

Abstract 83

***FMR1* GENE EXPANSION, LARGE DELETION OF Xp AND SKEWED X-INACTIVATION IN A GIRL WITH MENTAL RETARDATION AND AUTISM**

Marketa Havlovicova¹, Alzbeta Vazna¹, Zuzana Musova¹, Marketa Vickova¹,
Drahuse Novotna¹, Lenka Dvorakova², Michal Hrdlicka³, Zdenek Sedlacek¹
Department of Biology and Medical Genetics, Charles University 2nd Faculty of Medicine and
University Hospital Motol, Prague, Czech Republic¹
Institute of Inherited Metabolic Disorders, Charles University 1st Faculty of Medicine and
General University Hospital, Prague, Czech Republic²
Department of Child Psychiatry, Charles University 2nd Faculty of Medicine and University
Hospital Motol, Prague, Czech Republic³

We present a girl with mild facial dysmorphism, mild mental retardation and atypical autism with a remarkable behavioral phenotype of lasting anger, aggression and dysphoria. The occurrence of late-onset tremor and premature ovarian failure in the maternal branch of the family pointed to a possible defect in the *FMR1* gene. Indeed, the patient carried a full *FMR1* mutation. Unexpectedly, both alleles of the gene were almost completely methylated. Cytogenetic examination of the patient revealed in addition a large de novo deletion in band Xp22 on one of her X chromosomes. The deletion was fine mapped using oligonucleotide array CGH, and its breakpoints were localized using sequencing. The size of the deletion was about 17.4 Mb, and it contained more than 90 protein-coding genes. Microsatellite analysis indicated paternal origin of the aberrant chromosome. The large rearrangement was the most probable cause of the X-inactivation skewing, thus explaining the methylation of not only the expanded (maternal) but also the normal (paternal) *FMR1* alleles. This pattern of skewed X-inactivation was confirmed using the analysis of methylation at the *AR* locus. The relatively mild phenotype of the patient resulted most likely from unmasking of the *FMR1* defect. Although the deleted region contained many important genes, the phenotypic contribution of the rearranged X chromosome was probably limited due to its almost complete inactivation. However, reduced dose of several genes escaping X-inactivation might also play a role in the phenotype of the patient.

Acknowledgments: Supported by grants NR/9457-3 and MZO00064203 from the Ministry of Health of the Czech Republic, and INCORE and CHERISH from the European Commission.