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Expanded comparative mapping between man and rabbit and detection of a new conserved segment between HSA22 and OCU4

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Abstract. Rabbit, a domestic species exploited both in animal production and medical research has only recently begun to be included in gene mapping projects, in particular by the French National Institute of Agronomics. By 2002, less than 60 genes had been precisely localised on rabbit chromosomes, which led us to start a large-scale project on gene mapping in rabbit with the publication of 133 gene localisations in 2003 (Chantry-Darmon et al., 2003). Here, we report the localisation of 102 new genes resulting in good coverage of the rabbit genome and an eight-fold enrichment of the gene map. In addition, we have detected a new conserved segment between rabbit chromosome 4q15.3 and part of human chromosome 22 and thus improved the comparative map with the human genome.

As previously reported (Chantry-Darmon et al., 2003), rabbit is an interesting species both in animal production and medical research but its gene map was poorly developed until recently (Zijlstra et al., 2002; Chantry-Darmon et al., 2003). The production of gene-rich maps is a prerequisite both for high-resolution comparative mapping with man (or other map-rich species i.e. mouse, rat, cow, pig) and for projects on the identification of QTLs. Although bi-directional chromosome painting experiments have revealed an overall picture of the extent and distribution of conserved segments between human and rabbit chromosomes (Korstanje et al., 1999), a more detailed comparison would help to add neighbouring markers in regions of interest. In 2003, we reported a first contribution to the large-scale mapping project in rabbit initiated by the INRA with the localisation of 133 genes by fluorescent in situ hybridisation of gene-containing BAC clones to rabbit chromosomes (Chantry-Darmon et al., 2003). In our continuing goal to develop the comparative map between human and rabbit chromosomes, we have isolated and FISH-mapped rabbit BAC clones for 102 additional genes. Our aim here was to target the search of genes on chromosome bands with no mapped genes to date, based on the existing comparative mapping human/rabbit data.

Materials and methods

Choice of the genes and primer design, rabbit BAC library screening and sequencing of the PCR products

Previously described procedures (Chantry-Darmon et al., 2003) were used to design the primer sequences and to isolate gene-containing clones from our rabbit BAC library (Rogel-Gaillard et al., 2001) either by a standard PCR-based screening protocol or by hybridisation of high density filters representing the whole library. To check the identity of the sequence inserted in the BAC clones, the PCR product was sequenced and standard nucleotide-nucleotide BLASTN analyses were performed.

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Probe preparation for fluorescence in situ hybridisation

BAC DNA extracts were prepared according to standard protocols and purified with the S.N.A.P. K1900-01 Miniprep kit (Invitrogen life technologies). DNA was then labelled by nick-translation with biotin-14-dATP (BioNick 18247-015 labelling system, Invitrogen Life Technologies), mixed with 100× total sonicated herring sperm DNA and 100× total sonicated rabbit DNA, ethanol precipitated, slightly dried and resuspended in hybridisation buffer.

FISH on R-banded rabbit chromosomes

R-banded chromosome spreads were obtained from rabbit embryo fibroblast cell cultures synchronized with an excess of thymidine and treated with 5-bromodeoxyuridine (BrdU) during the second half of S phase (Hayes et al., 1991). Fluorescent in situ hybridisation, signal detection and R-banding were performed as previously described (Hayes et al., 1992) with 50–100 ng biotin-14-dATP-labelled probe per slide. Before hybridisation to the chromosomes, probes were denatured at 100 °C for 10 min and pre-hybridized at 37 °C for 30–60 min. Slides were examined under a Zeiss Axioplan 2 epifluorescence microscope and the Applied Imaging Cytovision (version 2.7) software was used for image capturing and analysis. Chromosome and band numbering follow Hayes et al. (2002).

Results and discussion

Choice of genes and recovery of BAC clones

The 102 new genes localized in this work were chosen based on their position on the human genome i.e. on human chromosome bands not included in our previous report (Chantry-Darmon et al., 2003) or to complete some human chromosome bands containing numerous genes such as 4q13.3 *(SLC4A4* and *GC)*, 5q33.3 *(ADRA1B)*, 6q15 *(CGA)*, 9p13.3 *(VCP)*, 17p13.3 *(MYH3)* and 18q12.1 *(MAPRE2)*. Table 1 presents the chosen genes with their localisation on human chromosomes. The table listing the primer pairs, the species from which the EST originated, GenBank accession numbers and expected size of PCR products is accessible online at http://dga.jouy.inra.fr/lgbc/donnees/pdf/Primer_Information_Rabbit_MS_CGR_2005.pdf. As explained in Chantry-Darmon et al. (2003), the availability of many rabbit ESTs and cDNAs in GenBank made it possible to design homologous primers for 93 genes. For the other nine genes, primers were designed from human cDNAs (two) and equine cDNAs (seven). At least one BAC clone was isolated from our rabbit BAC library for each of the 102 genes listed in Table 1 with 28 BAC clones recovered by PCR screening and 74 by hybridisation. In all cases, the sequence of the rabbit PCR product confirmed that the expected gene was contained in the isolated BAC clone.

Localisation of 102 genes on rabbit chromosomes by fluorescent in situ hybridisation

DNA extracted from each of the 102 rabbit gene-specific BAC clones was biotin-labelled and hybridised to rabbit metaphase chromosome spreads. Clear and consistent hybridisation signals were obtained and images were captured and analysed for at least ten spreads in each case. Results are summarized in Table 1 with those in bold characters indicating localisations obtained with genes from new human chromosomal bands. Indeed, among the 102 newly localized genes on rabbit chromosomes, 74 are positioned to chromosome bands or sub-bands devoid of any mapped gene to date. Figure 1 presents the current status of the rabbit cytogenetic map constructed in our laboratory, with genes localised during this work indicated in black and those obtained in earlier reports in grey. Newly localized genes are distributed over all the chromosomes except chromosome Y, which still has only *SRY* as the single mapped gene. Figure 1 clearly shows that globally we have enriched chromosomes or chromosome arms which were either little (i.e. OCU2, OCU4, OCU7, OCU12, OCU15) or not covered (OCU6q, OCU14p, OCU16p) in our previous work. The p arm of chromosome 15 is still devoid of mapped genes as well as the very small p arms of chromosomes 20 and 21. For these particular chromosomal regions, it is difficult to focus the search for genes because of the absence of any comparative mapping human/rabbit data. At present, about 43% of the bands of the rabbit karyotype at the 347-band level (Hayes et al., 2002) carry at least one mapped gene. Most of these bands are R positive, which correlates with the fact that in mammals the R positive bands are gene-rich (Saccone et al., 1996). However, the band level used for cytogenetic positions of genes on the human genome sequence (Ensembl database http://www.ensembl.org/) is the schematic representation of chromosomes corresponding to approximately 850 bands (ISCN 1981). This is a much higher resolution than that currently used in other species thus more precise comparisons of gene localisations on R or G bands between man and another species are not possible. Indeed, an R positive band at the 400-band level may subdivide in two R positive and one R negative bands at the 850-band level.

Rabbit/human comparative map and detection of a new conserved segment

We have compared our results (Fig. 1) with the human/rabbit heterologous chromosome painting data reported by Korstanje and colleagues (1999) and we reveal the existence of a previously undetected conserved segment between HSA22 and OCU4. Indeed the localisation of *FBXO7* (HSA22q12.3) and *DDX17* (HSA22q13.1) genes on rabbit chromosome 4q15.3 shows that a small region of OCU4 band q15.3 is homologous with part of HSA22. This band is a large R positive band in rabbit and we are currently searching for genes in the distal part of HSA22 i.e. on bands 22q13.2 to 22q13.33 to determine if this conserved segment extends right to the end of OCU4q15.3. Human/rabbit heterologous chromosome painting had revealed that the long arm of OCU4 is entirely painted by HSA12. Together, with our results, it appears that OCU4q corresponds in fact to a combination of ancestral chromosome forms of HSA12 and 22, an association frequently observed in other species as reviewed by Murphy and colleagues (2001). In addition, our results confirm the conservation between OCU6q and part of HSA7 with the localisation of the *EPO* gene, between OCU14p and part of HSA3 with the localisation of *SLC4A7* gene and between OCU16p and part of HSA10 with the localisation of the *AKR1C3* gene. These genes are the first to be mapped to these three rabbit chromosome arms and constitute anchors from which we can search for new genes on the corresponding human chromosomes to enrich these rabbit regions. In two cases, our results modify slightly the size of a conserved segment (i) on OCU8 the conserved segment with HSA13 extends to the centromere of OCU8 (localization of the

Table 1. List of genes mapped in this study, their localisation on human chromosomes, expected localisation in rabbit and FISH localisations. Results in bold characters indicate localisations obtained with genes from human chromosome bands not included in previous studies. Gene symbols follow the HUGO nomenclature (http://www.gene.ucl.ac.uk/nomenclature). For each human chromosome, genes are ordered from the p telomere to the q telomere according to the Ensembl database (http://www.ensembl.org/).

Gene symbol	Gene name	Human localization Ensembl Oct 04	Rabbit localization
PTAFR	**platelet-activating factor receptor**	**1p35.3**	**13q33**
AGL	**amylo-1, 6-glucosidase, 4-alpha-glucanotransferase**	**1p21.2**	**13q24-q25**
CD1D	CD1D antigen, d polypeptide	1q23.1	13q21med
CENPF	**centromere protein F, 350/400ka (mitosin)**	**1q41**	**16q16-q21prox**
LYST (CHS1)	**Chediak-Higashi syndrome 1**	**1q42.3**	**16q13.3**
CDC42EP3	**CDC42 effector protein (Rho GTPase binding) 3**	**2p22.2**	**2q22.3**
GGCX	**gamma-glutamyl carboxylase**	**2p11.2**	**2q14dist-q15**
EIF5B	**eukaryotic translation initiation factor 5B**	**2q11.2**	**2q13-q14prox**
PROC	**protein C (inactivator of coagulation factors Va and VIIIa)**	**2q14.3**	**7q14**
LCT	**lactase**	**2q21.3**	**7q15prox**
CXCR4	**chemokine (C-X-C motif) receptor 4**	**2q21.3**	**7q15prox**
ACVR2	**activin A receptor, type II**	**2q22.3**	**7q16prox**
C2orf25	**chromosome 2 open reading frame 25**	**2q23.2**	**7q16prox**
PLA2R1	**phospholipase A2 receptor 1, 180kDa**	**2q24.2**	**7q16dist**
MYL1	**myosin, light polypeptide 1, alkali; skeletal, fast**	**2q34**	**7q23.3-24**
RAF1	**v-raf-1 murine leukemia viral oncogene homolog 1**	**3p25.2**	**9p13dist (limit p14)**
SLC4A7	**solute carrier family 4, sodium bicarbonate cotransporter, member 7**	**3p24.1**	**14p13dist**
ACOX2	**acyl-Coenzyme A oxidase 2, branched chain**	**3p14.3**	**9p13prox (limit p12)**
SIAH2	**seven in absentia homolog 2**	**3q25.1**	**14q13prox**
FNDC3B (FAD104)	**factor for adipocyte differentiation 104**	**3q26.31**	**14q15dist**
CLCN2	**chloride channel 2**	**3q27.1**	**14q17dist**
LIPH	**lipase, member H**	**3q27.2**	**14q17dist**
WDR1	**WD repeat domain 1**	**4p16.1**	**2p25**
UGDH	**UDP-glucose dehydrogenase**	**4p14**	**2p21.3**
SLC4A4	solute carrier family 4, sodium bicarbonate cotransporter, member 4	4q13.3	15q23dist
GC	group-specific component (vitamin D binding protein)	4q13.3	15q23dist
PRKG2	**protein kinase, cGMP-dependent, type II**	**4q21.21**	**15q23prox**
SPP1	**secreted phosphoprotein 1**	**4q22.1**	**15q22-q23**
PDLIM5 (LIM)	**LIM protein (similar to rat protein kinase C-binding enigma)**	**4q22.3**	**15q22-q23**
ADH1B	**alcohol dehydrogenase IB (class I), beta polypeptide**	**4q23**	**15q21dist**
IL2	**interleukin 2**	**4q27**	**15q13**
UCP1	**uncoupling protein 1 (mitochondrial, proton carrier)**	**4q31.21**	**15q11.5**
TLR2	**toll-like receptor 2**	**4q31.3**	**15q11.3**
HAND2	**heart and neural crest derivatives expressed 2**	**4q34.1**	**2p21.1prox**
BRIX[a]	**BRIX**	**5p13.2**	**11q13prox**
CKMT2	**creatine kinase, mitochondrial 2 (sarcomeric)**	**5q14.1**	**11p14dist**
TCERG1	**transcription elongation regulator 1**	**5q32**	**3p13dist**
HAND1	**heart and neural crest derivatives expressed 1**	**5q33.2**	**3p13prox**
ADRA1B	adrenergic, alpha-1B-, receptor	5q33.3	3p13prox
RANBP9	**RAN binding protein 9**	**6p23**	**12p13**
PRL	**prolactin**	**6p22.3**	**12p11**
PGC	**progastricsin (pepsinogen C)**	**6p21.1**	**12q11.3**
BMP5	**bone morphogenetic protein 5**	**6p12.1**	**12q12med**
CGA	glycoprotein hormones, alpha polypeptide	6q15	12q15
REV3L	**REV3-like, catalytic subunit of DNA polymerase zeta**	**6q21**	**12q21**
T	**T, brachyury homolog**	**6q27**	**12q25.3dist**
AOAH	**acyloxyacyl hydrolase**	**7p14.2**	**10q14dist**
EGFR	**epidermal growth factor receptor**	**7p11.2**	**10q16dist**
EPO	**erythropoietin**	**7q22.1**	**6q12med**
CALU	**calumenin**	**7q32.1**	**7p21prox**
CALD1	**caldesmon 1**	**7q33**	**7p21dist**
ERP70[a]	**protein disulfide isomerase related protein**	**7q36.1**	**7p21dist**
EXT1	**exostoses (multiple) 1**	**8q24.11**	**3q23prox**
VCP	valosin-containing protein	9p13.3	1p31prox
PSAT1	**phosphoserine aminotransferase 1**	**9q21.2**	**1p12**
OGN	**osteoglycin (osteoinductive factor, mimecan)**	**9q22.31**	**1p11dist**
CEL	**carboxyl ester lipase (bile salt-stimulated lipase)**	**9q34.13**	**1p35dist**

Table 1 (continued)

Gene symbol	Gene name	Human localization Ensembl Oct 04	Rabbit localization
AKR1C1	**aldo-keto reductase family 1, member C1**	**10p15.1**	**16p12.1prox**
ANXA8	**annexin A8**	**10q11.22**	**18q12dist**
DDX21	**DEAD (Asp-Glu-Ala-Asp) box polypeptide 21**	**10q22.1**	**18q21.3dist**
LOXL4	**lysyl oxidase-like 4**	**10q24.2**	**18q31dist**
PNLIP	**pancreatic lipase**	**10q25.3**	**18q33prox**
CYP2E1	**cytochrome P450, family 2, subfamily E, polypeptide 1**	**10q26.3**	**18q33dist**
CAT	**catalase**	**11p13**	**1q23**
LPXN	**leupaxin**	**11q12.1**	**1q25dist**
RPS3	**ribosomal protein S3**	**11q13.4**	**1q21.1**
WNT11	**wingless-type MMTV integration site family, member 11**	**11q13.5**	**1q21.1**
TYR	**tyrosinase (oculocutaneous albinism IA)**	**11q14.3**	**1q14-q15**
MMP1	**matrix metalloproteinase 1 (interstitial collagenase)**	**11q22.2**	**1q14**
SLN	**sarcolipin**	**11q22.3**	**1q14**
HSPA8	**heat shock 70kDa protein 8**	**11q24.1**	**1q12.3prox**
OLR1	**oxidised low density lipoprotein (lectin-like) receptor 1**	**12p13.2**	**8p12.3**
EMP1	**epithelial membrane protein 1**	**12p13.1**	**8p12.3dist**
KRT3	**keratin 3**	**12q13.13**	**4q11prox**
KRT18	**keratin 18**	**12q13.13**	**4q11prox**
LUM	**lumican**	**12q21.33**	**4q15.1**
CRYL1	**crystallin, lambda 1**	**13q12.11**	**8q11**
ATP12A	**ATPase, H+/K+ transporting, nongastric, alpha polypeptide**	**13q12.12**	**8q11**
TPT1	**tumor protein, translationally-controlled 1**	**13q14.13**	**8q13.3-q21**
KLF5	**Kruppel-like factor 5**	**13q22.1**	**8q22prox**
COCH	**coagulation factor C homolog, cochlin**	**14q12**	**17q21dist**
HIF1A	**hypoxia-inducible factor 1, alpha subunit**	**14q23.2**	**20q12.1**
CYP19A1	**cytochrome P450, family 19, subfamily A, polypeptide 1**	**15q21.2**	**17q13prox**
MYO5A	**myosin VA (heavy polypeptide 12, myoxin)**	**15q21.2**	**17q13prox**
DPEP1	**dipeptidase 1**	**16q24.3**	**5q16dist**
MYH3	myosin, heavy polypeptide 3, skeletal muscle, embryonic	17p13.1	19q12.3prox
TOB1	**transducer of ERBB2, 1**	**17q21.33**	**19q21prox**
MRCL3[a]	**myosin regulatory light chain MRCL3**	**18p11.31**	**9q13**
MAPRE2	microtubule-associated protein, RP/EB family, member 2	18q12.1	9q14.2
ELAC1	**elaC homolog 1**	**18q21.1**	**9q15.1**
GPI	**glucose phosphate isomerase**	**19q13.11**	**5p12prox**
CST3	**cystatin C (amyloid angiopathy and cerebral hemorrhage)**	**20p11.21**	**4p11**
BCL2L1	**BCL2-like 1**	**20q11.21**	**4p13med**
NCOA6	**nuclear receptor coactivator 6**	**20q11.22**	**4p13dist**
GSS	**glutathione synthetase**	**20q11.22**	**4p13dist**
IGLL1	**immunoglobulin lambda-like polypeptide 1**	**22q11.23**	**21q12prox**
FBXO7	**F-box protein 7**	**22q12.3**	**4q15.3prox**
DDX17	**DEAD (Asp-Glu-Ala-Asp) box polypeptide 17**	**22q13.1**	**4q15.3prox**
DDX3X	**DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, X-linked**	**Xp11.4**	**Xp13dist**
RGN	**regucalcin (senescence marker protein-30)**	**Xp11.3**	**Xp11**
RPS4X	**ribosomal protein S4, X-linked**	**Xq13.1**	**Xq12**
SLC25A5	**solute carrier family 25, member 5**	**Xq24**	**Xq21.1**

[a] Symbol from NCBI Entrez Gene (http://www.ncbi.nlm.nih.gov/entrez/query).

ATP12A and *CRYL1* genes) and thus covers the whole of its long arm and (ii) on OCU16, the conservation with HSA10 includes the first band of the long arm of OCU16 while in Korstanje et al. (1999) it was restricted to the short arm only (localization of *ITIH2*, previous report Chantry-Darmon et al., 2003). Finally, the comparative human/rabbit cytogenetic map confirms all the painting data obtained by Korstanje and colleagues (1999), including the few readjustments previously discussed and concerning OCU6, 10 and 11 (Zijlstra et al., 2002 and Hayes et al., 2002).

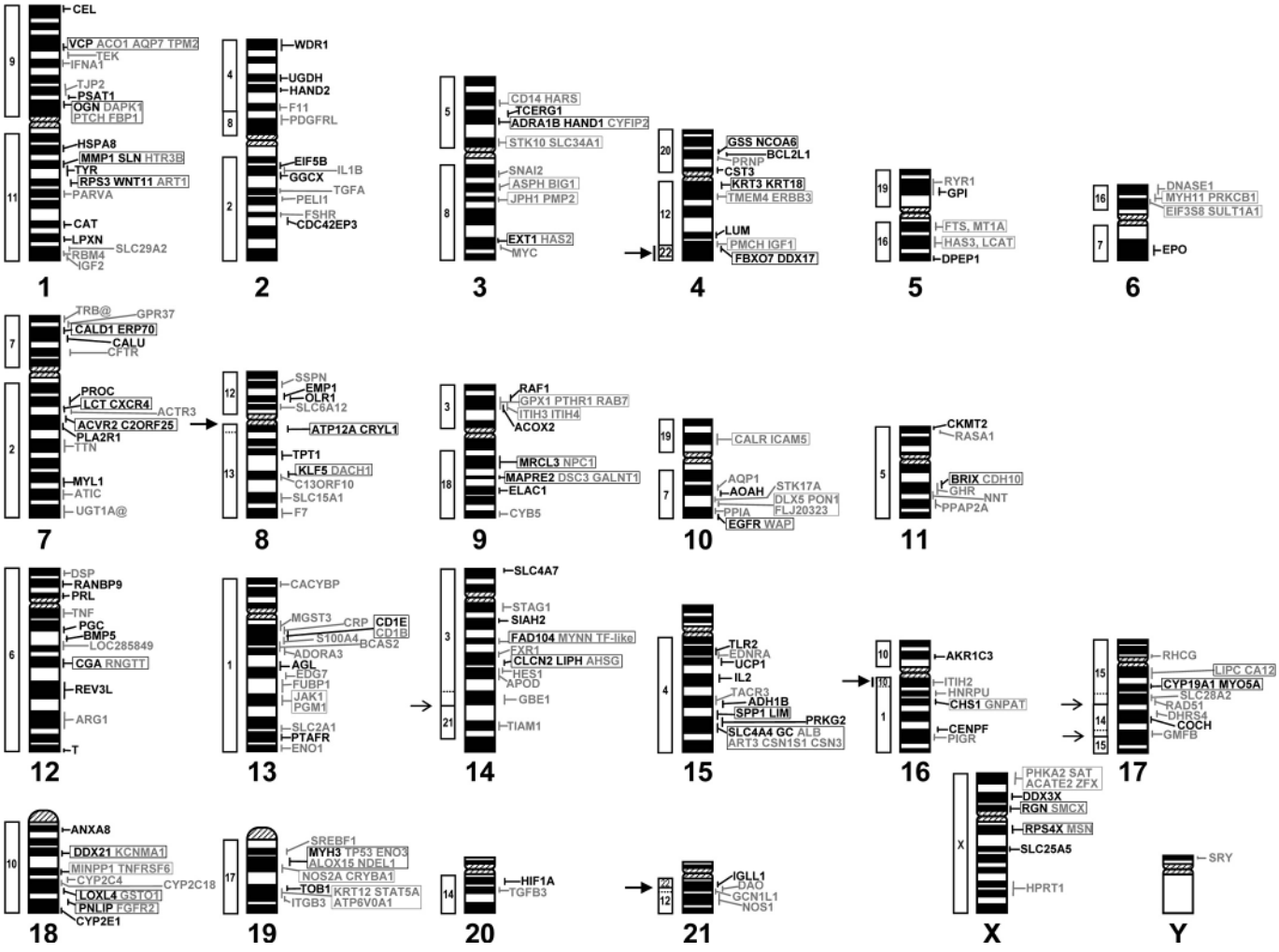

Fig. 1. Current rabbit cytogenetic map in our laboratory. The 102 newly localised genes are indicated in black characters on the right of each ideogram while previously mapped genes to R-banded chromosomes are given in grey (Martin-DeLeon et al., 2001; Hayes et al., 2002; Pauloin et al., 2002; Chantry-Darmon et al., 2003). Blocks on the left of each ideogram represent the chromosome correspondences with human chromosomes previously reported by Korstanje et al. (1999). Big arrows with vertical bars indicate a newly detected conserved segment between OCU4 and HSA22 and an extension of the conserved segment between OCU16 and HSA10 to the long arm of OCU16. Big arrows next to OCU8 and OCU21 denote slight modifications in the extension (dotted lines correspond to the previous limits reported by Korstanje et al., 1999) of conserved segments with the human genome (see text). The small arrows next to OCU14 and OCU17 indicate previously reported modifications (Chantry-Darmon et al., 2003).

With the growing number of genes mapped to bands and sub-bands of rabbit chromosomes and although the order of genes between rabbit and human chromosomes appears to be well conserved, it is possible to detect small inversions and rearrangements. In some cases, the series of genes involved include a centromere on the human chromosome while they are situated on a single chromosome arm in rabbit. For example, *CDC42EP3* (HSA2p22.2), *FSHR* (HSA2p16.3), *PELI1* (HSA2p14), *TGFA* (HSA2p13.3), *GGCX* (HSA2p11.2), cen, *EIF5B* (HSA2q11.2) and *IL1B* (HSA2q13) are positioned in the following order along the long arm of rabbit chromosome 2: *EIF5B*, *IL1B*, *GGCX*, *TGFA*, *PELI1*, *FHSR* and *CDC42EP3*, which can be explained by an inversion of the segment containing *EIF5B* and *IL1B*. The same situation is observed on human chromosome segment 11p15.4 *(ART1)*–11q13.2 *(RBM4)* versus rabbit chromosome segment 1q21.1→q21.2 *(ART1)*–1q27med *(RBM4)* or human chromosome segment 9p21.3 *(IFNA1)*–9q22.32 *(PTCH)* versus rabbit chromosome segment 1p23 *(IFNA1)*–1p11dist *(PTCH)*. Other single inversions are sufficient to restore the gene order between *ACTR3–PROC–LCT–CXCR4* on HSA2q and *(LCT*; *CXCR4)–ACTR3–PROC* on OCU7q or between *DAO–NOS1–GCN1L1* on HSA12q and *DAO–GCN1L1–NOS1* on OCU21q. Finally, complex rearrangements involving two successive or a segment transposition are necessary to explain differences between HSA7p21.3→p11.2 and OCU10 or HSA7q31.2→q36.1 and OCU7. However, it is clear that many more genes need to be mapped on rabbit chromosomes using high-resolution techniques such as

radiation hybrid mapping or even better genome sequencing, to analyse precisely the differences in gene order and organisation between the human and rabbit genomes.

Since the beginning of the INRA project on the rabbit map in 2002, we have increased eight-fold the number of precisely localised genes. This data has enabled us to produce directly an integrated cytogenetic and genetic map in rabbit using microsatellite markers isolated from anchored gene-containing BAC clones (in preparation) and to assemble a more precise comparative map, which in turn will speed up the construction of the genetic map.

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