

## Abstract 6

### X-LINKED MENTAL RETARDATION AND EPIGENETICS

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The underlying genetic cause has not been resolved for a significant percentage of XLMR patients despite extensive screening for disease-associated mutations and copy number variation. This strongly suggests that yet unidentified mechanisms could play important roles in the aetiology of XLMR. Since it is known that cognition as well as other developmental processes are epigenetically driven, we hypothesize that epigenetic changes at specific genomic loci constitute such a mechanism. These changes can either be the result of

- (1) environmental influences or transgenerational inheritance,
- (2) mutation in one of the components of the epigenetic machinery, or,
- (3) a structural genetic defect resulting in altered epigenetic imprints.

Chromatin immunoprecipitation (ChIP) is a powerful method to investigate epigenetic marks at specific loci (by qPCR) or genome-wide (by ChIP-chip). To introduce ChIP-qPCR, and ChIP-chip we first analysed such marks at the *FMR1* locus of fragile-X patients. We could clearly detect increased promoter DNA methylation as well as the expected histone modifications (H3K4me2, H4ac and H3ac) in cells derived from these patients. In a second step, we perform X chromosome-directed epigenetic profiling (ChIP-chip) of XLMR patients using X chromosome-specific high-resolution (19 bp) oligo arrays that cover all X genes as well as their regulatory sequences. Similarly, genome-wide ChIP-chip experiments will also be carried out to study epigenetic marks in patients with mutation in genes known as epigenetic players. Initial ChIP-chip experiments have been performed and will be discussed. In summary, these screenings might allow defining epigenetic modifications as a novel mechanism that disturbs normal cognitive development or unravel (epi)molecular defects associated with gene mutations. In addition, novel XLMR genes affecting epigenetic processes might be identified, which can then be characterized for their (epi)molecular function in cognition.