CHAPTER II

REVIEW OF THE RELATED LITERATURES

It is estimated that there are more than 20 genes responsible for non-syndromic X-linked mental retardation (MRX) but up to date there are only 12 genes identified. Genes which were cloned includes

- *IL1RAPL*: The IL-1 receptor accessory protein (IL1RAPL), located in Xp22.1, was found to be deleted in males from family MRX36. A nonsense mutation (G1377A), creating a stop codon at amino acid 459, was identified in a previously unreported MRX family [18-19].
- *RSK2*: The serine-threonine protein kinase (RSK2), known to be involved in the Coffin-Lowry syndrome (CLS), was shown to also be responsible for MRX19 [20]. A missense mutation (C1147T) in exon 14 resulted in decreased kinase activity, which is presumed to be the cause of the MR observed in MRX19 [21].
- *TM4SF2*: The transmembrane 4 superfamily member 2 gene (TM4SF2), located in Xp11.4, was found to be disrupted by an X:2 balanced translocation in a female patient with mild MR plus minor autistic features [22]. Two additional mutations (G128X and P172H) were found in two unrelated families with XLMR (ibid). Abidi et al. reported MRX58 resulted from a 2 bp deletion (564delGT) in *TM4SF2* [23]. The deletion causes a frameshift at amino acid 186 (FS186X) and a stop codon six amino acids later. This leads to truncation of the protein.
- *MECP2*: The methyl-CpG binding protein (MECP2), known to be involved in Rett syndrome, was found to also be responsible for some forms of XLMR. Orrico et al. found an A140V mutation in a family in which both males and females had MR [24]. The affected female

proband had microcephaly, an asthenic habitus, speech problems, genu valgum and an unsteady gait. Meloni et al. [25] found a G406X mutation in an XLMR family previously reported by Claes et al. [26]. The phenotype consisted of severe MR associated with progressive spasticity. They also had facial hypotonia and sialorrhea, with head circumferences in the 75^{th} - 90^{th} percentile. Of particular interest, the obligate carriers were not affected even though they did not exhibit skewed X-inactivation as would be expected. Couvert et al. reported finding a *MECP2* mutation (E137G) in MRX16 and another mutation, R167W, in a second XLMR family linked to Xq28 [27]. Furthermore, the authors screened 185 fragile X negative males and found two A140V mutations, a P399L mutation and a R453Q mutation. Based on these latter results, it was suggested that *MECP2* mutations may occur at a relatively high (about 2%) frequency in the male MR population. However, other publications raise the distinct possibility that many mutations in *MECP2* observed in males may actually be rare polymorphisms [28]. Thus, caution must be taken in interpreting *MECP2* alterations. Nonetheless, a mutation in *MECP2*, A140V, was found in a family with PPM-X (psychosis, pyramidal signs and macroorchidism) [29]. This same mutation has been observed in other patients [24, 27]. Thus, the authors raise the possibility this particular amino acid, A140, is a mutation hot-spot in *MECP2*.

- alpha-PIX: An X/21 translocation in a male with MR was found to disrupt a Rho guanine nucleotide exchange factor (ARHGEF6 or alpha-PIX) [30]. The male has severe MR, sensorineural hearing loss and mild dysmorphic features. Another mutation, in the first intron (IV31-11T-C) was identified in MRX46. This mutation apparently results in a

proportion of mRNA to be synthesized using exon 2 which contains a portion of the CH (calponin homology) domain. The authors (ibid) propose the presence of this altered mRNA gives rise to the MRX46 phenotype.

- *SLC6A8*: A nonsense mutation (R514X) in the creatine transporter gene located in Xq28 has been described in a seven year old boy with mild mental retardation and two female relatives by Salomons et al. [31]. Second families in which five males and two females are affected have been found to have a missense mutation (G1141C) which leads to a glycine being replaced by an arginine and also alternative splicing [32]. Affected males have increased creatine in plasma and urine, which may serve as an easy biochemical screening method.
- *FGD1*: A missense mutation (C935T) in the *FDG1* gene has been described in three males with mental retardation, but without the usual features of Aarskog syndrome [33].
- *XNP*: Mutations in the gene responsible for XLMR-hypotonic facies (alpha-thalassemia mental retardation) have now been described in the original families with Carpenter-Waziri syndrome [34] and Holmes-Gang syndrome [35]. Mutations have also been described in a family believed to have Juberg-Marsidi syndrome [36] and a family believed to have Smith-Fineman-Myers syndrome [37]. Schwartz and coworkers have recently found a nonsense mutation in the original Chudley-Lowry syndrome family [38]. These findings confirm that a number of named XLMR syndromes are allelic.
- *FLN1*: Mutations in the filamin-1 gene have been described in females and males with periventricular nodular heterotopia [39]. This large gene (48 exons) is located in Xq28. Mutations have been described in both

familial and sporadic cases. Mutations in several males indicate that not all mutations are male-lethal.

- *PAK3*: A novel missense mutation (R67C) was identified in MRX47 [40].
- *ARX*: Mutations in the human orthology of Aristaless (Xp22.2) were found to cause XLMR in association with epilepsy [41]. Novel mutations were found in 9 families with either syndromic or non-syndromic XLMR. One of the syndromic XLMR conditions was West syndrome. The epilepsy observed in patients included infantile spasms, myoclonic seizures and dystonia. Two mutations, present in 7 families, were expansions of polyamine tracts. Thus, mutations in ARX may account for a relatively large fraction of males with MR plus epilepsy [42-43].
- *FACL4*: Meloni et al. reported finding mutations in 2 nonsyndromic XLMR families in the fatty acid-CoA ligase 4 (*FAXL4*) gene located in Xq22. One mutation was a missense (R570S) in the signature motif of fatty acyl-CoA synthesis [44]. The second mutation was 1003-2A⟶C which resulted in a cryptic site being used at the 3' end of intron 10 and the inclusion of 28 novel amino acids with an inframe stop codon. All female carriers exhibited highly skewed X-inactivation. The identification of *FACL4* mutations in MRX males suggests normal lipid homeostasis is crucial for development and cognitive function.

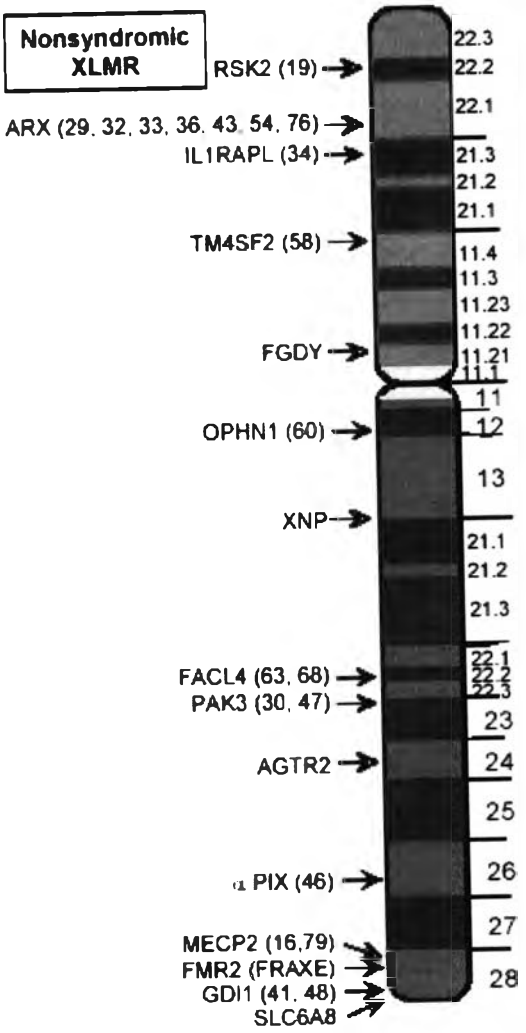

Figure 3. Mapping of non-syndromic mental retardation genes