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Comparative Gene Mapping in Baboon (*Papio*) Species

Kathleen Lou Moore Thiessen
University of Tennessee - Knoxville

To the Graduate Council:

I am submitting herewith a dissertation written by Kathleen Lou Moore Thiessen entitled "Comparative Gene Mapping in Baboon (*Papio*) Species." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Biomedical Engineering.

Peter A. Lalley, Major Professor

We have read this dissertation and recommend its acceptance:

Julian Preston, Raymond Popp, Wen Yang, Patrick O'Neill

Accepted for the Council:
Dixie L. Thompson

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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COMPARATIVE GENE MAPPING
IN
BABOON (PAPIO) SPECIES

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Kathleen Lou Moore Thiessen

June 1986

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ABSTRACT

Gene mapping in nonhuman mammalian species is a field of increasing importance in man's efforts to understand genome organization, to develop animal models for human genetic diseases, and to investigate phylogenetic relationships and evolutionary mechanisms. The primates are of particular interest in these studies because of their morphological and physiological similarities to man. The availability and convenient size of the baboons (Papio species) make them the primates of choice for various areas of research having applications to man. The baboons also appear to have many chromosomal and genetic homologies to man as well as to the other primates, although their precise taxonomic relationship to some of these other primates is not yet clear.

In order to evaluate some of the proposed chromosomal homologies between the baboons and other species, to shed additional light on the taxonomic relationships, and to further explore the baboons as models for human disease, this study sought to develop or extend the gene maps of two species of baboons, Papio papio and P. hamadryas. Baboon x mouse or Chinese hamster somatic cell hybrids segregating baboon

chromosomes were analyzed for baboon gene and chromosome content using enzyme electrophoresis and chromosome banding techniques. Eighteen genes were assigned to chromosomes in P. hamadryas and four in P. papio by their concordant segregation with the chromosomes or with previously assigned gene markers. Several other independently segregating gene markers or syntenic groups were also identified in these species. The gene maps of the two baboon species were found to be the same where they can be compared. These maps are compared with those available for man and other species, particularly the rhesus monkey (Macaca mulatta), which is considered to be closely related to the baboons. A possible primate model for human lymphoid disease is also discussed.

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I. INTRODUCTION TO COMPARATIVE GENE MAPPING IN BABOONS

Gene mapping is the area of genetics concerned with the location of genes in the chromosome set of a species: on which chromosome a gene is located, where on the chromosome, and how far--cytologically or genetically--from other known genes. Gene maps, many of them quite detailed, currently exist for a number of species of animals, plants, and microorganisms (see O'Brien, 1984). The human gene map is obviously of prime interest and is at present the best known of any mammalian gene map. A number of fine reviews of gene mapping in man and the implications or applications to various aspects of genetics and medicine are available (see for instance Ruddle, 1981; Puck and Kao, 1982; Shows et al., 1982), and these will not be discussed at length here.

Gene mapping in nonhuman mammalian species is also of great interest, both for potential applications to knowledge about humans, and for knowledge of these other species for their own sakes. The major objectives of comparative gene mapping include an increased understanding of genome organization in general and the genetics of domestic and laboratory animals in

particular, the discovery and evaluation of potential animal models for human genetic diseases, and the investigation of phylogenetic relationships and evolutionary mechanisms. The human and mouse gene maps are the best-defined mammalian maps thus far. Less detailed maps exist for other rodents (rat, Chinese hamster), rabbits, some carnivores (cat, dog, American mink), a few of the hoofed animals, and a number of primate species (Table 1; see also O'Brien, 1984; Lalley and McKusick, 1985). The primate species for which gene maps exist include most of the great apes, several Old World and New World monkeys, and one prosimian.

The primates are obviously of special interest for genetic studies because of their morphological and physiological similarities to man (see Curie-Cohen et al., 1983). Various primate species are widely used as laboratory animals in studies having application to man, and several primate models of human genetic disease or predisposition to disease have been described or proposed. For instance, the cotton-topped tamarin, Saguinus oedipus, has been suggested as a model for human gastrointestinal disease, including colon cancer (Lushbaugh et al., 1984). Various genetic factors possibly contributing to atherosclerosis or heart disease are under study in the baboon (Papio species),

Table 1. List of Mammalian Orders, Showing Members for Which Genes Have Been Mapped.

Monotremata
*Marsupialia - (several species)
Insectivora
Dermoptera
Chiroptera
Edentata
Pholidota
*Lagomorpha - rabbit
*Rodentia - MOUSE, rat, Chinese hamster
Cetacea
*Carnivora - cat, dog, American mink
Pinnipedia
Tubulidentata
Proboscidea
Hyracoidea
Sirenia
*Perissodactyla - horse
*Artiodactyla - cow, sheep, pig, (Indian muntjac)
*Primates - Families:
Tupaiidae
*Lemuridae - Microcebus
Indridae
Daubentoniidae
Lorisidae
Tarsiidae
*Cebidae - Cebus, Aotus
*Callithricidae - Saguinus, (Callithrix)
*Cercopithecidae - Cercopithecus, Macaca, Papio
*Hylobatidae - Hylobates
*Pongidae - Pan, Pongo, Gorilla
*Hominidae - HOMO

An asterisk (*) indicates an order or family in which syntenies or gene assignments are known for at least one member. Species or genus names in all capitals indicate species with more than 700 mapped genes; underlined names indicate species with more than 50 mapped genes; names in parentheses indicate species with less than 10 mapped genes each.

References: Walker, 1975; Lalley and McKusick, 1985; de la Chappelle, 1985.

including a heritable factor affecting serum cholesterol levels (Flow et al., 1981) and a polymorphism of complement component 3 (VandeBerg and Aivaliotis, 1984; Cheng et al., 1984).

Homologies of gene content or of banding patterns between chromosomes of various species have been noted (for instance Lalley et al., 1978b; Nash and O'Brien, 1982; Finaz et al., 1977; Dutrillaux et al., 1978), and these are of particular interest for phylogenetic or taxonomical studies. The problems to be addressed here include the correlation, if any, between banding patterns and regions of genetic homology; the relationship of chromosome rearrangements to speciation--whether chromosome rearrangement is a method or a by-product of speciation; and the interpretation of linkage group conservation (observation of the same linkage group in two species)--whether the arrangement is by necessity or by chance, perhaps simply a function of the distance betweeen two genes. The high degree of similarity of chromosome banding patterns between various primate species and man suggest large regions of chromosome homology between these different species (for review see de Grouchy et al., 1978; Dutrillaux, 1979), and phylogenetic trees based on the banding patterns and mechanisms of speciation by chromosome rearrangement

have been proposed. A key goal of gene mapping studies, therefore, is to determine whether regions of chromosomes which appear similar on the basis of banding patterns are, in fact, homologous on the basis of gene content.

The baboons, genus Papio, are members of the Old World monkey family Cercopithecidae, which is considered further removed from man than the Pongidae or Hylobatidae (the great apes and the gibbons) but closer than the Cebidae (New World monkeys). Their large size and their availability make them valuable animals for various areas of research, including reproductive biology, experimental surgery, and behavioral research (Goodwin and Coelho, 1982). Highly social animals whose natural range includes most of Africa and part of Arabia, the baboons include five species in two species groups (Napier and Napier, 1967) or superspecies (Jolly, 1966; Hill, 1967, 1970). The Papio cynocephalus group includes P. anubis (the olive baboon), P. cynocephalus (the yellow baboon), P. papio (the guinea baboon), and P. ursinus (the chacma baboon); P. papio is considered the type species of the group. The second species group contains the single member, Papio hamadryas (the sacred or hamadryas baboon). These classifications are based

primarily on geographical, morphological, and behavioral criteria.

Related species include the mandrill (Mandrillus sphinx), the drill (M. leucophaeus), the Gelada baboon (Theropithecus gelada), and the macaques (Macaca species), including the rhesus monkey, M. mulatta (nomenclature from Napier and Napier, 1967). Other classifications include the mandrill and drill as members of genus Papio (P. sphinx and P. leucophaeus, respectively; see for instance Walker, 1975). Buettner-Janusch (1966) suggests that the baboons, the mandrill and drill, and the Gelada baboon properly belong in the same genus, Papio, as members of only four species: P. cynocephalus, the common baboon; P. gelada, the Gelada baboon; P. hamadryas, the sacred baboon; and P. sphinx, the mandrill and drill. The other species would more accurately be considered subspecies, and P. hamadryas might also be a subspecies of P. cynocephalus.

Various members of Papio have successfully interbred with each other and with members of related genera such as Mandrillus, Theropithecus, and Macaca (reviewed by Buettner-Janusch, 1966, and Chiarelli, 1973; see also Maples, 1972; Nagel, 1973; Dunbar and Dunbar, 1974; Markarjan et al., 1974). Most of the intergeneric hybrids have occurred in captivity and have

not been fertile. Hybridization between Papio species does occur in the wild, and "intermediate" zones are found along some species borders (Maples, 1972; Nagel, 1973). In other cases, however, the species borders remain distinct, and no apparent hybridization occurs even though no obvious geographical obstacle is present to prevent it. Jolly and Brett (1973) suggest that large-scale population studies to examine gene flow between the various baboon species or races be conducted in order to make an accurate revision of the taxonomy. These studies have not yet been carried out, although a number of potentially useful genetic and immunological markers have been identified (see for instance Moor-Jankowski et al., 1973; Moor-Jankowski and Socha, 1979; Crawford et al., 1984; Lockwood et al., 1984; Dykes et al., 1985).

All species of Papio, Mandrillus, Theropithecus, and Macaca have forty-two chromosomes (reviewed by Bender and Chu, 1963; Ardito, 1979). Using current techniques of chromosome banding, Cambefort et al. (1976a, 1976b) and Dutrillaux et al. (1978, 1979, 1982) have shown that the karyotypes of the baboon (Papio) species are identical. The karyotypes of Mandrillus sphinx and M. leucophaeus are identical to each other and differ from those of Papio by one rearranged

chromosome. The banded karyotypes of various Macaca species are again nearly identical to each other, with that of M. mulatta being identical to that of Papio (Finaz et al., 1978; Dutrillaux et al., 1979). A banded karyotype of T. gelada is not available, but its unbanded karyotype is quite similar to that of Papio (Chiarelli, 1962). Gene mapping in these various species will be of interest to determine whether the maps agree as nicely as do the banded karyotypes. It will also help in the eventual determination of an accurate taxonomy for these primates.

The present study has involved the two type species of Papio (according to Napier and Napier, 1967), P. papio and P. hamadryas. A number of linkage groups were identified and genes assigned to chromosomes in these two species. Their gene maps are compared with each other and with those presently available for man, Macaca mulatta, and other species.

II. STRATEGY AND METHODOLOGY OF GENE MAPPING USING SOMATIC CELL HYBRIDS

The history, methodologies, and strategies of gene mapping are discussed in detail in several excellent reviews, including those by Ruddle and Creagan (1975), Ringertz and Savage (1976), McKusick (1980), Ruddle (1981), Shows et al. (1982), Womack (1982), D'Eustachio and Ruddle (1983), and Kao (1983). The key to any method of gene mapping is genetic variation. Classical gene mapping or linkage analysis, as done by family or breeding studies, requires distinguishable genotypes (indicated by differing phenotypes) within a group of related individuals. The pattern of inheritance of the variable trait is observed, and, if several such traits occur in the same family, linkage--a correlated or nonindependent pattern of inheritance--may sometimes be observed. Variation or structural polymorphism in a chromosome may correlate with that of a gene marker, permitting the assignment of the gene to that chromosome. For instance, Donahue et al. (1968) made the first autosomal gene assignment in man by demonstrating linkage in several families of the Duffy blood group to an anomalous uncoiled region of human chromosome 1.

A large linkage map for the mouse was worked out through breeding studies, and a few autosomal genes and a number of X-linked genes were assigned to chromosomes in man using family studies. Certain difficulties with this type of study exist, however, especially in man, but also with many other species. One is the relative scarcity of useful genetic variants. Those attributable to only one gene pair are often present in the population in too low a frequency to be of widespread use. The restriction fragment length polymorphisms produced by recent molecular techniques now provide a large number of genetic variants, but other disadvantages to family studies in man remain, including the long generation time, the small number of offspring, and the random (to the investigator) matings. In other species, such as the primates or the domestic animals, the investigator can control the matings, but the generation time and number of offspring are often still not optimal.

The development of two techniques in the early 1970's circumvented these difficulties to permit comparatively rapid gene mapping in man and virtually any other species of interest. These are the techniques of chromosome banding and of interspecific somatic cell hybridization.

Several new methods of chromosome staining became available in 1970 and 1971 which permitted the identification of each individual chromosome pair in a karyotype by a specific pattern of "bands" (for instance Caspersson et al., 1970; Arrighi and Hsu, 1971; Seabright, 1971; Sumner et al., 1971). Rearrangements of chromosomes such as translocations or inversions could also be readily identified by chromosome banding methods. While identification of specific chromosome pairs would not help gene assignment by family studies unless a chromosome pair which differed in banding pattern (due to an inversion in one member, for instance) were observed, the banding techniques did open the door for utilization of somatic cell hybrids.

Interspecific somatic cell hybridization is a parasexual technique--it does not require mating of two individuals for genetic analysis. Rather, it takes advantage of genetic variation between species, which in general is much greater and easier to find than variation within a species.

Spontaneous fusion of cells in culture was first observed by Barski et al., (1960, 1961). Subsequent work showed that hybrid cells can be produced at much higher rates by the use of inactivated Sendai virus (Harris and Watkins, 1965; Yerganian and Nell, 1966) or

polyethylene glycol (Pontecorvo, 1975), both of which cause the cell membranes to fuse, resulting in multinucleated cells. Fusion can occur between cells of two different species (Ephrussi and Weiss, 1965; Harris and Watkins, 1965), and both genomes can be expressed in the hybrid cells (Weiss and Ephrussi, 1966).

Cell fusions can be designed so as to permit the selection of hybrid cells from parental cells. The most commonly used selection system, HAT (for hypoxanthine, aminopterin, and thymidine), makes use of cell lines deficient in one of the nucleotide salvage pathway enzymes HPRT (hypoxanthine phosphoribosyltransferase) or TK1 (thymidine kinase; Szybalski et al., 1962; Littlefield, 1964). When aminopterin is present in the culture medium, a cell's normal de novo pathways for nucleotide synthesis are blocked, and the cell dies. If hypoxanthine and thymidine are supplied with the aminopterin, however, the cell can then use the nucleotide salvage pathways to replace the blocked de novo routes and thereby will survive. A normal cell can thus grow in HAT medium, but a cell deficient in either HPRT or TK1 cannot use the salvage pathways and therefore will die in HAT medium. If an HPRT- or TK1-deficient cell is fused with a cell containing the normal gene, the hybrid cell, because it now can make

the functional enzyme, can grow in the HAT medium, while the HPRT- or TK1-deficient parental cell cannot. Fusion of an HPRT-deficient cell with a TK1-deficient cell results in a cell containing both normal genes (one from each parental cell) and which can survive in HAT medium; both parental cell types die in HAT medium, thereby permitting selection of only hybrid cells, or those containing both genomes.

In a standard fusion procedure, a transformed rodent cell line deficient in either HPRT or TK1 is generally used as one of the parental cell types. Transformed cell lines are fast growing and essentially immortal in culture, and the deficiency of HPRT or TK1 permits selection against any unfused rodent parental cells by the use of HAT medium. The transformed rodent cells are fused with normal cells from some species of interest, for example a baboon or other primate species. The hybrid cells, having obtained the functional HPRT or TK1 gene from the normal parental cell, can grow in HAT medium. The unfused normal parental cells can often grow in HAT medium also, so that another means of selection must be used against them.

If the normal parental cells are lymphocytes or lymphoblastoid-type cells, they will be lost when the medium is changed; these types of cells do not attach to

the culture dishes, while the rodent cell lines used and the resulting hybrid cells will attach to the culture dish. Fibroblast-type normal parental cells, which also attach to the culture dish, will often grow much more slowly than the hybrid cells (which usually have the fast growth characteristics of the transformed rodent cell line), so that hybrid clones can be isolated before the normal parental cells have become very numerous. Occasionally the normal parental cells will grow rapidly, so that another type of selection must be applied against them; one often-used method takes advantage of species differences in sensitivity to the drug ouabain (Kucherlapati et al., 1974). Rodent cells and their hybrids can survive a concentration of ouabain which will kill most primate cells. A combination of HAT- and ouabain-selection thus ensures that only hybrid cells will grow.

After the fusion, each hybrid cell contains two nuclei, one from each species; these cells are known as heterokaryons. Following the first mitosis, the chromosomes of each original cell are combined in a single nucleus in the hybrid cell; the hybrid cells are now called synkaryons. The synkaryons proliferate, and each is eventually isolated as a separate hybrid clone. As each synkaryon proliferates, it tends to lose or

segregate chromosomes from the normal parental cell (Weiss and Green, 1967).

The result of an interspecific cell fusion experiment is a set of hybrid clones, each from a different synkaryon, and each of which has the full chromosome complement of the transformed rodent parental cell line and some number and combination of chromosomes from the normal parental cells. If a particular gene or gene product can be distinguished betwen the two species, it is then possible to correlate the presence or absence in the hybrid cells of a gene from the normal parental cells with the presence or absence of a particular chromosome from that parent, as determined by chromosome banding techniques.

Each somatic cell hybrid clone is examined for the presence or absence of a number of genes or gene products from the normal parental cells, and each clone is karyotyped for determination of the chromosome content. Two genes which segregate concordantly--are always both present or both absent (both expressed or neither expressed) in the set of hybrids--are most likely on the same chromosome and are said to be syntenic. ("Linkage" and "synteny" are not entirely synonymous--linked genes must be syntenic, but syntenic genes are not necessarily linked.) If a gene segregates

concordantly with a chromosome, it is assigned to that chromosome. A gene can also be assigned to a chromosome if it is shown to be syntenic with a previously assigned gene; this necessarily assumes the accuracy of the previous assignment. Subchromosomal or regional assignments of genes are possible when the parental cells contain a translocation or when breaks or translocations occur (spontaneously or induced) in a hybrid clone. Chromosome and gene analyses are done in parallel cell cultures (set up at the same time from the same dish of cells) in order to avoid confusion or error caused by continued segregation of chromosomes. Hybrid clones are often unstable--they continue to lose chromosomes--so that chromosome and gene analyses done weeks apart might not correlate with each other.

Enough hybrid clones must be examined to permit assignment of a gene to one particular chromosome while excluding all other chromosomes. An assignment can be made if there is less than ten percent discordancy in the segregation of a gene and a chromosome (and there is no other chromosome for which the concordancy is greater). Discordant results are sometimes caused by chromosome breakage; analysis of discordant clones can often give information on subchromosomal locations of genes.

A gene assignment made by one laboratory is considered provisional; when two or more laboratories have agreed upon an assignment or when two different mapping techniques give the same result, it is then considered confirmed. Except for the mouse, gene mapping in any particular nonhuman species has usually been done by only one laboratory; much of the comparative mapping data must therefore be considered provisional.

Several types of analysis of genes or gene products have been used in the characterization of somatic cell hybrids. One type takes advantage of cell culture markers which differ between the two species, such as ouabain or diphtheria toxin sensitivity, or at least between the parental cells, such as deficiencies of TK1 or HPRT. Another type of analysis involves electrophoretic differences between the species for various constitutive enzymes expressed in cell culture. The most recently developed methods use direct hybridization to the DNA of an RNA or cDNA probe, either by in situ hybridization to fixed metaphase chromosomes or by hybridization to Southern blots of hybrid cell DNA which has been treated with restriction enzymes (see for instance Ruddle, 1981; D'Eustachio and Ruddle, 1983; Kao, 1983).

The advantage of the enzyme markers in gene mapping is the comparative ease and speed with which they can be analyzed, as compared to various DNA hybridization methods. The latter are ultimately more powerful and are especially applicable for genes not expressed in cultured cells or for "unidentified" genes or DNA fragments. However, the enzyme markers permit a broad overview of the genome organization of a species in less time than is required for the molecular techniques and can, together with karyotyping, give good markers for many or most of the chromosomes of the species.

In comparative mapping it is important to show the homology of genes between species. Criteria for homology include similar nucleotide or amino acid sequence; immunological cross-reactivity; formation of functional heteropolymers in the case of polymeric enzymes; similar tissue distributions, time of developmental appearance, and subcellular location; similar substrate specificity of enzymes; and cross-hybridization to the same molecular probe (Lalley and McKusick, 1985). The present study has dealt primarily with consititutive enzymes expressed in cultured cells of baboon species and somatic cell hybrids of baboons and rodents. The main criteria of genetic homology (baboon to man or rodent) used here have been the

similar substrate specificities of the enzymes as evidenced in staining for them and the formation of functional heteropolymers between baboon and rodent enzyme in the case of polymeric enzymes.

III. MATERIALS AND METHODS

A. Cell culture and cell fusions

The *P. papio* x mouse somatic cell hybrids used in this study were made by P. A. Lalley and are those described in Lalley *et al.* (1979) and Thiessen and Lalley (in press). Baboon lung fibroblasts were fused with mouse B82 (TK1 deficient) cells in 1976, and lung fibroblasts from a second, unrelated baboon were fused with mouse RAG (HPRT deficient) cells in 1978. Both cell fusion experiments were done using inactivated Sendai virus according to standard cell fusion techniques (see Lalley *et al.*, 1974). Thirty-three hybrid clones segregating baboon chromosomes were isolated and maintained in HAT medium.

The *P. hamadryas* hybrids used in the latter part of this study were made from a *P. hamadryas* lymphoblastoid cell line, 26CB-1, which was obtained from the American Type Culture Collection (line CRL 1495). This cell line was originally established from splenic lymphocytes of a lymphomatous male baboon (Falk *et al.*, 1976). These cells were fused to Chinese hamster E36 (HPRT deficient) cells (Thiessen and Lalley, in preparation) using a

variation of the method described by Fazekas de St. Groth and Scheidegger (1980).

Baboon cells and hamster cells in a 3:10 ratio were fused in suspension using 45% polyethylene glycol (molecular weight 1540) in serum-free Dulbecco's modified Eagle's medium (DMEM), in a fusion volume of 1 ml, for 90 seconds at 37°C. This was followed by a slow dilution (to 5 ml over 10-12 minutes) with warm complete DMEM (5% fetal bovine serum, FBS). Fourteen hybrid clones from two fusion experiments were isolated and maintained in HAT medium according to Lalley et al. (1974).

Parental cell lines were maintained in DMEM with 5% (B82, E36) or 10% (RAG, baboon lung fibroblasts) FBS or in RPMI 1640 with 10% FBS (26CB-1).

B. Preparation of cell extracts

Cells were removed from two or three 150 mm dishes by trypsinization or scraping. Following centrifugation at 1000 x g for 10-15 minutes and removal of the supernatant, the cells were rinsed in 30 ml of cold serum-free minimum essential medium and centrifuged again. This was repeated twice. The cells were then suspended in the homogenization buffer (0.05 M Tris,

pH 7.4) at a dilution of 60 x 10^6 cells per ml or twice the volume of the cell pellet. Cells from line 26CB-1 were suspended at 120 x 10^6 cells per ml or an amount equal to the pellet volume. Cells were homogenized using a motor-driven teflon rod in a glass homogenization tube or by repeated (4 x) freezing in liquid nitrogen followed by rapid thawing in a 37°C water bath. Cell extracts were stored in a freezer at -70°C.

C. Enzyme electrophoresis and staining

Cellulose acetate or starch gel electrophoresis of the cell extracts followed by enzyme-specific staining was used to determine the enzyme content of the hybrid clones. The following conditions of electrophoresis were used:

1) Tris-EDTA-borate buffer system, pH 8.6 (0.90 M Tris, 0.0195 M ethylenediaminetetraacetic acid, 0.50 M boric acid, 0.41 M $MgSO_4$; used 1/20 for the gel, diluted 1/5 and 1/7 for the cathode and anode trays, respectively), run at 300 v for 18-20 hours (ACY1; ADA; GSR; ITPA; LDHA and B; MDH1; MPI; NP; PEPB, C, D, and S; PGM1 and 2; PKM2; PP; SOD1

and 2; see Appendix A for explanation of gene and enzyme symbols).

2) Tris-citrate system, pH 7.0 (0.45 M Tris, 0.17M citric acid, pH adjusted with 10 N NaOH; diluted 9/500 for the gel and 1/2 for the electrode trays), run at 200 v for 18 hours [ACP2, ME1 (mouse hybrids only), PGD]. The stock buffer diluted 1/20 was used with cellulose acetate gels (200 v for 30 minutes) for GPI.

3) Tris-citrate plus $MgSO_4$ system, pH 7.4 (0.1 M Tris, 0.026 M citric acid, 0.041 M $MgSO_4$; used full strength for the electrodes and diluted 1/10 for the gel), 250 v for 18 hours [IDH1 and 2, MDH2, ME1 (hamster hybrids)].

4) Sodium phosphate (0.2 M) system, pH 6.5 (diluted 1/20 for the gel, used full strength for the electrodes), 175 v for 18 hours (ACP1, ESD, HEXA).

5) Tris-histidine system, pH 7.8 (Kömpf et al., 1975; used full strength for the electrodes, diluted 1/10 for the gel), 150 v for 18 hours (GLO1, SORD).

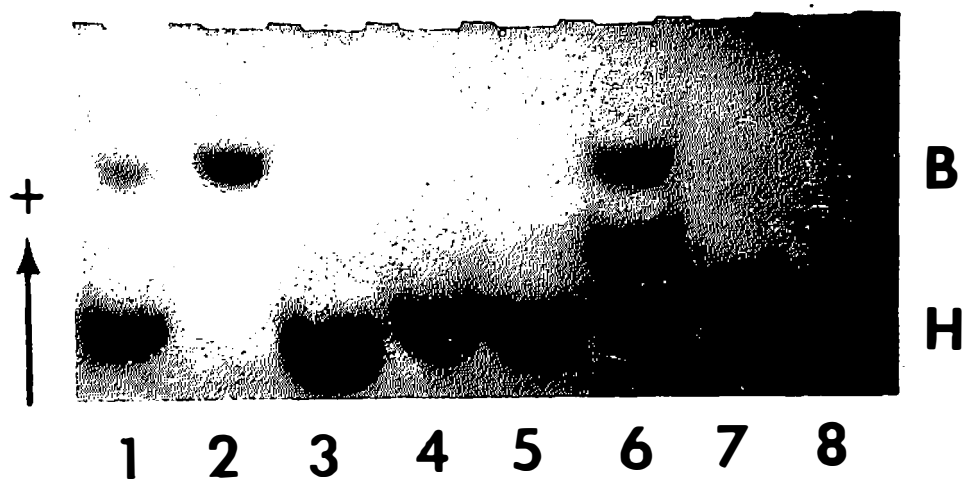
6) Tris-glycine system, pH 8.6 (0.025 M Tris, 0.19 M glycine), on cellulose acetate at 300 v for 15 minutes (LDHA and B, TPI1).

The rodent and baboon forms of several enzymes did not prove separable in these electrophoretic systems. The following markers were therefore not analyzed in one or both sets of hybrids: ACP1, GLO1, IDH2, and PEPB in the hamster hybrids; GSR, PEPD, PP, and TPI1 in the mouse hybrids (RAG and B82); PEPC in the mouse RAG hybrids; APRT, G6PD, GOT1, HEXB, PEPA, PGK, and PGM3 in all sets of hybrids. For various other technical reasons, SORD was not analyzed in the hamster hybrids; SOD2 in the mouse B82 hybrids; ACP2, ESD, GPI, HEXA, and LDHB in any of the mouse hybrids; or GUSB in any of the hybrids.

Staining for the enzymes was carried out as described by Harris and Hopkinson (1976) for all enzymes except ACY1 (Kit et al., 1980), GLO1 (Parr et al., 1977), GSR (Nichols and Ruddle, 1975; the amount of oxidized glutathione was doubled), and SORD (modified by doubling the concentrations of sorbitol and NAD as per Créau-Goldberg et al., 1983). Some representative gels are pictured in Figure 1.

D. Chromosome analysis

Karyotypes of the P. hamadryas and Chinese hamster parental cells and hybrid clones were studied following

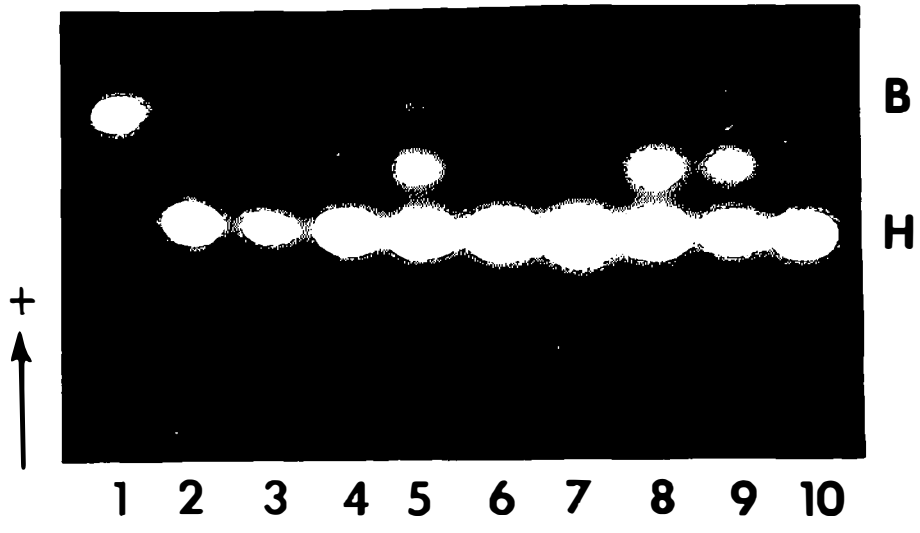


A. Mitochondrial malate dehydrogenase phenotypes in cultured cells of hamster, baboon, and somatic cell hybrids.

(1) Hamster + baboon mixture
(2) Baboon (P. hamadryas)
(3, 4, 5, 7) Baboon MDH2 negative hybrids
(6) Baboon MDH2 positive hybrid
(8) E36 Chinese hamster

Gel system: Tris-citrate + $MgSO_4$, pH 7.4.

Figure 1. Electrophoretic patterns for four typical enzymes following histochemical staining.

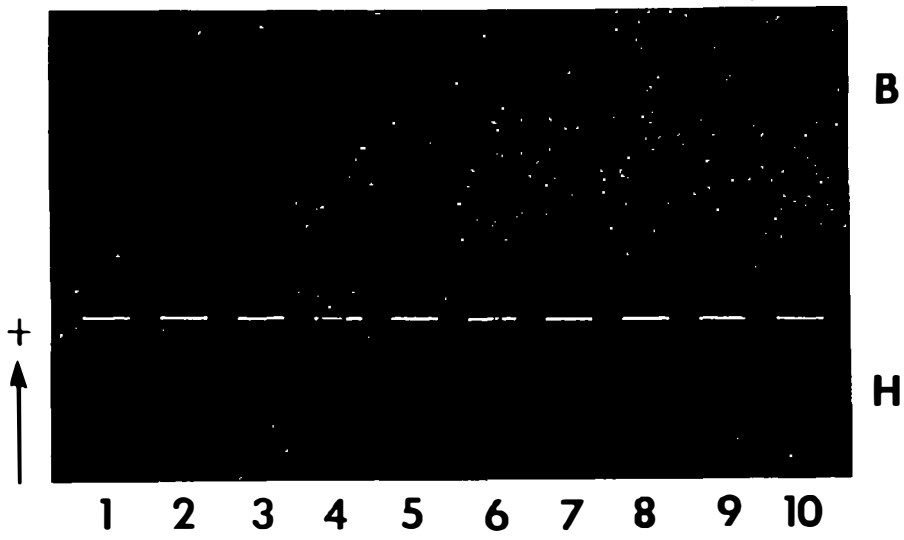


B. Esterase D phenotypes in cultured cells of hamster, baboon, and somatic cell hybrids.

(1) Baboon (P. hamadryas)
(2, 3, 4, 6, 7) Baboon ESD negative hybrids
(5, 8, 9) Baboon ESD positive hybrids
(10) E36 Chinese hamster

Gel system: Sodium-phosphate, pH 6.5.

Figure 1 (Continued)



D. Acid phosphatase 2 phenotypes in cultured cells of hamster, baboon, and somatic cell hybrids.

(1) E36 Chinese hamster
(2, 3, 4, 5, 7, 9) Baboon ACP2 positive hybrids
(6, 8) Baboon ACP2 negative hybrids
(10) Baboon (P. hamadryas)

Gel system: Tris-citrate, pH 7.0.

Figure 1 (Continued)

trypsin-Giemsa banding of standard metaphase chromosome preparations. Cells were treated with 0.01 μg/ml colcemid for 1.5 to 2 hours before harvesting. Following a 15-20 minute hypotonic treatment (either 0.062 M KCl plus 2% FBS or 0.075 M KCl) at 37°C, the cells were fixed in a 3:1 methanol-acetic acid mixture before being dropped onto wet slides. The slides were placed in a 60°C oven overnight and then left for 3-5 days in a 37°C oven. The dried slides were treated for 20-90 seconds at room temperature in a trypsin-EDTA mixture [0.05% and 0.02%, respectively, in a modified calcium- and magnesium-free phosphate buffered saline (0.14 M NaCl, 0.0027 M KCl, 0.021 M Na_2HPO_4, 0.0015 M KH_2PO_4, pH 7.75)]. They were then washed in the saline and stained in 4% Giemsa (in Gurr's phosphate buffer, pH 6.8) for 2-6 minutes (N. C. Sun, personal communication with P. A. Lalley).

Banded metaphase spreads were photographed using either a Zeiss or a Leitz photomicroscope and Kodak 2415 film. The film was developed with Kodak HC-110, Dilution D, for 8 minutes at 20°C, and later was printed on Kodak F3 paper.

The chromosome nomenclature used for P. hamadryas is from Cambefort et al. (1976b) and is the same as that used for P. papio (Cambefort et al., 1976a).

Nomenclature for M. mulatta is from Pearson et al. (1979).

Cell extracts for enzyme analysis were made at several different passages following isolation of the hybrid clones. Extracts made at the same passage as the chromosome preparations were used to correlate the enzyme and chromosome contents of the cells.

IV. GENE ASSIGNMENTS AND SYNTENIC GROUPS IN BABOONS

A. Papio papio

The first genes assigned to a chromosome in P. papio were those coding for the enzymes PGM1 and ENO1, which were assigned to P. papio chromosome 1 (PPA1; Finaz et al., 1977; see Appendix A for explanation of gene and enzyme symbols). Lalley et al. (1979) demonstrated the synteny of PGM1 with PGD and PEPC, permitting the assignment of PGD and PEPC to PPA1 as well. They also demonstrated the synteny of ME1 and GLO1 in P. papio and reported the asynteny of IDH1 with MDH1 and ACP1.

Another nineteen genes were assigned to nine chromosomes by Créau-Goldberg et al. (1982, 1983, 1984, 1985). These include SOD1, GUSB, and COL1A2 to PPA3; GLO1 and ME1 to PPA4; PGM2 to PPA5; NP, CKBB, MPI, PKM2, IDH2, and SORD to PPA7; ADA to PPA10; LDHB to PPA11; IDH1 to PPA12; LDHA to PPA14; and COL1A1, TK, and GAA to PPA16.

The first part of the present study involved the same set of P. papio x mouse somatic cell hybrids that was discussed by Lalley et al. (1979). Thirty-three

hybrid cell lines were successfully analyzed for the expression of twenty-three enzymes; the genes coding for fifteen of the enzymes had previously been assigned to baboon chromosomes. The results of enzyme electrophoresis for a representative subset of the hybrids are given in Table 2. Not every hybrid could be analyzed for every enzyme. The two mouse cell lines used (RAG and B82) carried different electrophoretic variants of some enzymes, including GPI, ITPA, and PEPC. Baboon PEPC could not be separated from the mouse enzyme expressed by the RAG cells. The baboon x RAG cell hybrids (BLRs) therefore could not be analyzed for the baboon enzyme. Another enzyme, SOD2, was too weakly expressed in the baboon x B82 cell hybrids (BBAs) to be scored accurately.

The genes coding for four enzymes were assigned to baboon chromosomes by virtue of their concordant segregation in the hybrid cells with previously assigned genes (Figure 2); this necessarily assumes the accuracy of the previous assignment. MDH2 segregated concordantly with SOD1 and was assigned to PPA3. SOD2 was syntenic with GLO1 and ME1 and was assigned to PPA4. Similarly, PEPS was assigned to PPA5 by its concordant segregation with PGM2, and ITPA to PPA10 by its concordance with ADA. In each case, the genes coding

Table 2. Distribution of Baboon Enzymes in 12 Papio papio x Mouse Hybrid Clones.

Chromosome Location		Enzyme	Clones											
PPA	HSA		BBA7	BBA8B	BBA9	BBA16	BBA24	BLR1	BLR9	BLR13	BLR16	BLR17	BLR21	BLR23
1	1	PGD	-	+	-	-	-	-	-	+	-	-	-	-
1	1	PGM1	-	+	-	-	-	-	-	+	-	-	-	-
1	1	PEPC	-	+	-	-	-	ND	ND	ND	ND	ND	ND	ND
3	21	SOD1	+	+	+	-	-	+	+	+	-	+	+	+
3*	7	MDH2	+	+	+	-	-	+	+	+	-	+	+	+
4	6	GLO1	-	+	+	-	-	+	-	-	-	-	-	+
4	6	ME1	-	+	+	-	-	+	-	-	-	-	-	+
4*	6	SOD2	ND	ND	ND	ND	ND	+	-	-	-	-	-	+
5	4	PGM2	+	+	+	-	-	+	-	-	-	-	-	-
5*	4	PEPS	+	+	+	-	-	+	ND	-	ND	-	-	-
7	14	NP	-	-	-	+	-	-	-	+	-	-	-	+
7	15	IDH2	-	-	-	+	-	-	-	+	-	-	-	+
7	15	SORD	-	-	-	+	-	-	-	+	-	ND	ND	+
7	15	MPI	-	-	-	+	-	-	-	+	-	-	-	+
7	15	PKM2	-	-	-	+	-	-	-	ND	-	-	-	+
10	20	ADA	-	+	-	+	+	-	+	-	-	-	-	-
10*	20	ITPA	-	+	-	+	+	-	+	-	-	-	-	-
12	2q	IDH1	+	-	+	-	+	+	-	+	-	+	+	+
	2p	ACP1	-	-	-	-	-	-	-	-	-	-	-	-
	2p	MDH1	-	-	-	-	-	-	-	-	-	-	-	-
14	11	LDHA	+	-	+	-	-	+	-	-	-	+	+	+
	3	ACY1	+	ND	+	-	-	-	-	ND	+	-	ND	+
	12	PEPB	-	+	-	-	-	+	-	+	-	-	-	-

+ present; - absent; ND not determined; * new assignment

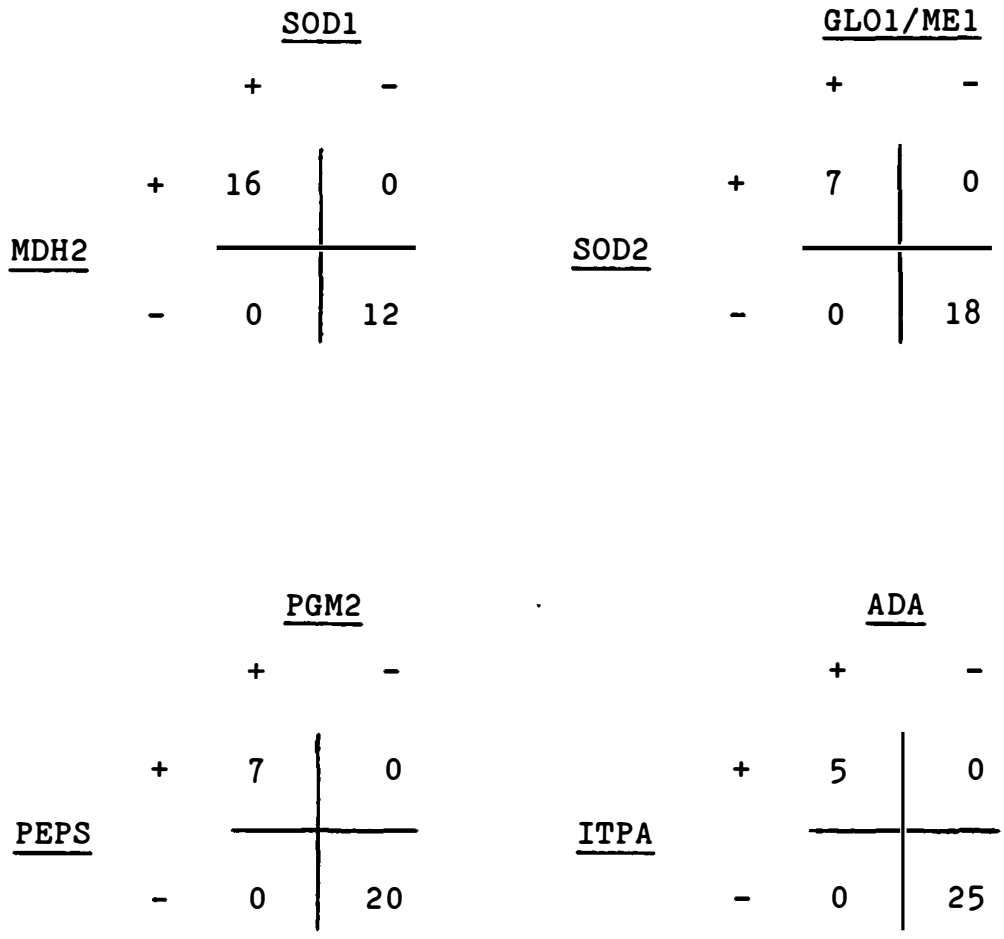


Figure 2. Segregation of MDH2, SOD2, PEPS, and ITPA with previously assigned Papio papio gene markers.

for these enzymes segregated discordantly with all other genes studied.

The segregation of NP, IDH2, SORD, MPI, and PKM2 was analyzed in twenty-four of the hybrids (Table 3). These markers segregated concordantly in twenty-two of the cell lines (92 percent). One hybrid was positive for NP but negative for the other four enzymes, and another hybrid was positive for NP, IDH2, and SORD but negative for MPI and PKM2. The discordant results were probably caused by chromosome breakage in the hybrid clones, although this was not checked. The data confirm the synteny of these genes, in agreement with their assignment to the same chromosome (Créau-Goldberg et al., 1982, 1983). In addition, the results from the discordant clones suggest a gene order of NP, IDH2 and SORD, MPI and PKM2.

At least three other independently segregating markers or syntenic groups have also been identified in P. papio. MDH1 and ACP1 segregate discordantly with IDH1 (Lalley et al., 1979) and with all the other genes examined, but it could not be established from these data whether or not MDH1 and ACP1 segregate separately from each other. ACY1 and PEPB each segregated independently of all other markers examined in this study, and they therefore represent two additional

Table 3. Linkage of NP, IDH2, SORD, MPI, and PKM2 in Papio papio.

Number of Clones	NP	IDH2	SORD	MPI	PKM2
2	+	+	+	+	+
1	+	+	+	+	ND
1	+	ND	+	+	ND
1	+	+	+	-	-
1	+	-	-	-	-
18	-	-	-	-	-

+ present; - absent; ND not determined

syntenic groups. This study examined at least one marker from every assigned syntenic group except those on PPA11 and 16; these data therefore cannot exclude synteny of MDH1, ACP1, ACY1, or PEPB with known PPA11 or 16 markers.

In summary, this work permitted four new gene assignments in P. papio, confirmed one large syntenic group, and identified two additional independently segregating markers or syntenic groups (Thiessen and Lalley, in press). A gene map of P. papio listing all known chromosome assignments is given in Appendix B. Twenty-seven provisional assignments have been made. The synteny of GLO1 and ME1 and of NP, MPI, PKM2, IDH2, and SORD can be considered confirmed. Of twenty possible autosomal syntenic groups, a maximum of fourteen have been identified.

B. Papio hamadryas

P. hamadryas was chosen for the major part of this study for two reasons: first, as the other type species of genus Papio, P. hamadryas would provide the best intrageneric comparison to P. papio, if any differences in the gene maps between baboon species were to be found; second, with a new set of hybrid cells, it might

be possible to examine genes which could not be studied in the earlier set of P. papio hybrids, thereby obtaining additional information on how the gene arrangement(s) of Papio compared with those of various other species.

The only chromosomal assignment reported in P. hamadryas prior to this study was for the ribosomal RNA genes (rDNA or RNR), which were shown to be on the marker chromosome (chromosome 10) in both P. hamadryas and P. cynocephalus (Henderson et al., 1977).

For the present investigation, fourteen P. hamadryas x Chinese hamster hybrid clones were analyzed for the expression of twenty-seven enzyme markers and the presence of baboon chromosomes. Five of the hybrids contained no identifiable baboon autosomes or autosomal fragments (although four of them did express one or more baboon enzyme) and were not considered further in this study. The results of electrophoresis for the remaining hybrid clones are given in Table 4.

In the parental baboon cell extracts, ACP2 and ME1 could not be detected by the staining methods used. Hybrid cells containing the baboon enzyme demonstrated both the heteropolymer(s) and the parental baboon form (see Figure 1D, p. 28). The explanation for this observation is not known. Also, the parental baboon

Table 4. Distribution of Baboon Enzymes in Early Passage Papio hamadryas x Chinese Hamster Hybrid Clones.

Syntenic Group	Enzyme	Clones PHE1	PHE2	PHE3	PHE4	PHE5	PHE6	PHE8	PHE9	PHE14
1	PGD	-	-	-	-	-	-	+	-	-
1	PGM1	-	-	-	-	-	-	+	-	-
1	PEPC	-	-	-	-	-	-	+	-	-
2	ACY1	-	+	+	-	+	-	-	+	-
3	MDH2	-	-	-	-	+	-	+	-	-
3	SOD1	-	-	-	-	+	-	+	-	-
4	ME1	-	+	+	-	-	-	+	+	+
4	SOD2	-	+	+	-	-	-	+	+	+
5	PGM2	+	-	-	-	-	-	-	+	-
5	PEPS	+	-	-	-	-	-	-	+	-
6	NP	+	+	-	-	-	-	+	-	+
6	MPI	.	+	.	.	.	.	+	.	.
6	PKM2	+	+	-	-	-	-	+	-	+
6	HEXA	+	+	-	-	-	-	+	-	+
7	PP	-	-	+	-	-	-	-	-	+
8	ADA	+	-	-	-	-	-	-	-	+
8	ITPA	+	-	-	-	-	-	-	-	+
9	LDHB	-	+	-	-	-	-	+	-	+
9	TPI1	-	+	-	-	-	-	+	-	+
10	IDH1	+	+	-	-	-	-	-	+	+
11	MDH1	-	+	-	+	-	-	+	-	+
12	LDHA	+	+	+	+	-	+	+	+	+
12	ACP2	+	+	+	+	-	+	+	+	+
13	ESD	+	+	-	-	+	-	-	-	-
14	GPI	+	-	-	-	-	-	-	-	+
14	PEPD	+	-	-	-	-	-	-	-	+
15	GSR	+	+	+	-	-	-	+	+	+

+ present; - absent; . not determined

The fifteen syntenic groups determined in P. hamadryas are indicated. The parental baboon cell line was heterozygous for MPI; one allelic form was not separable from the hamster enzyme.

cell line was apparently heterozygous for MPI, since it expressed two bands for the monomeric enzyme. One allelic form was not separable from the hamster enzyme and therefore could not be scored.

Karyotypes of the baboon parental cell line and of representative hybrid cell lines are shown in Figures 3 and 4, respectively. The P. hamadryas cell line was found to have the karyotype 42,XY,t(2;15)(q1;p1). It also contained a polymorphism in the length of the secondary constriction on the marker chromosome, PHA10. The chromosome content of the hybrid clones is given in Table 5, and marker enzyme expression of the hybrid clones at the time of the chromosome analyses is given in Table 6.

Fifteen syntenic groups or independently segregating markers in P. hamadryas were determined from the segregation patterns of the enzyme markers (Table 4). Ten of these, representing eighteen genes, were assigned to baboon chromosomes by their cosegregation with the chromosome (Tables 5 and 6). They include ACY1 to P. hamadryas chromosome 2 (PHA2); MDH2 and SOD1 to PHA3; ME1 and SOD2 to PHA4; NP, MPI, PKM2, and HEXA to PHA7; PP to PHA9; ADA and ITPA to PHA10; LDHB and TPI1 to PHA11; MDH1 to PHA13; ESD to PHA17; and GPI and PEPD to PHA20.

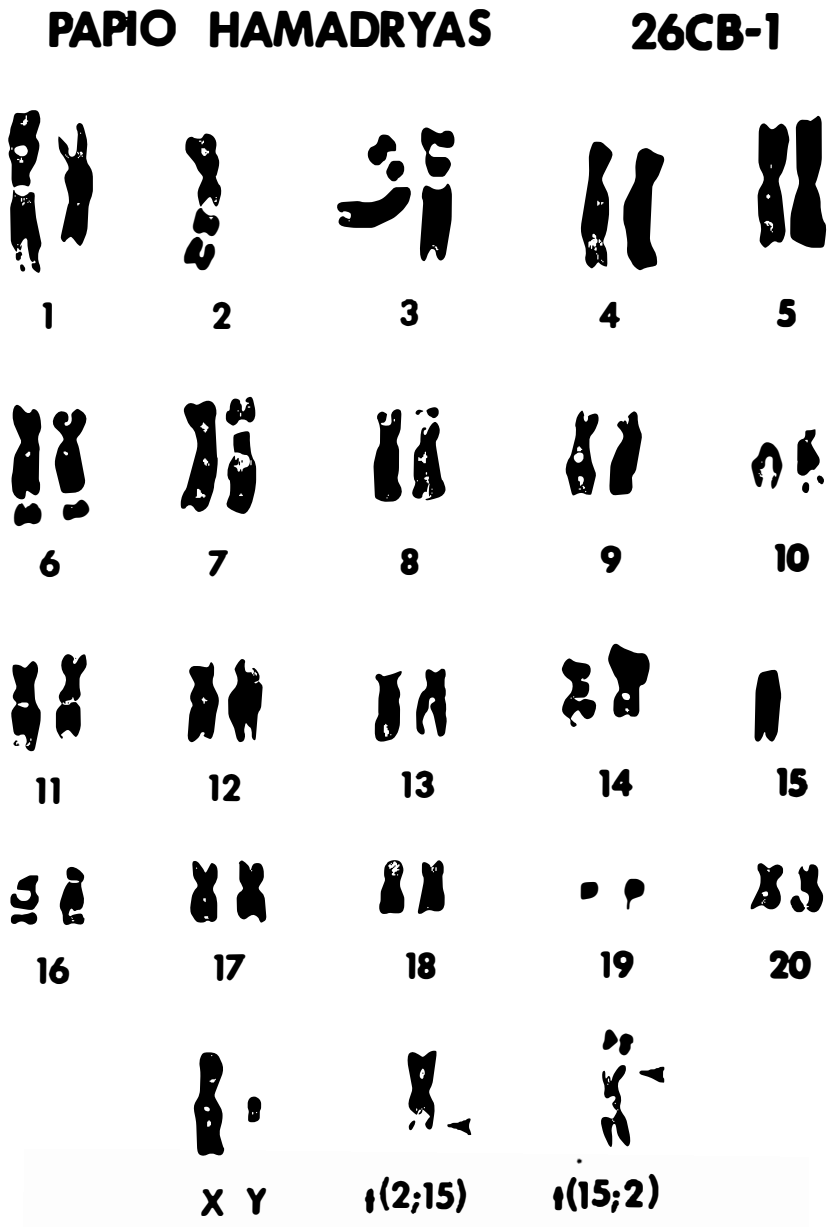
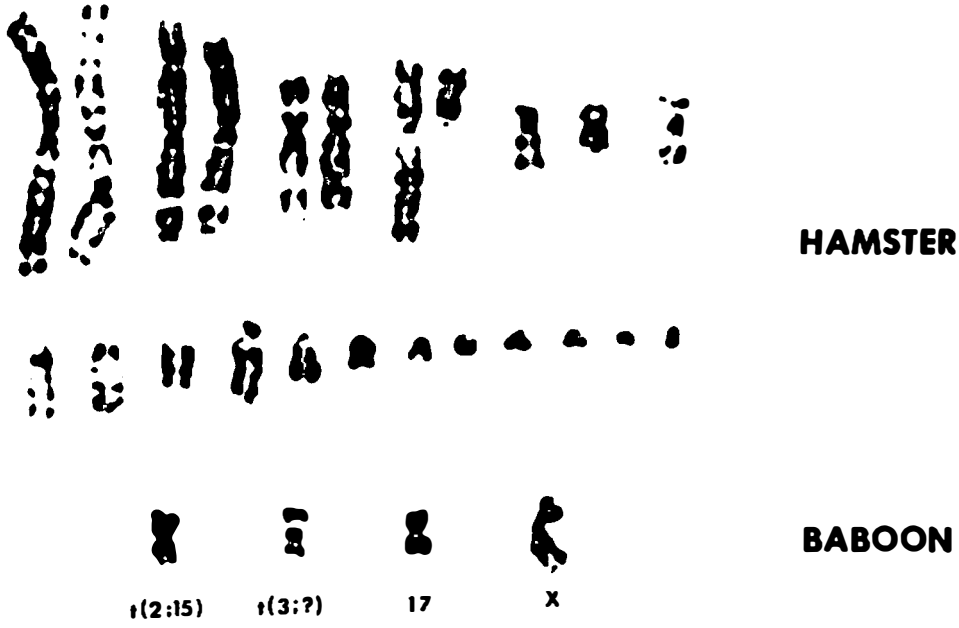
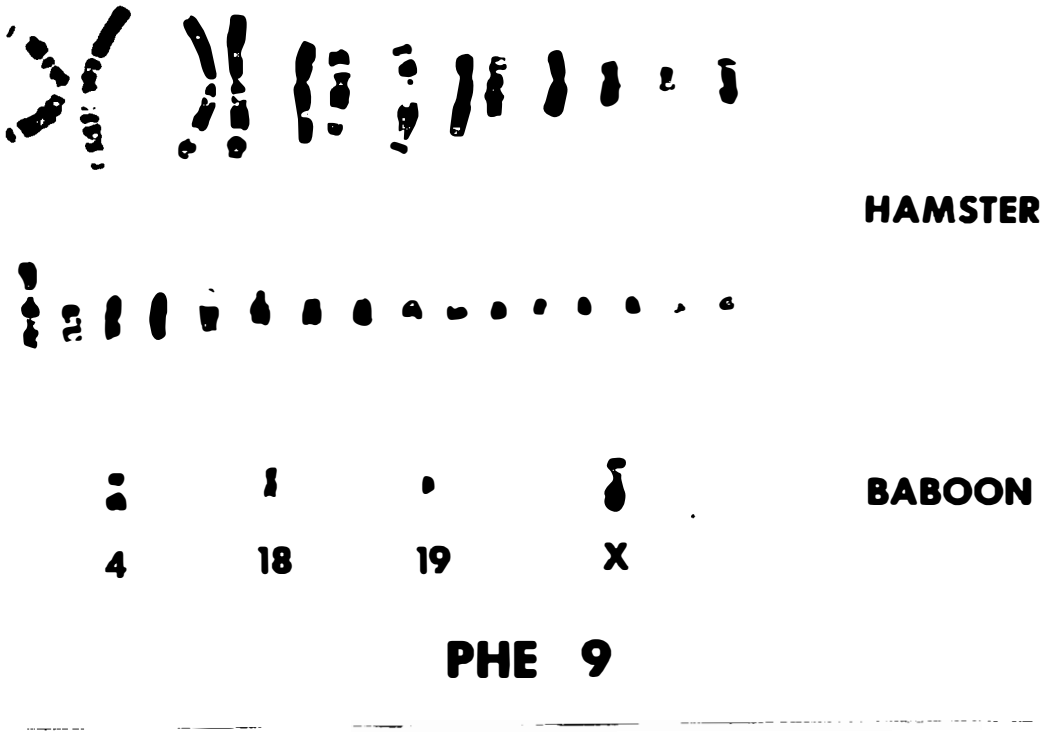


Figure 3. Karyotype of Papio hamadryas cell line 26CB-1, which has the chromosome complement 42, XY, t(2;15)(q1;p1). The breakpoints in the translocated chromosomes are indicated by arrows.



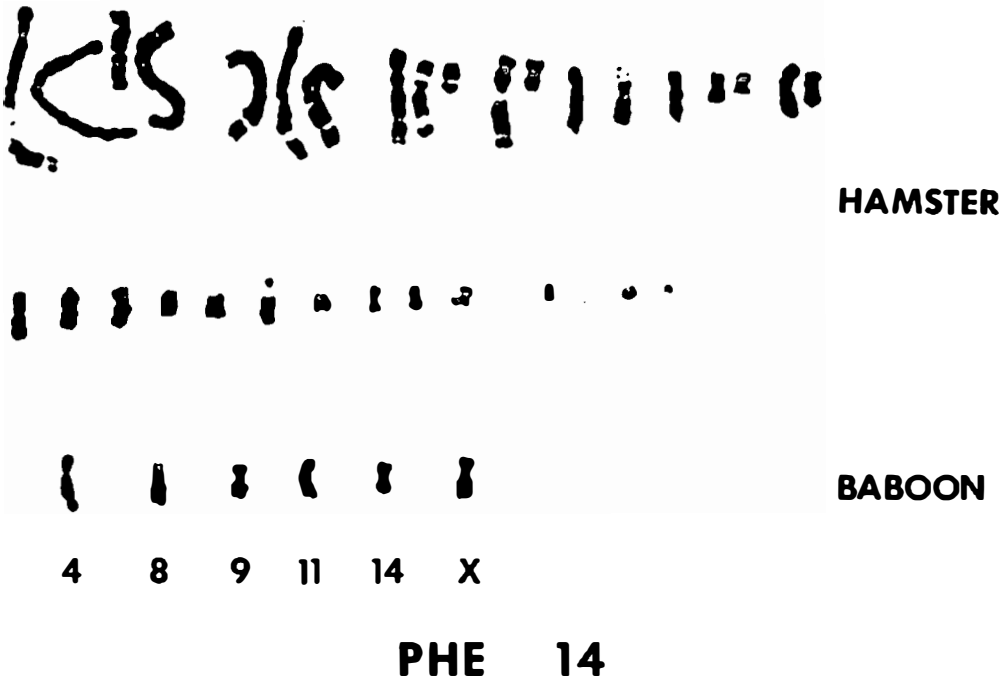
A. Karyotype of a cell from hybrid clone PHE5, containing baboon chromosomes 17, X, and 2/15. This cell also contains a translocation chromosome involving baboon chromsome 3.

Figure 4. Karyotypes of three Papio hamadryas x Chinese hamster hybrid clones.



B. Karyotype of a cell from hybrid clone PHE9, containing baboon chromosomes 4, 18, 19, and X.

Figure 4 (Continued)



C. Karyotype of a cell from hybrid clone PHE14, containing baboon chromosomes 4, 8, 9, 11, 14, and X.

Figure 4 (Continued)

Table 5. Chromosome Content of the Papio hamadryas x Chinese Hamster Hybrid Clones.

Baboon Chromosome	Clones								
	PHE1	PHE2	PHE3	PHE4	PHE5	PHE6	PHE8	PHE9	PHE14
1	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-
3	-	-	-	-	*+	-	-	-	-
4	-	+	+	-	-	-	+	+	+
5	+	-	-	-	-	-	-	+	-
6	-	-	-	-	-	-	-	-	-
7	+	-	-	-	-	-	+	-	-
8	+	-	+	-	-	-	+	+	+
9	-	-	+	-	-	-	-	-	+
10	+	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	+	-	+
12	+	-	-	-	-	-	-	+	-
13	-	-	-	-	-	-	+	-	-
14	+	-	+	-	-	-	+	+	+
15	+	-	(+)	-	-	-	-	-	-
16	-	-	+	-	-	-	(+)	-	-
17	+	-	-	-	+	-	-	-	-
18	-	-	+	-	-	+	+	+	+
19	-	-	+	+	-	+	+	+	+
20	+	-	-	-	-	-	-	-	(+)
X	+	-	+	+	+	+	+	+	+
2/15	-	-	-	-	+	-	-	+	-
15/2	-	-	-	-	-	-	-	-	+
Number of cells karyotyped	31	35	19	22	27	17	28	31	16

- present in less than 10% of the cells
(+) present in 10-20% of the cells
+ present in more than 20% of the cells

*PHE5 contained the short arm of PHA3.

Table 6. Marker Enzyme Expression of the Papio hamadryas x Chinese Hamster Hybrid Clones at the Time of Chromosome Analysis.

Enzyme(s)	Clones								
	PHE1	PHE2	PHE3	PHE4	PHE5	PHE6	PHE8	PHE9	PHE14
PGD, PGM1, PEPC	-	-	-	-	-	-	-	-	-
ACY1	-	-	-	-	+	-	-	+	-
MDH2, SOD1	-	-	-	-	+	-	-	-	-
ME1, SOD2	-	+	+	-	-	-	+	+	+
PGM2, PEPS	+	-	-	-	-	-	-	+	-
NP, MPI, PKM2, HEXA	+	-	-	-	-	-	+	-	-
PP	-	-	+	-	-	-	-	-	+
ADA, ITPA	+	-	-	-	-	-	-	-	-
LDHB, TPI1	-	-	-	-	-	-	+	-	+
IDH1	+	-	-	-	-	-	-	+	-
MDH1	-	-	-	-	-	-	+	-	-
LDHA, ACP2	+	-	+	w	-	+	+	+	+
ESD	+	-	-	-	+	-	-	-	-
GPI, PEPD	+	-	-	-	-	-	-	-	w
GSR	+	-	+	-	-	-	+	+	+

\+ enzyme(s) present
\- enzyme(s) absent
w weak enzyme activity

The genes coding for MDH2 and SOD1 were further assigned to the short arm of PHA3, since the one hybrid expressing these two enzymes (PHE5; see Tables 5 and 6 and Figure 4A) contained only the short arm of PHA3, which had been translocated to what was probably a small hamster chromsome; no hybrid contained an intact copy of PHA3.

The gene coding for ACY1 was further assigned to the pter-->q1 region of PHA2. The P. hamadryas parental cell line contained the reciprocal products of a (2;15)(q1;p1) translocation (Figure 3). Two hybrids contained the (2;15) chromosome and one the (15;2) chromosome (Table 5; see Figure 4A); none carried an intact copy of PHA2. ACY1 was expressed by the clones containing the (2;15) chromosome but not by the hybrid containing the (15;2) chromosome or by those carrying an intact copy of PHA15 (Tables 5 and 6). This permitted the assignment of ACY1 to the pter-->q1 region of PHA2.

The five syntenic groups or markers which could not be unambiguously assigned to chromosomes include PGD, PGM1, and PEPC (designated U1 for unassigned syntenic group 1); PGM2 and PEPS (U2); IDH1 (U3); LDHA and ACP2 (U4); and GSR (U5).

An important advantage of this particular P. hamadryas cell line was that it carried a reciprocal

translocation, which in principle could permit regional assignments of some genes, and which did in fact permit one. The disadvantage of using the cell line as opposed to normal diploid cells freshly or recently obtained from a live animal was the difficulty in generating a large number of hybrids. In two fusion attempts, only fourteen hybrids were obtained, only nine of which were informative. Several of the P. hamadryas hybrid clones were not stable and lost baboon enzyme markers which they had formerly expressed. This is presumably because the hybrid clones continued to segregate baboon chromosomes. These hybrid clones were karyotyped at only one time point, however, so this explanation was not verified. By the time the hybrids were karyotyped, there was less information available for several enzyme markers (that is, fewer or no hybrid clones expressing the enzymes) than there had been when the first enzyme analyses of the hybrids were done. In a few cases, therefore, it was not possible to assign a gene or syntenic group to a particular chromosome. For instance, IDH2 segregated concordantly with both PHA5 and PHA12, and therefore was not assigned to a chromosome.

The gene map of P. hamadryas now contains twenty-eight gene markers (see Appendix B), twenty-seven of

which are reported from this study. They belong to fifteen autosomal syntenic groups out of a possible twenty. Ten of the syntenic groups, including nineteen genes, are assigned to chromosomes, and three genes have regional assignments. These syntenies and assignments are considered provisional since concurring results from another laboratory are required for confirmation. Support of another kind is available, however, namely a comparison of gene maps between P. papio and P. hamadryas.

C. Comparison of P. papio and P. hamadryas gene maps

Nineteen genes have been examined in both species of Papio. Ten of these genes were mapped to the same chromosome in the two species (see Appendices B and C). MDH2 and SOD1 are on chromosome 3 in both species; ME1 and SOD2 are on 4; NP, MPI, and PKM2 on 7; ADA and ITPA on 10; and LDHB on 11. ACY1 and MDH1 were assigned to two different chromosomes in P. hamadryas but have not been assigned in P. papio, although each gene was shown to segregate independently of most of the mapped genes in P. papio. The other seven genes were assigned in P. papio but could not be assigned with certainty in P.

hamadryas because of the small number of hybrid clones available.

PGD, PGM1, and PEPC (all on PPA1) are also syntenic in P. hamadryas. None of the P. hamadryas hybrids still expressed these enzymes at the time they were karyotyped, nor did any of the hybrids contain PHA1. This is consistent with these genes being on chromosome 1 in this species also, but it is not sufficient for their assignment.

PGM2 and PEPS (also syntenic in both Papio species) and IDH1 were expressed in the same hybrids at the time of the chromosome analyses (IDH1 was not concordant with PGM2 and PEPS when the enzymes were first analyzed; see Table 4) and segregated together with PHA5 and 12. PGM2 and PEPS are on PPA5 (Créau-Goldberg et al., 1983; Thiessen and Lalley, in press) and IDH1 is on PPA12 (Créau-Goldberg et al., 1982), so again these results are consistent with the situation in P. papio but are not sufficient for assignment of the genes in P. hamadryas. LDHA (on PPA14) segregated with low discordance with PHA8, 14, 18, and 19; a location on PHA14 is consistent.

Six genes were assigned in P. hamadryas which have not been examined in P. papio. These include HEXA (PHA7), PP (PHA9), TPI1 (PHA11), ESD (PHA17), and GPI

and PEPD (PHA20). In addition, ACP2 was found to be syntenic with LDHA, which could not be assigned in P. hamadryas (see above), and GSR segregated concordantly with both PHA8 and 14 (but discordantly with LDHA and ACP2) and also could not be assigned.

Where they can be compared, then, the gene maps of P. papio and P. hamadryas are consistent with each other; no discrepancies between the two have been observed. This is expected if the karyotypes of the two species are identical. Several genes are assigned in one species, but not in the other; this information can be used to predict gene locations in the other species.

If the taxonomists determine that P. papio, P. hamadryas, and the other baboons all properly belong to the same species (and are perhaps separate subspecies), then the information for these two species and for P. cynocephalus (see below) could be compiled into a single gene map of Papio (see Appendix B). This would give a gene map containing thirty-nine genes assigned to sixteen chromosomes plus an additional three genes examined but not definitely assigned to chromosomes. This includes the three gene assignments in P. cynocephalus: RN5S to chromosome 1 (PCY1; Warburton et al., 1976), RNR to PCY10 (and to PHA10; Henderson et al., 1977); and TBG to PCYX (Lockwood et al., 1984).

The following syntenies and gene assignments could then be considered confirmed: PGD syntenic with PGM1; SOD1 on Papio chromosome 3; GLO1 and ME1 on Papio 4; NP, MPI, PKM2, IDH2, and SORD on Papio 7; ADA on Papio 10; and LDHB on Papio 11.

V. SIGNIFICANCE OF GENE MAPPING IN BABOONS

A. Comparison of baboon, rhesus monkey, and human gene maps

Several primate species, most notably members of *Mandrillus* and *Macaca*, have banded karyotypes very similar to, if not identical with, the karyotypes of the *Papio* species (discussed in Section I). The karyotype of *Papio* also bears similarities to those of the great apes and man, and numerous chromosome homologies between the baboons and man have been proposed on the basis of the banding patterns (Dutrillaux *et al.*, 1978). Of the species with karyotypes very similar to that of *Papio*, gene mapping has been done in only one, the rhesus monkey (*Macaca mulatta*), whose banded karyotype is indistinguishable from the baboon karyotype (Finaz *et al.*, 1978; Dutrillaux *et al*, 1979). It is of particular interest, therefore, to compare the gene maps of *Papio*, *M. mulatta*, and man, as well as to compare the *Papio* maps with maps available for various other species.

Of the four genes assigned to PPA1 (*PGD*, *ENO1*, *PGM1*, and *PEPC*; Finaz *et al.*, 1977; Lalley *et al.*, 1979), three were also shown to be syntenic in *P. hamadryas* (*PGD*, *PGM1*, and *PEPC*) and may be on PHA1. All

four genes are on human chromosome 1 (HSA1), and three of them (PGD, ENO1, and PGM1) have been mapped to M. mulatta chromosome 1 (MML1; Garver et al., 1978; see Appendix C). This is in keeping with the apparent morphological identity of PPA1 and PHA1 with MML1 and their proposed homology to HSA1.

The gene coding for ACY1 (on HSA3) was assigned to the pter-->q1 region of PHA2, the proposed homologue to HSA3. GPX1, which is also on HSA3, is located on the rhesus monkey homologue to HSA3 and PHA2, MML3 (Estop et al., 1978; Pearson et al., 1979).

The present study demonstrated the synteny of MDH2 (on HSA7) and SOD1 (HSA21) in both P. papio and P. hamadryas and assigned MDH2 to PPA3 and both genes to the short arm of PHA3. SOD1 had previously been assigned to PPA3 along with GUSB (HSA7; Créau-Goldberg et al., 1982, 1983). These results are therefore consistent with the proposed homology of PPA3 and PHA3 with HSA7 and 21. Another gene on HSA7, COL1A2, has recently been assigned to PPA3 (Créau-Goldberg et al., 1985). MDH2 and GUSB are also syntenic in the rhesus monkey and have been assigned to MML2 (Estop et al., 1983), which is considered to be homologous to PPA3 based on the banding patterns.

SOD2 was assigned to PPA4 along with GLO1 and ME1,

and both SOD2 and ME1 were assigned to PHA4, supporting the homology of this baboon chromosome to HSA6. SOD2 and two other HSA6 markers, PGM3 and the major histocompatibility complex (MHC), were shown to be syntenic in M. mulatta and were assigned to MML2 with GUSB and MDH2 (Garver et al., 1980a; Estop et al., 1983). The results of the present study demonstrate that SOD2 and MDH2 are not syntenic in P. papio or P. hamadryas, in agreement with the assignments by Créau-Goldberg et al. (1982, 1983, 1985) of HSA6 and 7 markers to two separate baboon chromosomes. SOD1, COL1A2, GLO1, and ME1 have not been mapped in the rhesus monkey, nor PGM3 and the MHC in the baboon. It would be interesting to have these results in order to compare more adequately the relationships between Papio chromosomes 3 and 4; HSA6, 7, and 21; and MML2.

The synteny of PEPS and PGM2 supports the suggested homology of PPA5 and HSA4. These two genes are also syntenic in P. hamadryas, possibly on PHA5, but they could not be assigned with certainty. PGM2 is reported to be on MML6 (Estop et al., 1978; Pearson et al., 1979), which is morphologically similar to PPA4 and PHA4; PGM2 is clearly not on PHA4 (Tables 5 and 6, pp. 45-46).

Synteny of human chromosome 14 and 15 markers has

been demonstrated in both species of baboons; they are assigned to PPA7 and PHA7. From a study of chromosome banding patterns, Dutrillaux et al. (1978) proposed a homology of HSA14, 20, and 3q26-->qter with PPA7 and of HSA15 and 22 with PPA10 (9 in their nomenclature). The assignments by Créau-Goldberg et al. (1982, 1983) and by the present study of HSA14 and 15 markers to PPA7 and PHA7 and of ADA and ITPA (HSA20) to PPA10 and PHA10 support instead the proposal of Créau-Goldberg et al. (1983) that PPA7 (and PHA7) is homologous to HSA14 and 15 and that PPA10 (or PHA10) contains a region homologous to HSA20. No gene mapping data are presently available in the baboon concerning possible homologies to HSA3q or 22.

In the rhesus monkey, NP (HSA14), PKM2, and HEXA (HSA15) have all been assigned to chromosome 7 (Estop et al., 1983), in agreement with the findings in the baboon. In addition, ITPA and NAGA (HSA22) have both been located on MML13 (homologous to PPA10), supporting a correspondence of this chromosome to HSA20 and 22, rather than to HSA15 and 22.

The gene coding for PP (HSA10) was assigned to PHA9, which is considered homologous (on the basis of banding patterns) to HSA10. PP has not been assigned in P. papio or M. mulatta. LDHB and TPI1 (on HSA12) were

both assigned to PHA11. LDHB had previously been assigned to PPA11 (Créau-Goldberg et al., 1983). PEPB (also on HSA12) and LDHB have not been examined in the same set of baboon hybrid clones, but LDHB, TPI1, and PEPB are syntenic in the rhesus monkey (MML12; Garver et al., 1978).

IDH1 (HSA2q) and MDH1 (HSA2p) are asyntenic in both baboon species: IDH1 is on PPA12 (Créau-Goldberg et al., 1982), and MDH1 is on PHA13. The reciprocal assignments have not yet been made. Baboon chromosome 12 is the expected homologue to HSA2q, and chromosome 13 to HSA2p (Dutrillaux et al., 1978). This agrees also with the assignments of IDH1 to MML9 and MDH1 to MML15. The relationship of MDH1 and ACP1 in the baboon is not yet known for certain (see Lalley et al., 1979; Thiessen and Lalley, in press); the data were insufficient for P. papio, and ACP1 could not be examined in the P. hamadryas hybrids.

LDHA (PHA14) and ACP2 were shown to be syntenic in P. hamadryas; they comprise a syntenic group found in man (HSA11) and in the rhesus monkey (MML11; Garver et al., 1980b) but not previously described in Papio. It was not possible to assign these genes in P. hamadryas, but their segregation was consistent with a location on PHA14. COL1A1, TK1, and GAA were assigned to PPA16 by

Créau-Goldberg et al. (1984); these genes are on the expected homologue chromosome 17 in man.

ESD (HSA13) was assigned to PHA17, although the proposed homologue to HSA13 is PPA or PHA18 (Dutrillaux et al., 1978). Similarly, GPI and PEPD (HSA19) were assigned to PHA20, rather than the proposed homologue PHA19. In the rhesus monkey, GPI has been assigned to MML19 (Estop et al., 1978), which is homologous by banding patterns to HSA19, PPA 19, and PHA19.

The gene coding for GSR could not be assigned in P. hamadryas, but the segregation was consistent with a location of GSR on PHA8. GSR is located on MML8 and HSA8, which are considered homologous (by banding patterns) to PPA8 and PHA8.

Many of the chromosome homologies between baboons and man proposed from studies of banding patterns (Dutrillaux et al., 1978) are thus borne out by gene mapping. The exceptions are the relationships of HSA14, 15, and 20 with Papio chromosomes 7 and 10; PHA17 or 18 with HSA13; and PHA19 or 20 with HSA19. Gene assignments in Papio and M. mulatta are consistent with the exceptions of the HSA6 and 7 markers, PGM2, and GPI.

These discrepancies are of two types. The first is a homology between baboon and human (nonidentical) chromosomes predicted by the banding patterns which

fails to be supported by the mapping data. The second type is a disagreement in gene assignments in species having indistinguishable chromosome sets (the baboon and the rhesus monkey). Several explanations are possible for both types.

One possibility of course is error, either in the gene assignments or in the comparisons of the banding patterns. The human gene assignments are by this time well established. The synteny and assignment data for HSA5, 6, 7, 14, 15, and 20 markers in baboons were determined by two laboratories. The data for the HSA13 and 19 markers in baboons were determined by only one laboratory, and likewise the data for M. mulatta. The need for further work in this area and confirmation of gene assignments in these species is obvious.

Error of another sort could have occurred in the comparison of banding patterns, particularly in this instance between humans and the baboons. At the level of resolution of chromosome banding used in most of the comparative karyology studies (and in the present mapping study), there remains some degree of subjectivity. One person's idea of "matching chromosomes" may well differ from another's, and for this reason it has been suggested that primate karyotypes should be standardized using an ordination by

chromosome length, rather than by apparent morphological similarities to human chromosomes (Chiarelli and Corruccini, 1982; Soares et al., 1982). At higher levels of resolution (e.g. prophase banding) the similarities or differences in banding patterns may be better discerned (see for instance the comparison of high-resolution chromosomes of man and the great apes done by Yunis and Prakash, 1982). It might be found, for instance, that at the higher level of resolution human chromosomes 14 and 15 correspond very nicely to Papio 7, better than do HSA 14 and 20. Difficulties in comparison of banding patterns are less likely to be a factor between the baboon and the rhesus monkey, as the similarities in chromosome morphology and banding patterns are much greater.

The possibility does exist, however, that similar banding patterns between species which in other ways have much similarity are not necessarily accurate predictors of regions of chromosome homology. It is possible that two chromosomes which appear identical (for instance MML2 and PPA3) do not necessarily carry the same genes, although a number of such predictions have been borne out, both between man and the baboons and between the baboons and the rhesus monkey. Also, changes in or transpositions of single gene loci or

short segments of DNA will often not be detectable by chromosome banding methods (Seuánez, 1982). For now the answer must be that both chromosome morphology and banding patterns and more precise data such as syntenic relationships and gene assignments should be carefully considered in defining chromosome homologies.

B. Conserved syntenic groups and mammalian chromosomal evolution

Several of the syntenic groups determined in Papio have also been observed in a number of other mammalian species besides the rhesus monkey and man (for comparisons of syntenic groups in various species, see Lalley and McKusick, 1985). For instance, the syntenic group ENO1-PGD-PGM1 (on P. papio chromosome 1 and human chromosome 1p) is found in nine nonhuman primate and six nonprimate species (PGD-PGM1 is found in two additional primate species in which ENO1 has not been mapped). In one primate (the gibbon) and two nonprimate species, PGD and ENO1 are syntenic with each other but not with PGM1. This syntenic group (ENO1-PGD-PGM1) covers a genetic distance of 25 centimorgans (cM) in the mouse and 55 cM in the human male (see Lalley et al., 1978a; Womack 1984; Povey et al., 1985; ENO1-PGD covers only 3 cM in

man), and represents the largest and most wide-spread (in terms of number of species) conserved chromosomal region yet observed in mammals.

PEPC (on HSA1q) is syntenic with PGD and PGM1 in Papio and in most of the other Old World primates studied. One exception is the gibbon (Hylobates concolor; Turleau et al, 1983), whose karyotype is in general highly rearranged when compared to karyotypes of most other Old World primates. The other exception is the African green monkey (Cercopithecus aethiops; Finaz et al., 1977), which, together with at least some of the New World monkeys, has two separate chromosomes corresponding in banding patterns to human chromosome 1p and 1q.

Other widely conserved syntenic groups include TPI1-LDHB (PHA11 and HSA12p) in ten primate and six nonprimate species (GAPD-TPI1-LDHB is conserved in ten species); MPI-PKM2 (Papio 7 and HSA15q) in nine primates and five nonprimates; ME1-PGM3 (HSA6q) in twelve species (ME1-SOD2, on Papio 4, is found in nine); and LDHA-ACP2 (HSA11p) in eight species. GUSB and MDH2 (PPA3 and HSA7) are syntenic in all three nonhuman species in which they have been examined, including P. papio, M. mulatta, and the mouse (Mus musculus). This syntenic group covers a genetic distance of 11 cM in the mouse (see Womack,

1984). In the baboon, GUSB and MDH2 are also syntenic with COL1A2 (also on HSA7) and SOD1 (HSA21). In the mouse, however, COL1A2 is asyntenic with GUSB and MDH2 but is syntenic with SOD1 (see Appendix C).

In man, IDH1 (HSA2q) is syntenic with MDH1 and ACP1 (HSA2p). In all nonhuman primates examined thus far, including the baboons, IDH1 is not syntenic with MDH1 or ACP1. In many if not all of these other species, two separate chromosomes are found which have similarities of banding patterns to HSA2p and HSA2q, respectively, in keeping with the synteny data.

NP (Papio 7 and HSA14) is reported to be syntenic with ITPA (Papio 10 and HSA20) in the gorilla and the chimpanzee (Pearson et al., 1978); this synteny has not been described in any other species. This syntenic group and the two syntenic groups corresponding to HSA2 are the only differences which have been observed between the gene arrangement of man and those of the chimpanzee and gorilla.

Thus while some differences in gene arrangement are found, there are a great many similarities of genome organization between the various primate species and man, and several syntenic groups, at least two of which cover substantial genetic distances, appear to be widespread in the mammalian orders studied so far.

Conservation of some syntenic groups might be attributable to the proximity of two genes and the subsequent high probability of their remaining together during chromosomal evolution, but the finding of a conserved region as large as that containing PGD-ENO1-PGM1 requires a different explanation. One explanation might be that functional or regulatory relationships exist between various genes in that region; such relationships may come to light as more detailed gene maps are available.

Most of these conserved syntenic groups constitute syntenic homologies between species (Lalley and McKusick, 1985), that is, two genes are known to be syntenic in each of two or more species. For a chromosomal region to be properly called homologous between two species, additional information is necessary. Homologous regions should contain the same genes, in the same order, at roughly the same map distances, and with no disruptions by other loci (Lalley and McKusick, 1985). This definition allows for differences between the two species such as some DNA base sequence differences while maintaining similar organization of genes. Knowledge of the homology of chromosomal regions, including the correlation between genetic homology and homology of banding patterns, is

essential for the evaluation of theories of chromosomal evolution and of the relationship of chromosomal rearrangement to speciation.

A detailed phylogenetic tree or evolutionary pathway for the primates has been described from comparison of the chromosome banding patterns (Dutrillaux, 1979); this phylogenetic tree is quite similar to those produced by comparison of amino acid sequences (molecular phylogeny) or of morphological criteria (taxonomic phylogeny; de Grouchy et al., 1978). Mechanisms of primate speciation by chromosome rearrangement have been suggested based on such comparisons of chromosome banding patterns (see especially de Grouchy et al., 1978; Dutrillaux, 1979). Gene assignments to corresponding chromosomes or chromosomal regions (i.e. having similar banding patterns) obviously support (but do not prove) these theories. A great number of the gene assignments in primates do agree with the comparisons of chromosome banding patterns; several of these were discussed earlier (see part A of this Section). There are also a few inconsistencies between banding patterns and gene assignments; these may be resolved when more data are available for some of the assignments or if banding patterns are compared at a higher level of resolution.

It remains to be demonstrated how close the correspondence between gene location and chromosome banding patterns is for those regions where a correspondence has been shown. For instance, PPA1 and HSA1 have similar banding patterns (allowing for an inversion in PPA1) and contain at least some of the same genes. Regional assignments for such genes as PGD, ENO1, and PGM1 are not yet available in the baboon; therefore, it cannot yet be said whether these genes have corresponding locations on chromosome 1 in both species.

As regions of chromosome homology between species become established, both from gene assignments and from banding patterns, the relationship of chromosome rearrangements and speciation can be more fully investigated. Four major types of chromosome rearrangement are proposed to account for the differences between banded karyotypes of various primate species. These are chromosome fusion (especially Robertsonian translocation), chromosome fission, and paracentric and pericentric inversion (de Grouchy et al., 1978). The inversions cause rearrangement of genetic material within a chromosome; fusions combine two (usually acrocentric) chromosomes into one

(metacentric) chromosome, while fissions reverse the process.

Some species whose karyotypes differ by apparent Robertsonian translocations (some of the lemurs, for instance) can often interbreed well (reviewed by Dutrillaux, 1979). A polymorphism for a Robertsonian translocation in the blue fox has no effect on the fertility even of heterozygotes (Møller et al., 1985). Other species are known which have no apparent karyotypic differences or have karyotypes differing by inversions but which cannot interbreed (see Dutrillaux, 1979). The baboons and related animals (including members of Mandrillus and Macaca) have karyotypes differing by small inversions if at all, and they can interbreed (although not all the hybrids are fertile). However, the baboons, mandrills, and macaques are all readily distinguishable by morphological criteria and are traditionally classified in a number of different species of several genera. On the other hand, the night or owl monkey (Aotus) of South America had long been considered a single species with several geographical subspecies (Napier and Napier, 1967; Thorington and Vorek, 1976). Recent studies have demonstrated at least nine different karyotypes (Ma et al., 1976, 1978), and Elliott et al. (1976) found that

reproductive performance improved considerably when animals were deliberately paired by karyotype.

It is likely then, that while chromosome rearrangement may be a mechanism of speciation, it is not the mechanism of speciation, at least not in the primates. Chromosome rearrangement appears to act as a mechanism of reproductive isolation in many cases, but whether the chromosome rearrangement caused the separation of species or occurred later and simply reinforced it is difficult to know.

While a number of syntenic homologies between primates and nonprimates have been observed, homologies of banding patterns between primates and nonprimates are less obvious, although they have been reported (see for instance Nash and O'Brien, 1982). Ohno (1984) suggests that an ancestral vertebrate karyotype may have consisted of twenty-four syntenic groups (forty-eight chromosomes) which are substantially conserved throughout much of the modern animal world, although often some are combined and a few occasionally split. As additional confirmed gene assignments in many more species become available, the relationship between karyotype arrangement or rearrangement and speciation should become clearer. A broader picture of mammalian

genome organization may also contribute to a greater understanding of gene function and regulation.

C. Gene mapping and primate taxonomy

Comparative gene mapping has already begun to shed light on some problems of primate taxonomic relationships. This study dealt with the gene maps of two baboons long considered to be separate species (see discussion in Section I). These animals have apparently the same karyotype (Cambefort *et al.*, 1976b), and in nineteen genes studied in both *P. papio* and *P. hamadryas*, no discrepancies of gene location were found. This work therefore supports a revision of the baboon taxonomy which would place these animals (probably all the baboon species) in a single species having several subspecies or races. The proper taxonomic relationship between *Papio* and *Macaca* is less clear: their karyotypes appear to be identical or close to identical, but discrepancies in the gene maps are found. Further gene mapping studies would be of value in clarifying the taxonomy of *Papio*, *Macaca*, *Mandrillus*, and *Theropithecus*.

It is worth noting that, in the course of this study, no significant electrophoretic differences

between enzymes of P. papio and P. hamadryas were found, while several differences between P. hamadryas and Mandrillus sphinx were noticed (unpublished observations). This is in keeping with a greater genetic separation between P. hamadryas and M. sphinx than between P. papio and P. hamadryas and with a potential placement of P. papio and P. hamadryas in the same species.

There is a marked contrast between this situation--a number of different species and even genera having similar karyotypes and with at least some of them having similar gene maps--and that found in the South American owl monkey, Aotus. This animal has tradtionally been considered a single species, Aotus trivirgatus, having several geographical subspecies (Napier and Napier, 1967; Thorington and Vorek, 1976). Ma et al. (1976, 1978) have demonstrated at least nine different karyotypes for the owl monkey, and gene maps corresponding to the different karyotypes have been described (see for instance Ma, 1984). Elliott et al. (1976) found that the reproductive performance of the animals improved considerably when they were paired by karyotype, supporting the idea that several separate species are probably involved here. Chromosome banding and gene mapping studies should continue to be useful in

clarifying similar taxonomic difficulties, for instance the relationships between the gibbons and siamangs (*Hylobates* species; see Turleau *et al.*, 1983).

D. The baboons as models for human genetic diseases

Knowledge of their gene maps will aid in any study of the baboons as models of human genetic disease or predisposition to disease. For instance, it may be possible to demonstrate (by breeding studies) linkage between an assigned gene (several of which are known to be polymorphic in baboons) and the heritable factor affecting serum cholesterol levels (see Flow *et al.*, 1981) or between assigned genes and various other traits observable in the live animals. This would permit the chromosomal assignment of genes expressed in the live animals but not in cultured cells. Comparison of syntenic groups in the baboon with the corresponding syntenic groups in man might suggest the identity of some of the "heritable factors" observed in the baboon or other laboratory species and thereby more closely describe the animal model proposed.

Several different genes can cause hyperlipidemia or hypercholesterolemia in man (see Motulsky, 1976). Two

such genes are those coding for lipase A (LIPA, on human chromosome 10) and the low density lipoprotein receptor (LDLR or FHC for familial hypercholesterolemia, on human chromosome 19; McAlpine et al., 1985). One gene on HSA10, PP, has been mapped in P. hamadryas (on PHA9), and two genes on HSA19 (GPI and PEPD) have been mapped to PHA20. If for instance the factor in the baboon described by Flow et al. (1981) were shown to be linked either to PP or to GPI and PEPD, it would suggest that the factor might be the gene coding for LIPA or the gene coding for the LDL receptor. These possibilities could then be examined in more detail, and a specific disease model could be developed.

The baboon may also prove to be a valuable model in the study of human cancer. The P. hamadryas lymphoblastoid cell line used in this study was established from a baboon with lymphoma (Falk et al., 1976); the cell line was shown to have an abnormal karyotype (Figure 3, p. 41). The reciprocal translocation which it carried, t(2;15)(q1;p1), permitted the subchromosomal assignment of ACY1 to PHA2 (pter-->q1). PHA2 therefore contains at least some region of homology to HSA3. PHA15 is thought from comparison of banding patterns to be homologous to HSA9 (Dutrillaux et al., 1978), but no marker has yet been

assigned to PHA15. Of nearly 400 cases of human lymphomas of various types which have been karyotyped (compiled by Mitelman, 1983), about one quarter contain some aberration involving HSA3, usually as one of a number of aberrations. Close to half of these cases contain either a deletion or a translocation of HSA3, and about an equal number contain an extra copy of HSA3.

It is not known whether the (2;15) translocation in the cell line was present in the lymphomatous tissue or occurred in the development of the cell line. The chromosomal constitution of the baboon from which the cell line was derived is also not known. Other cases of lymphoma in baboons have been described (see Crawford et al., 1984; Gleiser et al., 1984), but no karyotypes were reported. This cell line, two others from the same baboon (Falk et al., 1976), and several cell lines from additional baboons with lymphoid disease (Agrba et al., 1975; Rabin et al., 1977) were each reported to have 42 chromosomes (the normal number for baboons), but in most cases no banded karyotypes were made, and no specific chromosome aberrations or rearrangements were reported.

Cancers in man are associated with a high incidence of karyotypic abnormalities (see Mitelman, 1983; Berger et al., 1985), and in many cases, a specific chromosome rearrangement or aberration has been found to be

characteristic of a certain type of cancer [e.g. the (9;22) translocation associated with chronic myelogenous leukemia; Rowley, 1973]. The importance of karyotyping lymphomas or other cancers when they are found in various nonhuman primate species is obvious, as is the necessity for developing the gene maps of these animals. Are specific chromosome rearrangements associated with cancers in primate species, and if so, are the chromosomal regions involved in rearrangements in the primate cancers homologous to chromosomal regions rearranged in the comparable human cancers? Information of this sort has already been obtained in the mouse (summarized by Lalley and McKusick, 1985); a number of oncogenes have been mapped to regions of syntenic homology in man and the mouse, and at least some of these regions are known to be involved in chromosome rearrangements in similar cancers in the two species. Because of the greater physiolgical similarities of man and the nonhuman primates than of man and the mouse, baboons and other primates should prove to be even more useful models for this sort of human disease than is the mouse.

The hamadryas baboon is already under study as a possible model for human lymphoma (Crawford and O'Rourke, 1978; Crawford et al., 1984). In a colony of

P. hamadryas baboons at Sukhumi, U.S.S.R. (the lymphomatous baboon from which the cell line 26CB-1 was derived came from this colony), an association between lymphoma and a virus (Herpes virus Papio) has been found (Agrba et al., 1975; Crawford et al., 1984), and also an apparent association between incidence of lymphoma and genotype at two loci, PGM1 and PGM2 (Crawford et al., 1984).

The present study clearly demonstrated the asynteny of PGM1 and PGM2 in P. hamadryas. PGM1 is on P. papio chromosome 1 and PGM2 is on PPA5; they were not assigned in P. hamadryas, but their segregations were consistent with locations on PHA1 and PHA5, respectively (Section IV). Possibly the virus is integrated on the same chromosome as one PGM locus, and another factor involved in lymphoma susceptibility is syntenic with the other locus. Further study of additional lymphomatous baboons will be useful in clarifying the relationship of the virus to the disease and the relationship between the disease and the PGM or other gene loci. It is of interest that neither PHA1 nor PHA5 (the possible locations of PGM1 and PGM2, respectively) were involved in the translocation observed in the cell line from the lymphomatous baboon.

E. Conclusions

A gene map containing twenty-eight markers was described for P. hamadryas, for which only one gene assignment had previously been known. Four assigned genes and two unassigned markers were added to the gene map of P. papio. This is an important start in the understanding of the gene arrangement in species which have considerable physiological similarity to man and which are widely used in the study of various aspects of biology having relevance to man.

The development of gene maps for the baboons provides additional data in an ongoing effort to understand genome arrangements and karyotypic relationships, both in primates in particular and in mammals in general. The number of conserved syntenic groups between the various primate species, especially between the baboons and man, was extended, and several genes were mapped in one or both species of baboon which had not previously been mapped in Old World monkeys. A few inconsistencies were noted between the baboon and rhesus monkey maps in particular, which emphasizes the importance of obtaining confirmed gene assignments in primate species.

Gene mapping in baboons is already contributing to

the clarification of primate taxonomy and to the investigation of many aspects of human disease, and a number of exciting possibilities exist for future research.

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APPENDICES

APPENDIX A

GENE AND ENZYME SYMBOLS

Table A-1. List of Gene and Enzyme Symbols.

Symbol	Marker Name	E. C. Number
ACP1	acid phosphatase 1, soluble	3.1.3.2
ACP2	acid phosphatase 2, lysosomal	3.1.3.2
ACY1	aminoacyclase 1	3.5.1.14
ADA	adenosine deaminase	3.5.4.4
APRT	adenine phosphoribosyltransferase	2.4.2.7
CKBB	creatine kinase, brain form	2.7.3.2
COL1A1	collagen, type 1, alpha 1	
COL1A2	collagen, type 1, alpha 2	
ENO1	enolase 1	4.2.1.11
ESD	esterase D	3.1.1.1
G6PD	glucose-6-phosphate dehydrogenase	1.1.1.49
GAA	glucosidase, alpha, acid	
GLO1	glyoxalase I	4.4.1.5
GOT1	glutamic-oxaloacetic transaminase 1, soluble	2.6.1.1
GPI	glucose phosphate isomerase	5.3.1.9
GPX1	glutathione peroxidase 1	1.11.1.9
GSR	glutathione reductase	1.6.4.2
GUSB	glucuronidase, beta	3.2.1.31
HEXA	hexosaminidase A	3.2.1.30
HEXB	hexosaminidase B	3.2.1.30
HPRT	hypoxanthine phosphoribosyltransferase	2.4.2.8
IDH1	isocitrate dehydrogenase 1, soluble	1.1.1.42
IDH2	isocitrate dehydrogenase 2, mitochondrial	1.1.1.42
ITPA	inosine triphosphatase	3.1.6.3
LDHA	lactate dehydrogenase A	1.1.1.27
LDHB	lactate dehydrogenase B	1.1.1.27
LDLR	low density lipoprotein receptor	
LIPA	lipase A	3.1.1.3

In the text, underlined symbols refer to the genes non-underlined symbols to the enymes for which the genes code.

Table A-1 (Continued)

Symbol	Marker Name	E. C. Number
MDH1	malate dehydrogenase, NAD (soluble)	1.1.1.37
MDH2	malate dehydrogenase, NAD (mitochondrial)	1.1.1.37
ME1	malic enzyme 1, soluble	1.1.1.40
MHC	major histocompatibility complex	
MPI	mannose phosphate isomerase	5.3.1.8
NAGA	acetylgalactosaminidase; alpha-N-	3.2.1.49
NP	nucleoside phosphorylase	3.4.2.1
PEPA	peptidase A	3.4.11.* or 3.4.13.*
PEPB	peptidase B	3.4.11.* or 3.4.13.*
PEPC	peptidase C	3.4.11.* or 3.4.13.*
PEPD	peptidase D	3.4.13.9
PEPS	peptidase S	3.4.11.* or 3.4.13.*
PGD	phosphogluconate dehydrogenase	1.1.1.43
PGK1	phosphoglycerate kinase 1	2.7.2.3
PGM1	phosphoglucomutase 1	2.7.5.1
PGM2	phosphoglucomutase 2	2.7.5.1
PGM3	phosphoglucomutase 3	2.7.5.1
PKM2	pyruvate kinase	2.7.1.40
PP	pyrophosphatase (inorganic)	3.6.1.1
RN5S	5S RNA	
RNR	ribosomal RNA	
SOD1	superoxide dismutase 1, soluble	1.15.1.1
SOD2	superoxide dismutase 2, mitochondrial	1.15.1.1
SORD	sorbitol dehydrogenase	1.1.1.14
TBG	thyroxin binding globulin	
TK1	thymidine kinase (soluble)	2.7.1.21
TPI1	triosephosphate isomerase 1	5.3.1.1

Nomenclature is from McAlpine et al., 1985.

In the text, underlined symbols refer to the genes, non-underlined symbols to the enymes for which the genes code.

APPENDIX B

GENE MAPS OF PAPIO SPECIES

Table A-2. Gene Map of Papio papio (PPA).

PPA Chromosome	Genes and Syntenic Groups
1	PGD, ENO1, PGM1, PEPC
3	GUSB, MDH2, SOD1, COL1A2
4	GLO1, ME1, SOD2
5	PGM2, PEPS
7	NP, CKBB, IDH2, SORD, MPI, PKM2
10	ADA, ITPA
11	LDHB
12	IDH1
14	LDHA
16	COL1A1, GAA, TK1
U1	ACY1
U2	MDH1
U3	PEPB

References: Finaz et al., 1977; Lalley et al., 1979; Créau-Goldberg et al., 1982, 1983, 1984, 1985; Thiessen and Lalley, in press.

"U" indicates an unassigned syntenic group or independently segregating marker. The number of the syntenic group is arbitrary.

Table A-3. Gene Map of Papio hamadryas (PHA).

PHA Chromosome	Genes and Syntenic Groups
2	ACY1 (pter-->q1)
3p	MDH2, SOD1
4	ME1, SOD2
7	NP, MPI, PKM2, HEXA
9	PP
10	RNR, ADA, ITPA
11	LDHB, TPI1
13	MDH1
17	ESD
20	GPI, PEPD
U1	PGD, PGM1, PEPC
U2	IDH1
U3	PGM2, PEPS
U4	LDHA, ACP2
U5	GSR

References: Henderson et al., 1977; Thiessen and Lalley, in preparation.

"U" indicates an unassigned syntenic group or independently segregating marker. The number of the syntenic group is arbitrary.

Table A-4. Gene Map of *Papio cynocephalus* (PCY).

PCY Chromosome	Genes and Syntenic Groups
1	RN5S
10	RNR
X	TBG

References: Warburton *et al.*, 1976; Henderson *et al.*, 1977; Lockwood *et al.*, 1984.

Table A-5. Composite Gene Map of Papio species.

Papio Chromosome	Genes and Syntenic Groups
1	PGD, ENO1, PGM1, PEPC, RN5S PGD-PGM1 synteny
2	ACY1 (2pter-->q1)
3	SOD1 (3p), MDH2 (3p), GUSB, COL1A2
4	GLO1, ME1, SOD2
5	PGM2, PEPS
6	
7	NP, CKBB, IDH2, SORD, MPI, PKM2, HEXA
8	(GSR)
9	PP
10	RNR, ADA, ITPA
11	LDHB, TPI1, (PEPB)
12	IDH1
13	MDH1, (ACP1)
14	LDHA, ACP2
15	
16	COL1A1, TK1, GAA
17	ESD
18	
19	
20	GPI, PEPD
X	TBG

Underlined gene symbols indicate gene assignments determined by two laboratories. These assignments would be considered confirmed if P. papio and P. hamadryas are classified as the same species.

Gene symbols in parentheses indicate possible locations of genes which have not been assigned to chromosomes.

APPENDIX C

COMPARATIVE GENE ASSIGNMENTS

Table A-6. Chromosome Assignments of Selected Genes in *Papio papio* (PPA), *Papio hamadryas* (PHA), *Macaca mulatta* (MML), *Homo sapiens* (HSA), and *Mus musculus* (MMU).

Gene	PPA	PHA	MML	HSA	MMU
PGD	1	U1	1	1p	4
ENO1	1		1	1p	4
PGM1	1	U1	1	1p	4
PEPC	1	U1		1q	1
ACY1	U1	2		3p	9
GPX1			3	3	
SOD1	3	3		21q	16
COL1A2	3			7q	16
MDH2	3	3	2	7	5
GUSB	3		2	7q	5
MHC			2	6p	17
GLO1	4			6p	17
ME1	4	4		6q	9
PGM3			2	6q	9
SOD2	4	4	2	6q	17
PGM2	5	U2	6	4	5
PEPS	5	U2		4	5
NP	7	7	7	14q	14
CKBB	7			14q	
IDH2	7			15q	7
SORD	7			15	2
MPI	7	7		15q	9
PKM2	7	7	7	15q	9
HEXA		7	7	15q	
PP		9		10q	10

Table A-6 (Continued)

Gene	PPA	PHA	MML	HSA	MMU
ITPA	10	10	13	20p	2
ADA	10	10		20q	2
NAGA			13	22q	
LDHB	11	11	12	12p	6
TPI1		11	12	12p	6
PEPB			12	12q	10
IDH1	12	U3	9	2q	1
MDH1	U2	13	15	2p	
LDHA	14	U4	11	11p	7
ACP2		U4	11	11p	2
COL1A1	16			17q	11
TK1	16			17q	11
GAA	16			17q	
ESD		17		13q	14
GPI		20	19	19q	7
PEPD		20		19q	7
GSR		U5	8	8p	8

References for gene assignments in P. papio, P. hamadryas, and M. mulatta are given in the text (Section IV). Human gene assignments are from McAlpine et al., 1985; mouse gene assignments are from Lalley and McKusick, 1985.

VITA

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