. Double heterozygosity for MTR 2756 AG/MTRR 66 AG was a significant risk factor of Down syndrome [101]. It has been shown that there was a significant correlation between G allele of MTR A2756G polymorphism and elevated ASD susceptibility in Northern Iranian population. It could be used as a useful molecular biomarker to predict genetic susceptibility for autism among Northern Iranian patients. The GG was more frequent in autistic children than controls [37]. Another study has shown that there was significant correlation between G allele of MTR A2756G and increased ASD risk in Iraqi patients [38]. Cystathionine beta synthase (CBS) regulates the homocysteine metabolism through homocysteine to cystathionine [99]. There has also a critical role in H2S biosynthesis which contributes to several process such as cellular energetics, DNA methylation, and protein modification [102]. There was a correlation between CBS (C699T) polymorphism and autism in which the T allele was significantly more frequent among Egyptian autism cases compared with controls [39]. The rs594445 C>A polymorphism in MOCOS, His703Asn, might modify enzyme activity that lead to reduce metabolic capacity of xanthine dehydrogenase (XDH) and aldehyde oxidase 1 (AOX1) that are important for purine metabolism. MOCOS activate XDH and AOX1 by sulfurating the molybdenum cofactor [103]. It has been reported that the A allele of rs594445 polymorphism in MOCOS was markedly associated with risk of autism in Iranian ASD cases compared with controls [40].

Nuclear receptors and GTPases
Vitamin D is a steroid hormone that modulates expression of various target genes via the vitamin D receptor (VDR) during neural development and antioxidant mechanisms [104]. Vitamin D3 deficiency during pregnancy and early childhood might be a risk factor for the progression of childhood autism [105]. Genetic polymorphism in VDR can be associated with ASD symptoms by influencing the vitamin D3 metabolism [105]. TaqI (rs731236, T>C) polymorphism as a silent mutation alters the VDR protein structure [106]. VDR TaqI polymorphisms were identified in some diseases such as renal diseases, cancer, nephrolithiasis, and diabetes [105]. It has been found that TaqI (rs731236) variants can be the protective risk factors of ASD occurrence in children among Iranian subjects [41]. FokI, TaqI, and BsmI variants were also significantly associated with ASD in a sample of Turkish subjects [42]. The retinoic acid-related orphan receptors alpha (RORA) is a member of the NR1 nuclear receptors which are ligand-dependent transcription factors. RORA is involved in immunity, differentiation, and embryogenesis. There are associations between RORα expression and many cancers such as colorectal and breast carcinoma [107]. The RORA (rs4774388 C>T) is a functional polymorphism located in chromosome 15. It has been reported that there was a correlation between rs4774388 SNP and IFN-β response in multiple sclerosis patients [108]. There was also an association between rs4774388 SNP and susceptibility to bipolar disorder [108]. It has been shown that there was a correlation between T allele of RORA rs4774388 and ASD patients in a subpopulation of Iranian patients. The rs4774388-TT genotype was also significantly more frequent in patients compared with controls which contributed with autism risk in dominant state [43]. RIT2 belongs to the RAS superfamily of small GTPases involved in many important cellular pathways. The rs16976358 T>C RIT2 polymorphism is associated with RIT2 expression and function in autism, schizophrenia, and bipolar disorder [44]. It has been reported that the rs16976358 variant can be a risk factor of ASD among Iranian patients. Higher frequencies of rs16976358-C allele have been detected in healthy control compared with ASD. The rs16976358 CC and rs4130047 CC genotypes were also associated with ASD in recessive inheritance model. Moreover, the C/T haplotype block (rs16976358/ rs4130047) was correlated with ASD [45].

Transporters
Vesicular monoamine transporter 1 (VMAT1) is an integral membrane protein in synaptic vesicles, which serves to accumulate cytosolic monoamines into synaptic vesicles. It is a target of reserpine and tetrabenazine [109]. There is a correlation between rs1390938 G/A (Thr136Ile) polymorphism and presynaptic transport of monoamines [110]. Moreover, it is associated with anxiety, affective, and alcohol addiction disorders [110]. It has been demonstrated that the rs1390938 G/A genotypes of VMAT1 polymorphisms were significantly correlated with ASD risk in the Iranian population. The rs1390938-G allele was significantly more frequent in ASD compared with healthy control, and AA genotype was protective in dominant and recessive models. Moreover, the CATT and CATG haplotypes (rs2270637, rs1390938, rs2279709, and rs2270641 respectively) were protective against ASD [46]. The human dopamine receptor D4 (DRD4) gene is located on 11p15.5 chromosome. It is associated with psychiatric disorders and autonomic nervous system dysfunction through adenyllyl cyclase inhibition [111]. It has been demonstrated that there was associated between exon III 48 bp VNTR of
the DRD4 and autism which might be a risk factor for ASD [47]. The dopamine transporter DAT (SLC6A3) gene affects neuronal networks in working memory and episodic memory [112]. It has been reported that there was a correlation between DRD1 rs4532 polymorphism and autism among Egyptian population. The mother’s age at conception was also correlated with rs2550936 SNP at SLC6A3 [48]. Similarly, there was a significant association between rs2550936 A/C polymorphism of SLC6A3 and rs4532 A/G polymorphism of DRD1 with ASD in which the GA genotype of DRD1 and CA genotype of SLC6A3 can be risk factor of ASD in a subpopulation of Saudi patients [49].

Transcriptional and epigenetic regulation
MTHFR catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate that has a pivotal role in DNA methylation and epigenetic regulation [113]. Epigenetic changes are important molecular alterations associated with a variety of human disorders [114–116]. It has been reported that there was a correlation between MTHFR A1298C polymorphism and increased risk of ASD among Egyptian cases. Genotype frequency of MTHFR 1298 AC/CC was significantly higher in ASD compared with healthy controls. MTHFR 1298 AC was also significantly more frequent in autistic children mothers in comparison with control mothers [50]. Another study showed that there were significant associations between C677T and A1298C polymorphic genotypes and autism susceptibility among Egyptian patients [51, 52]. The 677C>T rs1801133 and 1298A>C rs1801131 were also significantly associated with autism risk in Saudi subjects [53]. A MTHFR polymorphism assessment among Iraqi autistic children has shown that there was a significant association between g. 16,505 del C and autism susceptibility [54]. EN2 is a homeobox transcription factor involved in regulation of midbrain and cerebellum development. It has been demonstrated that there was a significant association between rs1861972 polymorphism and autism risk in a sample of Iranian cases [55]. The protein inhibitor of activated STAT (PIAS) functions as an E3 SUMO-protein ligase. The PIAS family of proteins include PIAS1, PIAS2 (PIASx), PIAS3, and PIAS4 (PIASY). PIAS1 is known as a STAT1-interacting protein which inhibits the STAT1-mediated transcriptional activation [117]. It has been revealed that there was a significant correlation between the levels of PIASx expression and age among Iranian ASD patients [56].

Mitochondrial DNA and DNA repair
Defects in the mitochondrial genome are frequent in autistic patients [118, 119]. The reduced nicotinamide adenine dinucleotide (NADH) oxidase activity in lymphocytic mitochondria was lower, and plasma pyruvate levels were higher in autism children than healthy children [120]. The G8363A transition on tRNALys was associated with enhanced risk of autism [121]. It has been observed that there were significant associations between 16126T>C, 14569G>A, and 1811A>G mitochondrial polymorphisms and autism susceptibility in a sample of Iranian cases [122]. XRCC4 has a pivotal role in DNA double-strand break repair [123]. DNA ligase IV-XRCC4 complex is critical for double-strand break repair and completion of V(D)J recombination in immune cells. XRCC4 mediates the binding of DNA ligase IV to DNA [124]. It has been reported that there was a correlation between XRCC4 variants and ASD risk among a subpopulation of Turkish patients in which the XRCC4-1394 T/G+G/G genotypes were more frequent in patients compared with healthy subjects [57].

Conclusions
ASD is a heterogeneous neurological disorder with diverse clinical manifestations that mainly result in social problems in patients. Therefore, it is really essential to clarify the genetic and molecular biology of ASD to introduce novel effective diagnostic and therapeutic options. Genetic aberrant of receptors and neurotransmitters is the main genetic risk factors of ASD progression among Middle East population. Regarding the various reported genes in these countries, it is not possible to introduce an efficient panel marker for all of these countries. However, assessment of MTHFR and DRD gene alterations can be suggested for the ASD screening among Arab population. Since, the reported genes among Iranians were different from the Turkish and Arab populations, a panel of five markers (based on sample size assessments) including GRM7, SNAP25, FOXP3, RORA, and RIT2 can also be suggested for the ASD screening among Iranian population. This review clarifies the genetic and molecular biology of ASD to introduce a population-based panel of genetic markers for the early ASD management and detection among Middle East population.

Abbreviations
ASD: Autism spectrum disorder; DRD3: Dopamine D3 receptor; GRM7: Glutamate metabotropic receptor 7; GPCR: G protein-coupled receptor; CC2D1A: Coiled-coil and C2 domain containing 1A; HTR1A: 5-Hydroxytryptamine receptor 1A; GABRE3: Gamma-aminobutyric acid receptor subunit beta-3; NRP1: Neurexophil; VEGF: Vascular endothelial growth factor; CYFIP1/CYFIP2: Cytoplasmic FMRI-interacting proteins 1/2; WRC: WAVE regulatory complex; SNAP-25: Synaptosomal-associated protein 25; ADHD: Attention-deficit hyperactivity disorder; CNTNAP2: Contactin-associated protein 2; ACE: Angiotensin-converting enzyme; APP: Amyloid precursor protein; AD: Alzheimer’s disease; BDNF: Brain-derived neurotrophic factor; TRK: Trk neurotropin receptor kinase B; TNF-a: Tumor necrosis factor a; G-CSF: Granulocyte colony-stimulating factor; Tregs: Regulatory T cells; MTR: Methyltetrahydrofolate reductase; MTHF R: Methylene tetrahydrofolate reductase; TS: Thymidilate synthase; ZDH: Xanthine dehydrogenase; AOX1: Aldehyde oxidase 1;
CBS: Cystathionine beta synthase; VDR: Vitamin D receptor; RORA: Retinoic acid-related orphan receptor alpha; VMAT1: Vesicular monoamine transporter 1; DRD4: Dopamine receptor D4; PIAS: Protein inhibitor of activated STAT; NADH: Nicotinamide adenine dinucleotide

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Declarations

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Page 9 of 12

Rahmani et al. Human Genomics (2021) 15:17
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