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IS THE EXCESS OF MALE MENTAL RETARDATION CAUSED BY FUNCTIONAL AND STRUCTURAL PECULIARITIES OF THE X CHROMOSOME?

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The excess of ~30% in male MR as compared to females is well recognized. The simple explanation usually proffered is that of X-linked recessive mutations. However, although >80 XLMR genes have been identified, these only account for a small proportion of presumptive XLMR families. A major study has recently reported the full sequencing of X chromosome exons in 208 probands from presumptive XLMR families. In 155 families nonsense mutations could be excluded as the cause of MR. Other factors on the X chromosome possibly associated with MR include SNP or CNVs (copy number variations) in coding or non-coding regions, either alone, or in combination with other modulating factors. While CNVs normally segregate in a mendelian fashion, they multiply the range of phenotypes arising from copy variations in a limited number of genes: families may exhibit duplications or deletions comprising different combinations of genes, and the phenotype in each family is a consequence of a rare or unique combination of genes. We reviewed the distribution of different features on the X compared to the autosomes from several databases (DGV, Decipher and Esembl). The gene density (genes per megabase) on the X chromosome is reduced to 0.71 of the autosomal average. Interestingly, although gene and miRNA densities are highly correlated for the entire genome (0.88), the miRNA density on the X-chromosome is increased to 1.37, providing additional targets for pathogenic mutations. The reduced SNP density on the X chromosome, first detected by the group of Pearson 20 years ago and subsequently confirmed by many others is mirrored by an even greater reduction in CNV density relative to the autosomes. The normalized frequencies of SNPs (0.70) and common CNVs (0.55) on the X are only higher than those of the Y chromosome (0.31 and 0.15, respectively). The reduction in SNPs and CNVs on the X and Y are likely to be a combination of the proportion of circulating copies for each chromosome, i.e., $\frac{3}{4}$ of autosome number for the X and $\frac{1}{4}$ for the Y and the reduced meiotic recombination on the X and complete lack on the Y except for the PARs. The more pronounced reduction of CNVs compared to SNPs is probably due to reduced Non-Allelic Homologous Recombination (NAHR), which is one of the most likely causes of copy number variation. Interestingly, although the density of common CNVs found in normal controls is reduced on the X, pathogenic CNV density is slightly increased (1.2), probably because abnormal phenotypes associated with CNVs are more easily expressed due to hemizyosity. An additional issue is the criterium of when to consider a CNV as pathogenic: while we tend to disregard CNVs present in one of the normal parents as pathogenic, that does not occur with the X chromosome in which it is not only accepted but even expected that the mother will be a normal carrier. This selection leads to an overrepresentation of familial cases associated with X-chromosome pathogenic CNVs

Conclusions: The X chromosome has a reduced density of genes, SNPs and common CNVs, but a higher density of miRNA (1.75).

SNPs and CNVs are probably reduced on the X because of the reduced number of copies exposed to mutagenic stress and meiotic recombination.

CNVs tend to be more pathogenic when on the X chromosome leading to a greater proportion of MR individuals.

These considerations point to several mechanisms that may account for the male excess of MR without invoking more complex mechanisms of inheritance, including incomplete penetrance, multiple genes or environmental effects.

Chromosome	Mb	SNPs	Genes	Common CNVs	Pathogenic CNVs	miRNA
X	155	0.70	0.71	0.55	1.18	1.35

