Abstract
Non-syndromic mental retardation is one of the most serious neurodevelopmental disorders, which has a serious impact not only on the affected individuals and their families but also on the health care system and society. Previously research has been more focused on the X-linked mental retardation and only recently studies have shown that non-syndromic autosomal recessive mental retardation is extremely heterogeneous and contributes much more than the X-linked mental retardation. But very little is known about the genes and loci involved in nonsyndromic autosomal recessive mental retardation than the X-linked mental retardation. To date only thirty loci and ten genes have been established associated with the non-syndromic autosomal recessive mental retardation. This short review presents an overview of the current knowledge on clinical information available for the ten genes associated with this unexplored group of genetic disorder.

Keywords: Non-syndromic, Mental retardation, Genes.

Introduction
Mental retardation/intellectual disability (MR/ID) affects approximately 1-3% of the general population.\(^1\) It is one of the most common reasons for referral to the clinical genetic clinic and one of the most important unsolved issues in health care. Diagnosis of MR/ID requires an intelligence quotient (IQ) of 70 or below and at least two deficits in adaptive behaviours such as delayed language, social skills or self-help skills.\(^2\) Mental retardation can be subdivided into syndromic forms, in which MR is associated with either dysmorphic features or malformations or neurological abnormalities. Whereas in the non-syndromic form, MR is present without any additional feature. However, the dysmorphic or neurological features may be subtle, thus making the clinical distinction between the syndromic form of MR and the non-syndromic form of MR difficult.

Etiological factors of MR are diverse and include genetic and acquired causes. Van Karnebeek et al in a systemic review in 2005 showed that a diagnosis can be reached approximately in half of the patients with nonspecific MR. But the diagnostic yield differs depending on the study setting, MR severity and gender. Diagnostic yield of chromosomal aberration in MR detected by classical karyotype was ~9.5%, additional yield of 4.4% with subtelomeric screen was noted. For Fragile X syndrome, the yield of cytogenetic technique was 5.4%, while it was only 2% with the molecular studies. Inborn errors of metabolism were found after metabolic investigations in only 1%. The yield of neuroimaging studies for abnormalities was significantly high and was 30%,
especially when carried on an indicated basis.\textsuperscript{3}

Mental retardation/intellectual disability is more common in males than in females, therefore it had been assumed that mutations in X-linked genes are responsible for up to 25\% of MR cases but data suggest that X-linked genes contribute to only 10\% of cases with MR.\textsuperscript{4} More than 90 genes responsible for X-linked MR have been reported on X chromosome.\textsuperscript{5} Only \textasciitilde4\% of the estimated 25,000 human genes reside on the X chromosome and about half of them are expressed in the brain, thus, total number of gene defects causing autosomal recessive mental retardation (ARMR) could run into thousands.\textsuperscript{6} Generally it is believed that \textasciitilde25\% of genetic MR/ID patients are thought to have autosomal mode of inheritance.\textsuperscript{7} Despite this very little is known about the genetics of non-syndromic autosomal recessive mental retardation (NS-ARMR). To date only ten genes are known to cause NS-ARMR. Here we present an overview of the present information on genetics of NS-ARMR including clinical and molecular knowledge. Structure of the ten genes on the bases of longest transcript, indicating protein size,
exons and introns along with position of gene on reverse or forward stand of DNA is shown in Figure-1. Locations of genes with known molecular bases NS-ARMR are shown on ideograms in Figure-2.

**PRSS12 gene:**
The PRSS12 gene (MIM # 606709) was the first gene identified, which was found to be associated with NS-ARMR in a large Algerian consanguineous family in 4 out of 8 children. It is located on chromosome 4q26 and contains 13 exons and encodes neuronal serine protease neurotrypsin, which is associated with neural development. In situ hybridization studies of neurotrypsin expression in human foetal brain found that it was expressed from day 44 to 15 weeks of gestation. The highest gene expression was detected at 15 weeks of gestation in the cortical plate, the hippocampal formation and the tegmental nuclei of brainstem. All affected children were homozygous for a four base pair deletion in exon 7 of PRSS12 gene. They were reported to have normal development in the first 1 to 2 years of life, after which neurological deterioration was observed and eventually these children were moderately to severely MR with IQ below 50.8

**CRBN gene:**
The CRBN gene (MIM # 609262) was the second gene identified in consanguineous kindred of German ancestry with 10 individuals having NS-ARMR. It is located on chromosome 3p26.2 and contains 11 exons and encodes cereblon protein, which plays its putative role in cerebral development and is abundantly expressed in human brain. A homozygous c.1274C>T transition in exon 11 of CRBN gene resulting in nonsense mutation, R419X was seen in these individuals. Clinical features described with CRBN gene are consistent with mild developmental delay and mild MR with IQ ranging from 50 to 70; males more severely affected than females. No dysmorphic features or autistic features were observed in these individuals.9

**CC2D1A gene:**
The CC2D1A gene (MIM # 610055) was the third gene identified in nine consanguineous Israeli- Arab families from the same village with same family name having NS-ARMR. It is located on chromosome 19p13.12 and contains 31 exons, which encodes coiled-coil and C2 domains protein 1A protein also called as CC2D1A protein. CC2D1A protein is highly expressed in the embryos of mouse brain which persisted into adulthood, strongest expression in the cerebral cortex and hippocampus. A large homozygous deletion of 3,589 nucleotides beginning in intron 13 and ending in intron 16 of CC2D1A gene causing a frame shift, creating a 30-amino acid nonsense peptide and a stop codon at position 438 of the mutant protein was detected in all affected individuals (G408fsX437). Clinical presentation of these individuals was noted to be psychomotor delay in early childhood with severe MR, none of them any speech. No dysmorphic features or autistic features were noted.10

**GRIK2 gene:**
Fourth gene causing NS-ARMR, GRIK2 (MIM # 138244) was identified in a large consanguineous Iranian family. It is located on chromosome 6q16.3 and contains 16 exons, which encodes a kainite receptor subunit involved in synaptic transmission and is highly expressed in the brain. A complex mutation in GRIK2 gene was reported that comprises of a deletion of exon 7 and exon 8 resulting in an in-frame deletion of 84 amino acids between 317 and 402 along with an inversion of approximately 80kb including exons 9, 10 and 11 in combination with a deletion of 20kb of intron 11. The phenotype of the affected individuals was described as MR ranging from mild to severe with no facial dysmorphism, normal head circumference and no abnormality was detected in the magnetic resonance imaging of brain done for one patient.11

**TUSC3 gene:**
TUSC3 (MIM # 601385) is the fifth gene identified to be associated with NS-ARMR located on chromosome 8p22 and contains 11 exons. TUSC3 gene encodes a 348 amino acid protein, which seems to be involved in catalyzing the central step in N-linked protein glycosylation pathway involved in congenital disorders of glycosylation. It is one of the two genes involved in NS-ARMR in which three different mutations have been identified. Two siblings from a French family with NS-ARMR have been reported to have a homozygous frameshift mutation due to 1bp insertion in exon 6, c.787_788insC.12 In a large consanguineous Iranian kindred with seven individuals having NS-ARMR found to have a homozygous 120-150kb deletion in exon 1 of TUSC3 gene.13 Deletion of almost the entire TUSC3 gene (minus the promoter and exon 1) and its downstream region have been described in a large consanguineous Pakistani family with six individuals with NS-ARMR.14 Similar clinical phenotype is reported in French, Iranian and Pakistani patients with mutation s in TUSC3 gene, which includes moderate to severe MR, no facial dysmorphism, normal head circumference and a normal neuroimaging of brain.

**TRAPPC9 gene:**
TRAPP9 (MIM # 611966) is the sixth gene identified to be associated with NS-ARMR located on chromosome 8q24.3 and contains 23 exons. TUSC3 gene encodes the 1148-1246
a amino acid protein, NIBP. TRAPP9 gene is highly expressed in the postmitotic neurons of the cerebral cortex. Like TUSC3 gene, it is also one of the genes associated with NS-ARMR in which three different mutations have been identified. In a consanguineous Israeli Arab kindred, three girls were reported to have a homozygous nonsense mutation R475X in exon 7 resulting from c.1422C>T transition.\textsuperscript{15} Same mutation has been reported in a large consanguineous Pakistani family.\textsuperscript{16} In a consanguineous Iranian family previously described by Najmabadi et al,\textsuperscript{17} a homozygous 4bp deletion:c.2311-2314 delTGTT, resulting in frameshift and premature truncation causing p.Leu772TrpfsX7 has been reported. Three Tunisian brothers from a consanguineous family were found to have a homozygous nonsense mutation p.Arg570-to-ter (R570X) due to c.1708C>T transition. Clinical phenotype of patients having mutations in TRAPP9 gene is similar for moderate to severe MR, variable postnatal microcephaly. Mild facial dysmorphism and truncal obesity was reported for Tunisian brothers otherwise no facial dysmorphism was reported in Pakistani, Israeli Arab and Iranian patients. MRI findings described in these individuals are diminished cerebral white matter volume, with sulcal enlargement, thinning of corpus callosum and mild cerebellar volume loss.

TECR gene:
Seventh gene, TECR (MIM # 610057) located on chromosome 19p13, has been described in a consanguineous family belonging to a religious community that traces its ancestry to Europe. A homozygous C to T transition in exon 8 of TECR gene resulting in a missense mutation P182L has been reported in this family.\textsuperscript{18} These individuals were noted to have developmental delay since birth and attended a special education classroom setting. They were able to communicate verbally but had speech delays; they had minimal reading or writing skills however were able to read and write their names. They were unable to live independently as adults and performed jobs requiring manual labour. They had no facial dysmorphic features, and a normal head circumference. All individuals demonstrated an initiation tremor but had no ataxia or other movement disorder.\textsuperscript{19}

ST3GAL3 gene:
The ST3GAL3 gene (MIM # 606494) was recently identified in two consanguineous Iranian families with NS-ARMR. It is located on chromosome 1p34.1, contains 12 exons and encodes beta-galactoside-alpha-2,3-sialytransferase-II, which is a golgi membrane protein. Two different missense mutations were identified in two Iranian families. First family with eight individuals having NS-ARMR was shown to have a homozygous 38C-A transversion in exon 2, which resulted in substitution (p.Ala13Asp). Four members with NS-ARMR from another Iranian family was found to have a homozygous c.1108G-T transversion in exon 14, resulting in substitution (p.Asp370Tyr).\textsuperscript{20}

MED23 gene:
MED23 (MIM # 605042) is a subunit of mediator complex, which is a key regulator of protein coding gene expression. It is located on chromosome 6q23.2 and contains 29 exons. It was the identified gene in a large consanguineous Algerian family with five individuals having NS-ARMR. A homozygous missense mutation p.R617Q resulting from arg-to-glu substitution at codon 617 was reported in these affected individuals.\textsuperscript{21}

MAN1B1 gene:
MAN1B1 (MIM # 604346) was identified in four Pakistani and one Iranian consanguineous family. It is located on chromosome 9q34.3 and contains (...exons. It encodes endoplasmic reticulummannosyl-oligosaccharide 1,2-alpha-mannosidase, which is an enzyme involved in the maturation of N-linked glycans in secretory pathway. A homozygous missense mutation resulting from c.1189G>A transition (p.Glu397Lys) was seen in three consanguineous Pakistani families. In fourth consanguineous Pakistani family a homozygous nonsense mutation resulting from c.1418G>A transition (p.Try473Ter) was found. In the Iranian consanguineous family with three children a homozygous missense mutation resulting from c.1000C>T transition (P.Arg334Cys) was identified.\textsuperscript{22}

Impediment in Research of Non-syndromic Autosomal Recessive Mental Retardation:
It has been complex to explicate genes and loci for NS-ARMR and still very scanty knowledge is available about this group of disorders. It is due to the presence of high levels of genetic heterogeneity and presence of isolated cases of NS-ARMR in small families. Mainly the research on etiology of mental retardation has been focused in Western developed countries, where culturally family sizes are small and statically recurrence risk of one in four for autosomal recessive mental retardation makes the possibility of finding more than one individual with NS-ARMR within the same family is quite usual.

Consanguinity; a Robust Tool to Explicate Non-syndromic Autosomal Recessive Mental Retardation Genes:
All seven genes responsible to cause NS-ARMR recognized so far have been identified in large consanguineous families utilizing autozygosity (homozygosity by descent) mapping. At present, the main
strategy for identification of molecular defects causing NS-ARMR is positional cloning in single family based on linkage analysis and homozygosity mapping in consanguineous families. The larger these families are, the better it is to achieve a significant logarithm of odds (LOD) scores. Pooling of homozygosity data from different consanguineous families and sequencing the overlapping genomic intervals will help in the identification of other genes causing NS-ARMR and expand the pool of current information available on the molecular basis of NS-ARMR.

Benefits of Identification of Genetic Cause of Non-syndromic Autosomal Recessive Mental Retardation:

In countries where there is high rate of consanguinity, there is significant burden of autosomal recessive disorders including NS-ARMR. In Pakistan there is 62.7% consanguinity, of which 84% marriages are between first cousins. Identification of the molecular cause of NS-ARMR in an individual or a family may allow genetic counseling and genetic screening and therefore, may greatly reduce the number of affected babies born by avoiding marriages among carriers of the same gene. Molecular information about the etiology of NS-ARMR in the proband can also provide opportunity for performing subsequent pre-natal genetic testing or pre-implantation genetic diagnosis in a specific family which may also be the source of better IVF outcome.

References