Introduction

Intellectual disability is a neurodevelopmental disorder characterized by impaired cognitive functions, significant below-average intellectual ability, and functional limitations in some adaptive traits with onset prior to the age of 18 years [1-2]. Sometimes, this disorder manifests in infancy which is manifested by feeding problems, impaired visual acuity, and diminished motor skills, or sometimes in early childhood accompanied by abnormal play and delayed achievement of developmental skills. Clinically, individuals with an intelligence quotient (IQ) below 70 are considered intellectually disabled. Milder forms of intellectual disability, with IQ between 50 and 70, are more common than moderate and severe forms with IQ below 50 [3]. ID may be a syndrome accompanied by additional physical, metabolic and neurological abnormalities, or non-syndromic, lacking these additional abnormalities [4].

Environmental factors include intoxication during pregnancy, viral infection in the mother, complications of delivery, premature birth, low birth weight and childhood diseases, which are responsible for damage of the nervous system [7]. It has also been reported that 25–50% of ID cases are influenced by genetic factors [8] including chromosomal abnormalities and monogenic defects. Chromosomal abnormalities have been reported in ID; most common being aneuploidies, duplications and submicroscopic deletions [9]. However, among the
autosomal trisomies, trisomy 21 is the most common genetic form of ID. Fragile X syndrome has been reported to be the most common form of inherited intellectual disability in individuals [10]. The best approach to the genetic evaluation of a child with ID is to record a family history from three generations and examine dysmorphologic and neurologic features.

Majority of researchers work focused on the characterization of ID causing genes located on X-chromosomes. More than 90 genes have been identified on only two X chromosomes causing ID, among them, 40 genes are responsible for non-syndromic X-linked intellectual disability [7,9] that affects between 1/600-1/1000 males, and a significant number of females also [11]. It has been reported that autosomal intellectual disability has high degree of genetic heterogeneity due to fact that about one half of all human genes are expressed in the brain. Hence, it is expected that the number of underlying gene defects will reach to the thousands [12]. Autosomal ID, either due to dominant or recessive gene mutations is presumably more common than X-linked intellectual disability [13], and it is believed that approximately 25% of patients with genetic ID are thought to have an autosomal pattern of inheritance [14]. Moreover, elucidation of the genetic etiology of NS-ARID may provide the opportunity of prenatal diagnosis, carrier screening and genetic counseling as well as guidance for disease management for a considerable number of patients.

Online Mendelian Inheritance in Man (OMIM) has listed 53 loci for both syndromic and nonsyndromic autosomal recessive intellectual disability, for which there are 33 genes reported. Among those 33 genes, only 14 are responsible for causing NS-ARID. In this review, a comprehensive description of the molecular genetics of NS-ARID will be given, including 14 genes that carry various mutations among people of different ethnic backgrounds (Table 1) and the normal functions of the encoded proteins in brain development (Table 2).

### PRSS12

The PRSS12 (Protease, Serine, 12 Neutrotrypsin or Motopsin) gene (OMIM# 606709) was identified as a NS-ARID causing gene by Molinari et al. [15] in a large consanguineous Algerian family. The PRSS12 gene (NCBI RefSeqGene: NG_023350.1) contains 15 exons and spans a 72 kb region on chromosome 4q28.1. Human PRSS12 encodes an 850 amino acid protease of 97 kDa (UniProtKB # P56730) that

<table>
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<tr>
<th>Genes</th>
<th>Loci</th>
<th>Type of mutation</th>
<th>Ethnicity</th>
<th>References</th>
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<tbody>
<tr>
<td>PRSS12</td>
<td>4q28.1</td>
<td>Nonsense</td>
<td>Algerian</td>
<td>Molinari et al., 2002</td>
</tr>
<tr>
<td>CRBN</td>
<td>3p26.2</td>
<td>Nonsense</td>
<td>American</td>
<td>Higgins et al., 2004</td>
</tr>
<tr>
<td>CC2D1A</td>
<td>19p13.12</td>
<td>Nonsense</td>
<td>Israeli-Arab</td>
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<tr>
<td>GRIK2</td>
<td>6q16.3</td>
<td>Complex mutation (deletions+ inversion), and nonsense</td>
<td>Iran and Argentina</td>
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<tr>
<td>TUSC3</td>
<td>8p22</td>
<td>Deletion, nonsense</td>
<td>French, Iranian, Pakistani</td>
<td>Molinari et al., 2008, Garshasbi et al., 2011, Khan et al., 2011</td>
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<tr>
<td>TRAPPC9</td>
<td>8q24.3</td>
<td>Nonsense</td>
<td>Israeli Arab, Pakistani, Iranian, Tunisian, Syrian, Italian</td>
<td>Mochida et al., 2009, Mir et al., 2009, Philippe et al., 2009, Abou Jamra et al., 2011, Marangi et al., 2013</td>
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<td>TECR</td>
<td>19p13.12</td>
<td>Missense</td>
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<td>1p34.1</td>
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<td>MAN1B1</td>
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<td>Pakistani, Iranian</td>
<td>Rafiq et al., 2011</td>
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<td>MED23</td>
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<td>Khan et al., 2012, Abbasi-Moheb et al., 2012, Martinez et al., 2012</td>
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<tr>
<td>FMN 2</td>
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<td>Egyptian and Pakistani</td>
<td>Law et al. (2014)</td>
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<tr>
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<td>2q22.1</td>
<td>Missense</td>
<td>Turkish and Kurdish</td>
<td>Heidari et al. (2015)</td>
</tr>
</tbody>
</table>
shares 82.5% sequence identity with its mouse ortholog [16], and is abundantly expressed in fetal human brain [15]. Functionally, **PRSS12** is a regulatory serine protease, playing a role in the regulation of pathways associated with neural development and plasticity [17]. In parts of brain associated with learning and memory, the balance between the **PRSS12** along with other proteolytic enzymes and their inhibitors is critical for the regulation of neural plasticity. Moreover, proteolysis mediated by **PRSS12** is required for normal synaptic function in neural development [15].

To date, a consanguineous Algerian family with NS-ARID, caused by homozygous mutation in the **PRSS12** gene has been reported. In this family, four of the affected children carried a homozygous 4 bp deletion in the **PRSS12** gene in exon 7 (c.1350ACGT) [15]. This deletion not only disrupted a restriction site for an AatII enzyme but also introduced a premature termination codon at a position 147 nucleotides downstream of the deletion. This truncation affects its function as a protease in the neural development and plasticity of children carrying a homozygous mutation, and consequently causes ID.

### Table 2: NS-ARID genes, their encoded proteins and normal functions in brain development

<table>
<thead>
<tr>
<th>Genes</th>
<th>Encoded Proteins</th>
<th>Functions in normal brain development</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Size (a. acids)</td>
<td>Molecular Mass (kD)</td>
</tr>
<tr>
<td>PRSS12</td>
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<td>97</td>
</tr>
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<tr>
<td>CC2D1A</td>
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<td>GRIK2</td>
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<td>TUSC3</td>
<td>348</td>
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<td>MED23</td>
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</table>
CRBN

The CRBN (CEREBLON) gene (OMIM # 609262) was identified by Higgins et al. [18] as a NS-ARID causing gene in a large American family of German ancestry. The CRBN gene (NCBI RefSeqGene: NG_016864.1) contains 12 exons and spans a 30 kb region on chromosome 3p26.2. This gene encodes a 442-amino acid cereblon protein of 50 kDa (UniProtKB # Q96SW2) and is 98% identical to mouse Cehl protein [19]. Cereblon is abundantly expressed in the human brain, and plays a role in cerebral development in brain [18]. Cereblon is a receptor for the Cullin-RING E3 ligase complex that along with the ubiquitin ligase performs ubiquitination of specific target proteins [20]. The C-terminus of Cereblon functions as an autoinhibitory domain that reduces its own rate of ubiquitination. Moreover, results of a study conducted by Sawamura and his colleagues showed that CRBN is recruited to the aggresome and has functional roles in cytoprotection [21].

To date, an American family with NS-ARID, caused by homozygous mutation in the CRBN gene has been reported. In the affected members of this family, a nonsense homozygous mutation in exon 11 (c.1274C>T, p. Arg419ter) was identified. This mutation introduced a premature stop codon, which terminated protein translation at amino acid 419 (arginine), resulting in a truncated protein missing the N-terminal 24 amino acids [18]. As a result of this truncation, the C-terminal ubiquitin autoinhibitory domain of Cereblon that is between amino acids 339 and 418 was removed. The truncation in CRBN at the C-terminus region promoted autoubiquitination and faster degradation of mutated Cereblon [22], and the subsequent reduction of Cereblon in cells during embryonic development caused ID [23]. Recently, Papuc et al. [24] hypothesized that a copy number gain of the CRBN gene might be responsible for developmental delay/intellectual disability due to identification of an overlapping microduplication involving 3p26.2-26.3 in patients with intellectual disability and behavior abnormalities.

CC2D1A

The CC2D1A (Coiled-Coil and C2 Domains-Containing Protein 1A) gene (OMIM# 610055) was identified as a NS-ARID causing gene by Basel-Vanagaite et al. [25] in consanguineous Israeli-Arab families. The CC2D1A (NCBI RefSeqGene: NG_013089.1) gene is comprised of 29 exons and spans a 24 kb region on chromosome 19p13.12. This gene encodes a 951 amino acid protein of 104 kDa (UniProtKB # Q6P1N0), expressed in human embryonic tissues and is crucial for normal brain function in humans. Orthologs of CC2D1A have been detected in embryonic tissues of mouse and drosophila [25-26]. The CC2D1A encoded protein is a transcription factor that regulates multiple intracellular signaling pathways, but its strongest effect as a transcription factor is in nuclear factor κB (NF-κB) pathway. NF-κB is involved in the regulation of neuronal differentiation and intracellular trafficking during brain development. NF-κB signaling is affected by gain or loss of function of CC2D1A in developing neurons, leading either to an increase or decrease of neuronal dendritic complexity, which can lead to deficits in learning and memory [13, 27].

To date, consanguineous Israeli-Arab, Saudi and Pakistani families with NS-ARID caused by homozygous mutations in the CC2D1A gene have been reported. In affected individuals of Israeli-Arab families, Basel-Vanagaite et al. [25] identified a homozygous deletion of 3,589 nucleotides in the CC2D1A gene beginning in intron 13 and ending in intron 16. In the mutant protein, this deletion introduced a frameshift mutation, a nonsense codon at amino acid 438, and also created a 30-amino acid nonsense peptide. The Saudi and Pakistani families with autism spectrum disorder and NS-ID phenotypes were reported by Manzini et al. [27] did not carry the Israeli-Arab deletion. Instead, in the Saudi families, a homozygous transversion was identified at the exon-intron junction of exon 6 (c.748+1 G > T) leading to the skipping of exon 6, a frameshift mutation at amino acid 172, and an early stop codon at position amino acid 223 (p. Thr172Valfs*51). However, in Pakistani families, a 1 bp deletion in exon 3 (c.346 delA) leading to an early frameshift mutation (p.Lys116Argfs*81) was identified. This loss of function of the CC2D1A protein in neurons results in increased NF-κB activity and reduces dendritic complexity, consequently disrupting learning and memory in individuals [13,27].

GRIK2

The GRIK2 gene (OMIM# 138244) was identified as a NS-ARID causing gene by Motazacker et al. [28] in a large consanguineous Iranian family. The GRIK2 gene (NCBI RefSeqGene: NG_009224.2) is comprised of 22 exons and spans a 671 kb region on chromosome 6q16.3. The GRIK2 gene encodes a 908 amino acid Glutamate Receptor, Ionotropic, Kainate 2 protein of 102 kDa (UniProtKB # Q13002), that shares high sequence similarity with
its rat ortholog [29]. GRIK2 is highly expressed in the human brain and mediates the majority of excitatory neurotransmission in the brain. This receptor may also be important in neural development and plasticity [28].

To date, two consanguineous families of Iranian and Argentinian descent displaying NS-ARID caused by homozygous mutations in the GRIK2 gene, have been reported. In affected children from the Iranian family, Motazacker et al. [28] identified a complex mutation that comprises a deletion of 120 kb, removing exons 7 and 8, an inversion of 80 kb in exons 9, 10, and 11, along with another deletion of 20 kb in intron 11. This mutation resulted in loss of the ligand-binding domain, adjacent transmembrane domain and the putative pore loop of the receptor. Similarly, in affected children of an Argentinian family, Cordoba et al. [30] identified a homozygous nonsense mutation in the GRIK2 gene at position (c.592C>T, p.Arg198Ter). In such cases, mutations resulted in complete loss of function of the mutant GRIK2 protein in neural tissues during brain development.

**TUSC3**

The TUSC3 (Tumor Suppressor Candidate 3) gene (OMIM # 601385) was identified as a NS-ARID causing gene by Molinari et al. [31] and Garshasbi et al. [32] in consanguineous French and Iranian families. TUSC3 (NCBI RefSeq: NC_000008.11) contains 12 exons and spans a 226 kb region on chromosome 8p22. Human TUSC3 shares significant sequence identity with its orthologs in Caenorhabditis elegans and yeast [33]. This gene encodes a 348 amino acid protein of 39 kDa (UniProtKB # Q13454), highly expressed in ovary, cervix, placenta, prostate, testis, adipose and lung tissues, and is a candidate tumor suppressor gene in these tissues [34]. However, to understand its role in intellectual disability, it has been postulated that TUSC3 interacts with the alpha isoform of the catalytic domain of phosphatase 1 protein [35] which has a role in the modulation of neural synaptic and structural plasticity [36], thereby influencing learning and memory functions of brain [37]. It is, therefore, conceivable that autosomal recessive intellectual disability in patients with a loss of functional TUSC3 is actually caused by an impaired function of phosphatase 1 protein [31]. More recently, Garshasbi et al. [38] postulated that TUSC3 has Mg$^{2+}$ transmembrane transport activity, and imbalanced magnesium levels due to mutations in the TUSC3 gene may play a role in the pathogenesis of ID.

To date, four unrelated consanguineous families with NS-ARID caused by homozygous mutations in TUSC3 have been reported. In affected children from a French family, Molinari et al. [31] identified a homozygous 1 bp insertion in TUSC3 in exon 6 (c.787_788insC, p.N263fsX300) that resulted in a frameshift mutation and premature termination of the protein. However, in affected children of a large Iranian family, Garshasbi et al. [32] found a homozygous 120 to 150 kb deletion in the first exon of TUSC3. In a Pakistani family, a homozygous deletion of 170.673 kb, which encompassed TUSC3, was also reported by Khan et al. (2011). In affected children of another Iranian family, Garshasbi et al. [38] identified a homozygous nonsense mutation in TUSC3 in exon 2 (c.163C>T, p. gln55ter) that resulted in a premature termination of the protein. The identified insertion, deletion and nonsense mutations in TUSC3 resulted in loss of function of TUSC3 in neural tissues during fetal brain development.

**TRAPPC9**

In three different studies, the TRAPPC9 (Trafficking Protein Particle Complex, Subunit 9) gene (OMIM # 611966) was identified as a NS-ARID causing gene in Israeli Arab family by Mochida et al. [39], in Pakistani and Iranian families by Mir et al. [40] and in Tunisian family by Philippe et al. [41]. TRAPPC9 (RefSeqGene: NG_016478.2) contains 29 exons and spans a 728 kb region on chromosome 8q24.3. This gene encodes a 1,148 amino acid protein of 128 kDa (UniProtKB # Q96Q05) sharing 90% homology with its mouse ortholog [42]. TRAPPC9 is also known as NIBP (NIK and IKKβ-binding protein). Its expression is strong in postmitotic neurons [39], and it binds NIK and IKKβ resulting in neuronal NF-κB pathway activation, and thus plays a role in nerve growth factor induced neuronal differentiation [42] and synaptic plasticity in the human embryonic brain [43].

To date, six families of different origin with NS-ARID caused by homozygous mutations in the TRAPPC9 gene have been reported. In the affected children of an Israeli Arab family, Mochida et al. [39] identified a same homozygous nonsense mutation at different positions in exon 7 (c.1423C>T, p. arg475ter) in variant 1 and (c.1129C>T, p.arg377ter) in variant 2 of the TRAPPC9 gene. Moreover, Mir et al. [40] and Abou Jamra et al. [44] also reported homozygosity for the same (c.1423C>T, p. arg475ter) mutation in affected children of large consanguineous Pakistani and Syrian families, respectively. Philippe et al. [41] also identified a homozygous nonsense mutation in TRAPPC9 in exon 9 (c.1708C>T, p.arg570ter) in affected sons of consanguineous Tunisian parents.

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In affected members of an Iranian family with mental retardation which was ascertained and mapped previously by Najmabadi et al. [45] to locus 8q24, Mir et al. [40] identified a 4-bp deletion mutation (c.2311-2314 delTGTT) in TRAPPC9 that resulted in a frameshift mutation and premature termination (p.L772W fsX7) of the translated protein. Similarly, in the affected daughters of unrelated parents from Italy, with mental retardation, Marangi et al. [46] identified a homozygous splice site mutation in TRAPPC9 in intron 17 (c. 2851-2A-C), resulting in the skipping of exon 18, a frameshift mutation, and premature termination (Thr951TyrfsTer17) of the translated protein.

In all these cases the nonfunctional protein variants of TRAPPC9 are produced due to premature translation termination in embryonic brain cells thereby resulting in ID.

**TECR**

The **TECR** (Trans-2, 3-Enoyl-CoA Reductase) gene (OMIM# 600057) was identified as a NS-ARID causing gene by Caliskan et al. [47] in a large Hutterite family. The **TECR** (NCBI RefSeq: NC_000019.110) gene consists of 15 exons and spans a 38 kb region on chromosome 19p13.12. This gene encodes a 308 amino acid protein of 36 kDa (UniProtKB # Q9NZ01), that is 95% and 34% identical with mouse Tecr and yeast Tsc13 orthologs, respectively. The **TECR** encoding enzyme is expressed in all tissues of human [48], and catalyzes a reaction in the fatty acid elongation cycle [47]. The synthesis of fatty acids is important for brain development and functions during the fetal and postnatal periods [49].

To date, a large Hutterite family with NS-ARID caused by homozgyous mutations in **TECR** has been reported. In children from this family which was ascertained and mapped previously by Ober et al. [50] to 19p13.12 locus, Caliskan et al. [47] identified a homozygous missense mutation in **TECR** in exon 8 (c. 38C>A, p. Ala13Asp) or in exon 14 (c.1108G>T, p.Asp370Tyr), which resulted in a loss of activity in the transmembrane and catalytic domains, respectively. The identified genetic alterations in the N-terminal transmembrane domain and C-terminal catalytic domain of sialyltransferase prevented the formation of sialo-glyco conjugates for cellular communication in human neural fetal tissues [55]. In this process, the correct localization of **ST3GAL3** in the golgi apparatus of neural cells is a prerequisite for sialyltransferase activity [56].

To date, an Iranian family with NS-ARID, caused by homozgyous mutation in **ST3GAL3** has been reported. In affected members of this family, which was ascertained and mapped previously by Najmabadi et al. [45] on locus 1p34.1, Hu et al. [1] identified two missense homozygous mutations in **ST3GAL3** at positions either in exon 2 (c. 38C>A, p.Ala13Asp) or in exon 14 (c.1108G>T, p.Asp370Tyr), that is 95% and 34% identical with mouse TECR and yeast Tsc13 orthologs, respectively. The **TECR** encoding enzyme is expressed in all tissues of human [48], and catalyzes a reaction in the fatty acid elongation cycle [47]. The synthesis of fatty acids is important for brain development and functions during the fetal and postnatal periods [49].

**MAN1B1**

The **MAN1B1** (Mannosidase, Alpha, Class 1B, Member 1) gene (OMIM# 604346) was identified by Rafiq et al. [58] as a NS-ARID causing gene in consanguineous Pakistani and Iranian families. The **MAN1B1** gene (NCBI RefSeqGene: NG_031978.1) is composed of 13 exons and spans a 22 kb region on chromosome 9q34.3. This gene codes to a 699 amino acid protein of 79 kDa (UniProtKB # Q9UKM7) that shows high sequence similarity with its mammalian and yeast orthologs [59], and is expressed in fetal brain [60]. **MAN1B1** is an endoplasmic reticulum mannosyl-oligosaccharide 1, 2-alpha-mannosidase that is involved in the maturation of N-linked glycans in the secretory pathway, as well as trimming and removal of misfolded glycoproteins in the degradation pathway [58].

To date, Pakistani and Iranian consanguineous families have been reported with NS-ARID caused by homozgyous mutations in **MAN1B1**. In the affected members of three Pakistani families, Rafiq et al. [58] identified a homozygous missense mutation in **MAN1B1** in exon 8 (c.1189G>A, p. glu397lys). While investigating children of an Iranian family, which was ascertained and mapped previously [61] to locus 9q34.3, Rafiq et al. [58] identified a homozygous splice site mutation in **MAN1B1** in intron 17 (c. 2851-2A-C), resulting in the skipping of exon 18, a frameshift mutation, and premature termination (Thr951TyrfsTer17) of the translated protein.
[58] identified a homozygous missense mutation in the \textit{MANIBI} gene in exon 8 (c.1000C>T, p.Arg334Cys). This mutation was later on identified in two Turkish families and a family of unknown origin with congenital disorders of glycosylation by Rymen \textit{et al.} \cite{62} and Van Scherpenzeel \textit{et al.} \cite{63}, as well as in the affected children of a Turkish family with syndromic ID by Hoffjan \textit{et al.} \cite{64}. They further suggested that this mutation in \textit{MANIBI} leads to a syndromic disorder rather than NS-ARID. However, in the affected children of another Pakistani family, Rafiq \textit{et al.} \cite{58} identified a homozygous nonsense mutation in \textit{MANIBI} at position in exon 9 (c.1418G>A, p.Arg473Ter). In all these cases, missense and nonsense mutations were identified in the base of the active site pocket of the \textit{MANIBI} enzyme and subsequently, affected its interaction with glycan substrates. As a result, significantly decreased catalytic activity of the mutated \textit{MANIBI} enzyme in fetal brain tissue was observed and resulted in ID.

**\textit{MED23}**

The \textit{MED23} (Mediator Complex Subunit 23) gene (OMIM\#605042) was identified as a NS-ARID causing gene by Hashimoto \textit{et al.} \cite{65} in a large Algerian consanguineous multiplex family. The \textit{MED23} (NCBI RefSeqGene: NG_031860.1) gene contains 34 exons and spans a 54 kb region on chromosome 6q22.33-q24.1. This gene encodes a 1,368 amino acid protein of 154 kDa (UniProtKB # Q9ULK4), that is expressed in the human embryonic brain, and has crucial role in brain development and function \cite{65}. An ortholog of \textit{MED23} has been detected in embryonic tissues of Caenorhabditis elegans \cite{66}. The \textit{MED23} encoded mediator subunit in the multi-subunit complex that affects the basal transcription of a subset of genes important for cell growth, cell differentiation, and apoptosis in human brain development by regulating CDK9 (Cyclin-dependent kinase 9) occupancy at the promoter region \cite{67}.

To date, a consanguineous Algerian family with NS-ARID caused by homozygous mutations in \textit{MED23} has been reported. A homozygous missense mutation (c.1850GA, p.Arg617Gln) identified by Hashimoto \textit{et al.} \cite{65} in affected individuals of this family, resulting in transcriptional dysregulation of genes involved in various processes of brain development, and subsequently caused cognitive deficit. Recently, Trehan \textit{et al.} \cite{68} identified several novel compound heterozygous, disease-segregating mutations (c.3656A>G, p.His1219Arg and c.4006C>T, p.Arg1336X) in \textit{MED23} in two brothers of a non-consanguineous family with syndromic ID. This represents the first case of \textit{MED23}-associated syndromic ID in a non-consanguineous family.

**\textit{NSUN2}**

The \textit{NSUN2} (Nol1/Nop2/Sun Domain Family, Member 2) gene (OMIM \# 610916) was identified first as a NS-ARID causing gene by Abbasi-Moheb \textit{et al.} \cite{69} in large consanguineous Iranian families. The \textit{NSUN2} (NCBI RefSeqGene: NG_028215.1) is composed of 19 exons and spans a 34 kb region on chromosome 5p15.31. The \textit{NSUN2} gene encodes a 767-amino acid protein of 86 kDa (UniProtKB # Q0BJ23) that shares 35% sequence identity with yeast ortholog Trm4 \cite{70}, and is expressed in the human brain at various times during development. Expression of an ortholog of \textit{NSUN2} was also detected in brain cells of mouse \cite{71}. \textit{NSUN2} is an RNA- methyltransferase that plays a role in the development of higher cognitive functions \cite{69}. This methyltransferase also catalyzes formation of 5-methylcytosine at C34 of tRNA-leu (CAA) during chromosomal segregation in mitosis. For this purpose, expressed \textit{NSUN2} protein localizes to the nucleolus of brain cells during fetus development \cite{2}.

To date, five consanguineous families of different origins with NS-ARID caused by homozygous mutations in the \textit{NSUN2} gene have been reported. In the affected individuals of two Iranian families which were ascertained and mapped by Najmabadi \textit{et al.} \cite{45}, and Kuss \textit{et al.} \cite{61}, homozygous nonsense mutations in \textit{NSUN2} either between exons 3-6 (c.679C>T, p.Gln227Ter) or exons 7-9 (c.1114C>T, p.Gln372Ter) were identified, respectively. While investigating the affected individuals of a Kurdish family, Abbasi-Moheb \textit{et al.} \cite{69} also identified a homozygous nonsense mutation in the \textit{NSUN2} gene upstream of exon 6 at position (g.6622224A>C) that resulted in the skipping of exon 6 splicing, a frameshift mutation and premature termination (Ile179ArgfsTer192) starting at nucleotide 71 of exon 7. Similarly, in affected children of a Lebanese family, Martinez \textit{et al.} \cite{72} identified a homozygous splice site mutation (G>C transversion) in \textit{NSUN2} at position 1-bp upstream of the start of exon 6 and abolished the splice site of exon 6. Moreover, among the three affected daughters of a Pakistani family, with NS-ARID, Khan \textit{et al.} \cite{2} identified a homozygous missense mutation in \textit{NSUN2} in exon 19 (c.2035G>A, p.Gly679Arg), resulting in a failure of the mutant protein to localize correctly to nucleolus. In all these cases, the identified missense, nonsense and splice site mutations resulted in either a nonfunctional variant of \textit{NSUN2} or complete loss of \textit{NSUN2} transcripts in fetal brain tissues.
**CRADD**

The CRADD (Casp2 and Ripk1 Domain-Containing Adaptor with Death Domain) gene (OMIM# 603454) was identified as a NS-ARID causing gene by Puffenberger et al. [73] in Mennonite patients. The CRADD (NCBI RefSeqGene: NG_032159.2) gene contains 12 exons and spans a 173 kb region on chromosome 12q22. This gene encodes a 199 amino acid cysteine protease of 22 kDa (UniProtKB # P78560). As a part of the cell death signal transduction complex, it regulates apoptosis induced by genotoxins in the mammalian fetal brain tissue [74]. In reported Mennonite patients with NS-ARID, Puffenberger et al. [73] identified a homozygous missense mutation in the CRADD gene at position (c.382G>C, p. gly128arg). This mutation altered the affinity of the CRADD death domain as well as a decrease in interaction with other members in cell death signal transduction complex, thereby resulting in dysregulation of apoptosis and ID.

**FMN2**

The FMN2 (Formin 2) gene (OMIM# 606373) was identified as a NS-ARID causing gene by Law et al. [75] in consanguineous Egyptian and Pakistani families. The FMN2 (NCBI RefSeqGene:NG_042054.1) gene consists of 24 exons and spans a 383 kb region on chromosome 1q43. This gene encodes a 1,722 amino acid formin-2 protein of 180 kDa (UniProtKB # Q9NZ56), that has high homology to mouse and drosophila orthologs [76]. FMN2 is highly expressed in fetal brain, and is involved in neuronal migration and differentiation [75-76]. FMN2 localizes to the membrane dendritic spines of hippocampal neurons as well as intracellular sites near spines. In the brain, these dendritic spines are the major site of neuronal activity, and receive neurotransmitters associated with learning and memory [75].

To date, Egyptian and Pakistani consanguineous families have been reported with NS-ARID caused by homozygous mutations in FMN2. In four siblings of the Turkish family, Heidari et al. [77] identified a homozygous missense mutation in the FMN2 gene at position (c.179G-A, p. gly60asp) in the conserved MTase region I, which is part of the SAM cofactor-binding pocket, thus disrupting FMN2 catalytic activity. In three siblings of a consanguineous Kurdish family, Heidari et al. [77] identified a homozygous transition in FMN2 at position (c.623T-C, p. leu208pro) in a highly conserved residue and resulted in reduced protein stability.

Thus, both identified mutations impaired the function of FMN2 and decreased the inactivation of histamine, subsequently affecting its role as a neurotransmitter in the fetal brain.

**HNMT**

The HNMT (Histamine N-Methyltransferase) gene (OMIM# 605238) was identified as a NS-ARID causing gene by Heidari et al. [77] in unrelated consanguineous families of Turkish and Kurdish origin. HNMT (NCBI RefSeqGene: NG_012966.1) consists of 9 exons and spans a 52 kb region on chromosome 2q22.1. This gene encodes a 292-amino acid protein of 33 kDa (UniProtKB # P50135), sharing 82% sequence identity with rat HNMT [78]. HNMT is highly expressed in the trachea and bronchi, playing an important role in degrading and regulating the airway response to histamine. It is also expressed in brain at low levels but it lacks the catalytic histamine and S-adenosine-L-methionine binding sites of full-length HNMT, and acts as a neurotransmitter important for the developing brain [79].

To date, two consanguineous families of Turkish and Kurdish origin have been reported with NS-ARID caused by homozygous mutations in the HNMT gene. In four siblings of the Turkish family, Heidari et al. [77] identified a homozygous missense mutation in HNMT at position (c.179G-A, p. gly60asp) in the conserved MTase region I, which is part of the SAM cofactor-binding pocket, thus disrupting HNMT catalytic activity. In three siblings of a consanguineous Kurdish family, Heidari et al. [77] identified a homozygous transition in HNMT at position (c.623T-C, p. leu208pro) in a highly conserved residue and resulted in reduced protein stability.

Thus, both identified mutations impaired the function of HNMT and decreased the inactivation of histamine, subsequently affecting its role as a neurotransmitter in the fetal brain.

**Conclusion**

NS-ARID is a common and genetically homogeneous neurodevelopmental disorder. According to our knowledge, fourteen causative genes of NS-ARID have been identified so far. Identification of new genes that cause NS-ARID can be expected as a result of the development of molecular genetic techniques, and the application of new biotechnologies. This will lead us to understand their role in converging pathways in addition to the genetic causes. Further, characterizing the functions and interactions of proteins encoded by these genes will help us to deduce similarity between genes and their respective molecular pathways which will undoubtedly lead to rapid genetic
or biochemical diagnosis and directional treatment of NS-ARID. Additionally, since a majority of the genes recognized to play a role in the development of NS-ARID have been identified in large consanguineous families, consanguinity is highlighted as a strong tool for the discovery of NS-ARID genes which can easily be further characterized. Overall, the evaluation of new genes will not only expand the pool of current information about the molecular basis of NS-ARID, but may also facilitate genetic counseling and genetic screening, and therefore, may greatly reduce the number of affected babies born.

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