Acta Genet Med Gemellol 45: 251-253 (1996)

Parental Source Effect on Inherited Mutations in the Dystrophin Gene of Mice and Humans

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INTRODUCTION

Skewed X inactivation has been suspected as the genetic cause for some female carriers of Duchenne/Becker muscular dystrophy (DMD/BMD) presenting symptoms [1], as well as in manifesting females in other X-linked recessive diseases. No clear "parental source effect" – a difference in phenotype depending upon transmission of the mutated allele by either the father or the mother – has been observed [Cremer]. To date, most studies in this field have analysed the methylation status of flanking polymorphic sites (a measure of the maintenance of X inactivation and imprinting), not the expression of the causal gene itself.

To test the parental source effect on the protein expression of the dystrophin gene, we have set up crosses of *mdx/mdx* and *mdx/y* mice – the well-known DMD animal model [2] with the respective wild-type mice of the same strain (Table 1). The obligate heterozygous F_1 females show a mosaic expression of dystrophin in skeletal and cardiac muscle upon immunehistological staining. Because the source of the mutation in the litters is well defined, the mosaic pattern should reflect a parental source effect, if any. Such an effect should also change the level of muscle enzymes in serum and may thus be easily testable in humans, too. Since DMD is genetically lethal in humans, one can test the hypothesis of a parental source effect in BMD families only.

RESULTS

Histological cross sections of the myocardium from 45-day-old female hetterozygous *mdx/normal* mice were assessed for dystrophin expression by immunohistochemistry. A striking difference in the number of fibres expressing dystrophism was found, depending on whether the mutation was inherited from the mother (mdx^M/*normal*) or from the father (mdx^P/*normal*; Table 1). 47% dystrophin-positive fibres were observed in mdx^M/*normal* mice versus 68% positive fibres in the mdx^P/*normal* mice.

Table 1 - Dystrophin expression in myocardial fibres of heterozygote *mdx* mice

Co-isogenetic inbred strain: C57/BL10		
Father	*normal/y*	*mdx/y*
Mother	*mdx/mdx*	*normal/normal*
Daughter	*mdx^M/normal*	*mdx^P/normal*
Dystrophin expression in the myocardium	maternal *mdx* about 47% dystrophin positive fibres	paternal *mdx* about 68% dystrophin positive fibres

These results correlate well with the serum levels of muscle-specific enzymes in mice, such as pyruvate kinase (PK) (results not shown). PK values were significantly lower in *mdx^P/normal* mice than in *mdx^M/normal* mice. This may be due to less necrosis in the muscles of the former animals, since they show a lower proportion of dystrophin-negative muscle fibres.

Table 2 shows that the same trend holds for creatine phosphokinase (CK) in human BMD carrier females. The plasma CK values are significantly lower if the mutation is inherited from the father. Mean values are about three fold higher in females who inherited the mutation from their mothers. The difference is statistically significant at the 95% level. Only those families were considered which showed clear Xlinked inheritance in their pedigree or had a known *in frame* deletion in the dystrophin gene.

DISCUSSION

The quantitative differences in the dystrophin expression of myocardial cells or serum muscle enzyme values in relation to the parental origin of the mutation in *mdx/normal* female mice can be explained in terms of a skewed X inactivation or of genomic imprinting. Among the factors skewing X inactivation in mice are the X-controlling elements (*Xce*) [3]. Different alleles of *Xce* can influence (in *cis*) the silencing of the respective chromosomal region. These factors are unlikely to play a role in our experiment which was done in a co-isogenic inbred strain. By definition, any uniparental-dependent transmittance of a genetic trait is termed imprinting [4]. The differential dystrophin expression reported here differs from other imprinting phenomena as it is merely a quantitative effect and not "all or none".

Several factors may complicate the problem, e.g. in 45-day-old mice, selection against dystrophin negative fibres has already taken place since birth, veiling the initial ratio of dystrophin-positive to dystrophin-negative fibres. Experiments should be repeated with other Xchromosome genes which are less likely to underlay selective forces.

In the absence of detailed knowledge about the interrelation between Xinactivation and genomic imprinting, we propose to call the observed phenomen a "parental source effect" on gene expression.

https://doi.org/10.1017/S0001566000001409 Published online by Cambridge University Press

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