SHORT COMMUNICATION

PREGNANCY FAILURE AND ALKALINE PHOSPHATASES: FROM MOUSE GENETICS TO HUMAN DISEASE

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In mammals, fertility is governed by a considerable number of genes, as materialized by the decreased or impaired fertility of ~20% of knock-out mice. We wished to study fertility parameters as quantitative genetic characters (QTL), using a very original model of interspecific recombinant congenic mice developed at the Pasteur Institute [1]. This model is composed of 53 mouse strains harboring ~1.5% of genome from the Mus spretus species in a Mus musculus background. Any phenotypic variation from the musculus parent is thus attributable to a well-mapped genomic fragment encompassing a limited number of genes [2]. In a first study based on ultrasonography, we studied embryonic resorption in these mouse strains and discovered that one of them (66H) presented an abnormal embryonic death rate [3]. From this strain, we derived a substrain containing only a ~32 Mb chromosome 1 fragment (66H-Chr1) and a series of 15 recombinant strains that had crossing over inside this fragment. The initial fragment contains 215 annotated genes. The analysis of the recombinant strains showed that the effect could be due to two complementary epistatic genes located into two contiguous ~6 Mb regions [4]. In one of these regions, an interesting candidate for explaining the phenotype was the homologue of the human gene ALPP. This gene was sequenced in a series of 100 controls and 100 human patients affected by Recurrent Spontaneous Abortions, from the same ethnic background. This phenotype is considered similar to embryonic resorption in mice. We showed that several alleles and allelic combination are more frequent in RSA women. In particular, one of the polymorphism induces an amino-acid change in the protein. Both the normal and modified versions of the gene were cloned in an expression vector and their activity analyzed. This analysis revealed a significant difference in activity between the two variants. This alteration may contribute to the phenotype of the patients. This study of mouse models is helpful to decipher complex multifactorial diseases in humans.

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