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Localization on pig chromosome 6 of five markers: GPI, APOE, TGF β 1, ENO1 and PGD, carried by human chromosomes 1 and 19, using *in situ* hybridization

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pig / molecular *in situ* hybridization / comparative mapping / halothane gene

INTRODUCTION

In the pig, the linkage group S-GPI-HAL-A1BG-PGD bearing the halothane gene (HAL: responsible for malignant hyperthermia (MH)) has been assigned to the p12 \rightarrow q21 region of chromosome 6 by Davies *et al* (1988) and Chowdhary *et al* (1989). This region includes part of the short arm, the centromere, and part of the long arm. Using *in situ* hybridization combined with high-resolution chromosome banding analysis, we increased the precision of the localization of glucose phosphate isomerase (GPI) on pig chromosome 6. Then, with the objective of finding new markers around the HAL gene, we selected information from comparative mapping. GPI and 6-phosphogluconate dehydrogenase (PGD) are linked in the pig, but are located on different chromosomes in many other species, including man and mouse. GPI is situated on human chromosome 19 (q13.1 region) and PGD on human chromosome 1 (pter \rightarrow p36.13 region). Thus, parts of pig chromosome 6 correspond to parts of human chromosomes 1 and 19. We chose markers near the human GPI and PGD loci: APOE (apolipoprotein E), TGF β 1 (transforming growth factor β 1), ENO1 (enolase 1), in addition to GPI and PGD, to study their localization in the pig by molecular *in situ* hybridization.

MATERIALS AND METHODS

All the techniques used have been described elsewhere (Yerle *et al*, 1990a). The chromosomes were G-banded before hybridization using the GTG technique. The technique of Rønne *et al* (1987) was slightly modified and used to obtain

prometaphase chromosomes with high-resolution G-banding (Yerle *et al*, 1991). The best metaphases were selected and photographed before hybridization. Metaphase and prometaphase chromosomes were classified according to the recommendations given by the Committee for the Standardized Karyotype of the Domestic Pig (1988).

The characteristics of the DNA probes used have been described elsewhere (Yerle *et al*, 1990a, b).

For each marker, a histogram showing the grain distribution on the chromosomes was produced. One of these histograms is presented in figure 1. A statistical evaluation of the number of silver grains per unit chromosome length was made using a Poisson distribution.

RESULTS AND DISCUSSION

The results, which are summarized in table I, demonstrate that the markers are situated on the long arm of pig chromosome 6 and, more precisely, GPI on band q12, APOE on band q21.2, TGF β 1 in the cen \rightarrow q21 region, ENO1 in the q22 \rightarrow q24 region, and PGD in the q22 \rightarrow q25 region.

Table I. Localization of GPI, APOE, ENO1, PGD and TGF β 1 on pig chromosome 6 by molecular *in situ* hybridization.

<i>Locus</i>	<i>No of cells analyzed</i>	<i>Total no of grains on the chromosomes</i>	<i>No of grains on chromosome 6</i>	<i>No of grains in the precise region of localization</i>
GPI	metaphases: 74	914	219	106 (48%) in p1.1 \rightarrow q12
	prometaphases: 67		80	52 (65%) in cen \rightarrow q12 42 (53%) on band q12
APOE	metaphases: 158	914	112 (12%)	48 (43%) in cen \rightarrow q21
	prometaphases: 28		42	22 (52%) in q12 \rightarrow q21.2 19 (45%) on band q21.2
ENO1	metaphases: 201	1413	216 (15%)	102 (47%) in q22 \rightarrow q24
PGD	metaphases: 75	714	181 (25%)	96 (53%) in q22 \rightarrow q25
TGF β 1	metaphases: 79	559	96 (17%)	61 (64%) in cen \rightarrow q21

From these data, it can be concluded that pig chromosome 6q contains regions homologous to human chromosome 19 (region q13.1 \rightarrow q13.2) and human chromosome 1 region (pter \rightarrow p36.13), which in turn are homologous to regions of murine

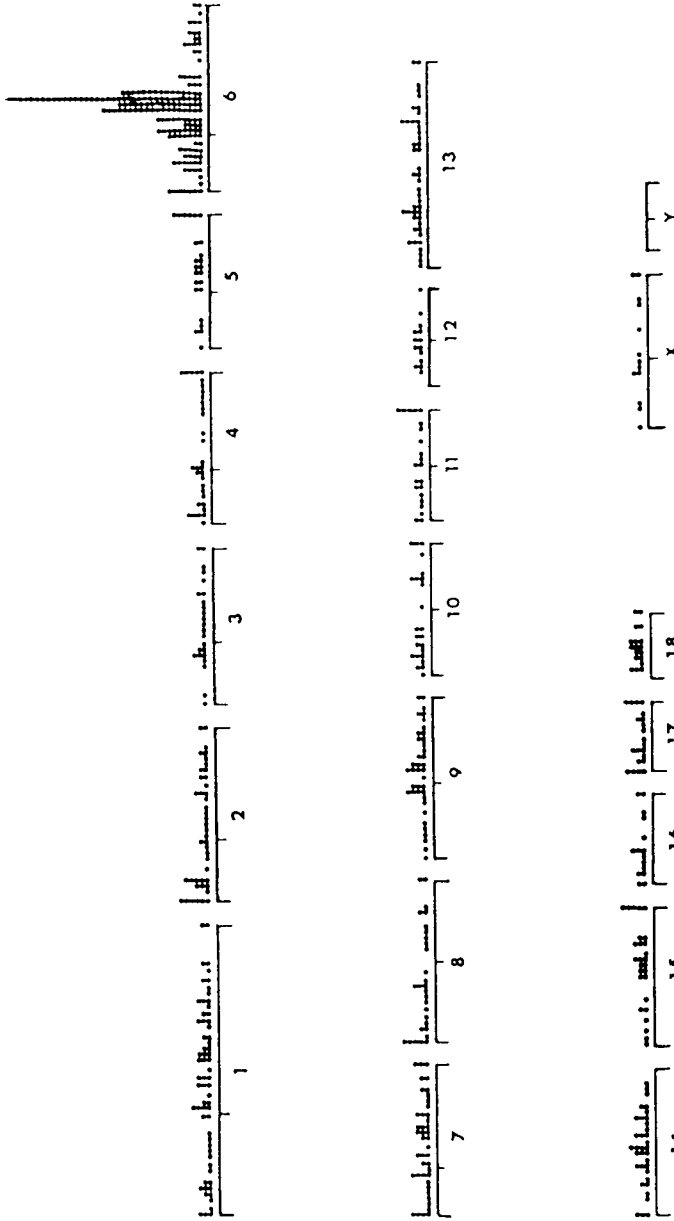


Fig 1. Chromosomal assignment of PGD by *in situ* hybridization. Histogram showing the grain distribution in 75 pig metaphases. A highly significant number of grains was found on chromosome 6.

chromosomes 7 and 4, respectively (fig 2). It is of further interest that the locus responsible for malignant hyperthermia (MH) in man has recently been mapped to the q13.1 region of HSA 19 (McCarthy *et al*, 1990). The assignment of the ryanodine receptor gene (RYR) to HSA 19 cen \rightarrow q13.2 in man (MacLennan *et al*, 1990), to chromosome 6 region p11 \rightarrow q21 in the pig (Harbitz *et al*, 1990) and to chromosome 7 in the mouse (Cavanna *et al*, 1990) further enhances the likelihood that the same gene is responsible for MH in man and pig. However, another gene, the hormone-sensitive lipase (LIPE) gene, which has been localized in the same region of human chromosome 19, could also be a good candidate for the gene responsible for malignant hyperthermia as suggested by Levitt *et al* (1990).

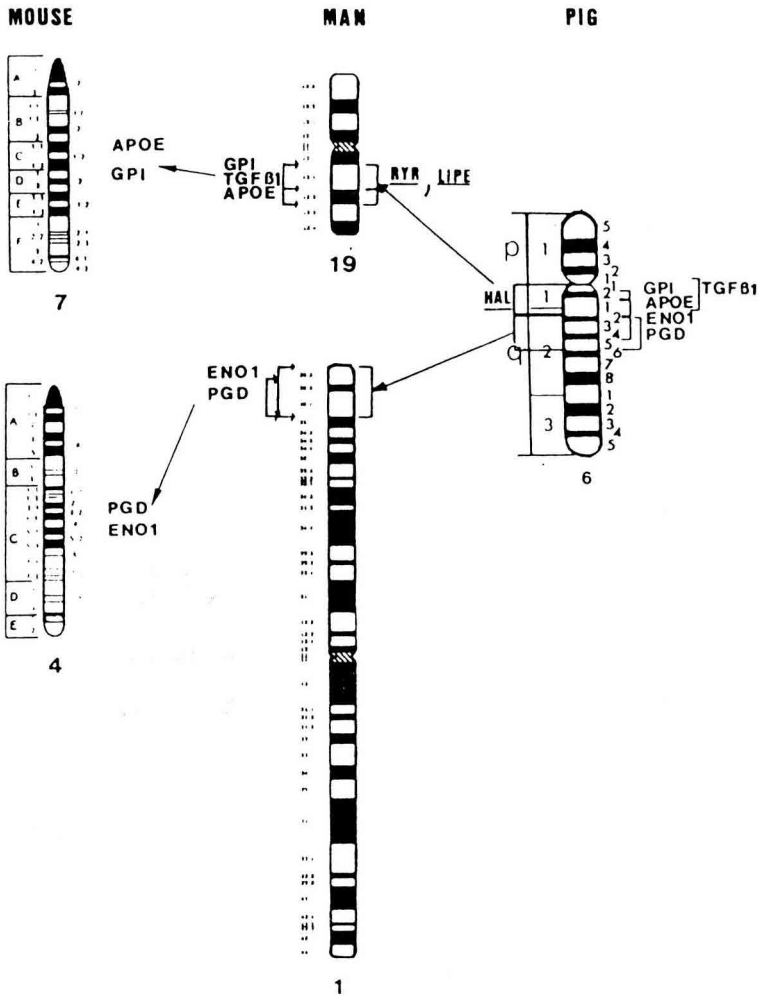


Fig 2. Comparative mapping in man, pig and mouse. Determination of homologous regions.

The results presented here confirm that the conservation of the syntenic groups around GPI and PGD is also maintained in pigs and that malignant hyperthermia in man and pigs is likely to be the result of mutations in homologous genes.

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