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Evolution of the Human Chromosome 13 Synteny: Evolutionary Rearrangements, Plasticity, Human Disease Genes and Cancer Breakpoints

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Received: 10 February 2020; Accepted: 27 March 2020; Published: 1 April 2020

Abstract: The history of each human chromosome can be studied through comparative cytogenetic approaches in mammals which permit the identification of human chromosomal homologies and rearrangements between species. Comparative banding, chromosome painting, Bacterial Artificial Chromosome (BAC) mapping and genome data permit researchers to formulate hypotheses about ancestral chromosome forms. Human chromosome 13 has been previously shown to be conserved as a single syntenic element in the Ancestral Primate Karyotype; in this context, in order to study and verify the conservation of primate chromosomes homologous to human chromosome 13, we mapped a selected set of BAC probes in three platyrrhine species, characterised by a high level of rearrangements, using fluorescence in situ hybridisation (FISH). Our mapping data on Saguinus oedipus, Callithrix argentata and Alouatta belzebul provide insight into synteny of human chromosome 13 evolution in a comparative perspective among primate species, showing rearrangements across taxa. Furthermore, in a wider perspective, we have revised previous cytogenomic literature data on chromosome 13 evolution in eutherian mammals, showing a complex origin of the eutherian mammal ancestral karyotype which has still not been completely clarified. Moreover, we analysed biomedical aspects (the OMIM and Mitelman databases) regarding human chromosome 13, showing that this autosome is characterised by a certain level of plasticity that has been implicated in many human cancers and diseases.

Keywords: FISH; evolution; human synteny; painting; BAC probes; plasticity

1. Introduction

Comparative chromosome banding, followed by the advent of mapping by fluorescence in situ hybridisation (FISH), whole Chromosome Painting (CP) and Bacterial Artificial Chromosome (BAC) probes, have been used to detect chromosomal homologies, rearrangements and breakpoints among many mammalian species, defining major pathways of chromosome evolution in the class [1–6]. Indeed, these data are then analysed using cladistics and parsimony in order to define ancestral chromosomal syntenies as well as derived ones [2]. All of these approaches have paved the way to a reconstruction of the evolutionary history of human (Homo sapiens, HSA) chromosomes.

The CP approach consists in the localisation of a whole chromosome probe mapped onto cytogenetic preparations by FISH [2,7]. First, human chromosome probes are mapped onto
metaphases of target species; then animal probes of the target species can be mapped in a reciprocal hybridisation (RP) [8] on human metaphases, or on other animal genomes in an approach known as Zoo-FISH (Z-F) [9]. The analysis of these data regarding a single chromosome permits researchers to track each inter-chromosomal change involving the human chromosome under study. In yet another approach, human DNA sequences cloned inside vectors such as BACs are used as a mapping probe hybridised onto metaphases of target species, at a finer level, permitting the detection of fine chromosomal dynamics; these latter chromosome changes consist of small intra and inter-chromosomal rearrangements such as inversions, Evolutionary New Centromeres (ENC; new centromeres arise without the occurrence of inversions, maintaining the marker order) and duplications [3] which are not detectable by painting [5,6]. Animal BACs can be purchased from de Jong P. at the BAC/PAC Resource Centre (BPRC). Many works regarding the reconstruction of human chromosomes have been published so far, mainly by mapping BAC probes onto primate chromosomes [2,10].

Other chromosome features can be evaluated by mapping specific loci and repetitive probes that permit the localisation of sequences often believed to be responsible for the plasticity of chromosomes [11–17] and the detection of human genes involved in cancers [18].

Currently, homologies can be analysed by the Sequence Alignment (SA) data integrated with cytogenetic information using the new approach known as cytogenomics [19–23]. Sequence data are available from genomic browsers such as NCBI (https://www.ncbi.nlm.nih.gov/), UCSC (https://genome.ucsc.edu/) and Ensembl (https://www.ensembl.org/index.html), and can be integrated with molecular cytogenetic ones to analyse chromosome features, phylogenomic hypotheses and chromosome organisation.

All these approaches are useful not only to analyse chromosomal rearrangements that affect the syntenies, to define real homologies and the order of homologous sequences to avoid false breakpoints, but also to identify segmental duplications and copy number variants. Indeed, determining the order of conserved chromosome segments in the genomes of mammals is important not only for phylogenetic purposes but also for understanding speciation events and lineage specific adaptations [23].

The human chromosome 13 (HSA13) sequence has been released [24]; it is the largest acrocentric chromosome (114.36MB) in the karyotype, with 1381 genes, 41 novel genes and 477 pseudogenes; furthermore, it is among the human chromosomes with the lowest percentage of duplicated sequences [25]. Classic and molecular cytogenetic approaches (banding, CP and BAC mapping) allow researchers to formulate hypothesis about its evolutionary conservation despite some fusion or fission events in a few taxonomic groups [2,26,27]. The analysis of BAC probe signals on chromosomes of representative mammalian species permits researchers to make an initial reconstruction of the history of the chromosome, but particular focus has been given to the potential relationships between ENCs and neocentromeres occurring in clinical cases [27], as indeed has been previously shown [28]. Furthermore, a revision on human synteny 13 evolution in eutherian mammals has been recently proposed in a comprehensive review [29]. Furthermore, the cytogenomic approach applied by Kim and colleagues [23] showed that, in general, human chromosome evolution has been affected mostly by inversions and complex rearrangements observed during the evolution of the eutherian ancestor to human, whereas fusions and fissions were less prevalent. In this perspective, in order to study and verify the conservation of syntenic homologues to human chromosome 13 and to look for intrachromosomal rearrangements not easily detectable through other methods, we used FISH to map specific BAC probes in platyrrhine species. The species were chosen among taxa characterised by a high level of rearrangements, which suggested that they could be a useful model for the study of chromosome evolution. Our mapping data on Saguinus oedipus (Linnaeus, 1758), Callithrix argentata (Linnaeus, 1766), also known as Mico argenteus, and Alouatta belzebul (Linnaeus, 1766) let us discuss chromosome 13 evolution in light of previously published data, with a comparative perspective involving not only primates. Indeed, we also made an update regarding cytogenomic literature data on human chromosome 13 evolution in eutherian mammals [29], permitting us to reconstruct the main evolutionary steps of human 13 synteny. Furthermore, we
analysed the OMIM and the Mitelman databases on human chromosome 13 in order to shed light on its plasticity and other evolutionary and biomedical aspects.

2. Materials and Methods

Following the standard protocol [30], metaphases were obtained for specimens of cotton-headed tamarin, *Callithrix argentata* (CAR), silvery marmoset, *Saguinus oedipus* (SOE) (Cebidae) and red-handed howler, *Alouatta belzebul* (ABE) (Atelidae) from primary fibroblast cell lines or lymphoblasts (human), detailed in Table 1.

| Family    | Latin name | Code | Cell type                | Sample/Cell line acknowledgement                                                                 |
|-----------|------------|------|--------------------------|--------------------------------------------------------------------------------------------------|
| Cebidae   | *Saguinus oedipus* | SOE   | fibroblast cell line     | Melody Roelke (Frederick National Laboratory of Cancer Research, Leidos Biomedical Research, Frederick, MD, USA), June Bellizzi and Director Richard Hann (Catoctin Wildlife Park and Zoo, Thumont, MD, USA) |
| Cebidae   | *Callithrix argentata* | CAR   | fibroblast cell line     | Stephen O’Brien (Laboratory of Genomic Diversity, National Cancer Institute, Frederick, MD, USA) and Hector Seuánez (Departamento de Genética, Instituto de Biología, Universidade Federal do Rio de Janeiro, Brazil) |
| Atelidae  | *Alouatta belzebul* | ABE   | fibroblast cell line     |                                                                                                  |

All experiments were performed in accordance with relevant institutional and national ethical guidelines and regulations.

Samples were karyotyped by G-banding or DAPI inverted banding. BAC probes for human chromosome 13 were purchased from de Jong P. J. of the BACPAC Resources Center (BPRC), Oklahoma, USA (currently in Richmond, CA, USA). The BACs with human chromosome 13 sequences from the RP11 library were selected from the UCSC genome browser (GRCh 37/Dec 2004). *Escherichia coli* (Migula, 1895) with human chromosome 13 sequences cloned in BACs were grown in LB broth (Gibco, ThermoFisher Scientific, MA, USA). BAC DNA was isolated by BIORAD Miniprep Kit (CA, USA), and amplified by a Whole Genome Amplification Kit, WGA1 (Sigma Aldrich, St. Louis, MO, USA). BAC probe labelling was performed by adding dUTP with fluorochromes using a WGA3 Kit (Sigma Aldrich, St. Louis, MO, USA).

In situ hybridisation of probes on the chromosomal spreads was performed according to previously published protocols [10] using an avidin-FITC/biotinylated anti-avidin system or DIG/Alexa system (Invitrogen, ThermoFisher scientific). Probes were also mapped on human metaphases as control.

BAC signals, for each species studied, were analysed by microscope Axioscope 2 (ZEISS, Jena, Germany). Chromosomes with BAC signals were identified by inverted DAPI or G-banding in accordance with previous painting data.

Furthermore, previous chromosome painting and genome data on human chromosome 13 evolution were analysed and upgraded presenting data on the mammalian molecular phylogenetic tree, drawn according to previous reconstructions [23,29,31] and modified using the Mesquite program v.2.75 [32]. The platyrrhine tree was also here drawn using the same program and according to a previous molecular phylogenetic reconstruction [4].

We analysed disease loci (365) reported for HSA13 chromosome in the OMIM database (http://www.ncbi.nlm.nih.gov/Omim/mimstats.html) as well as many cancer breakpoints (519) involving this chromosome from the Mitelman database (http://www.gap.nci.nih.gov.Chromosomes/Mitelman) in order to study the distribution of the disease loci, considering only representative ones with phenotype (109 among 365) and all cancer breakpoints.
3. Results

The literature data on human chromosome 13 evolution, here considered in Table 2 accordingly with [29], were analysed and presented on the mammalian molecular phylogenetic tree [23,29,31]. This tree was drawn and modified using the Mesquite program v.2.75 [32] (Figure 1).

Table 2. The list of species analysed by Chromosome Painting (CP), Reciprocal Painting (RP), Zoo-FISH (Z-F) and/or comparison of Sequence Alignments (SA) and respective references. For each species, human chromosome 13 homologues and other human associations are reported. The * indicates an alternative chromosome identification reported in a different reference. The shaded areas in the second column indicate ancestral conserved state of human chromosome 13 (HSA13) synteny as a single chromosome element: green shading—acrocentric morphology, light green shading—non-acrocentric morphology, prox—proximal part, ter—terminal part, q—q-arm, p—p-arm. Note that this table is a modified version of the original by Scardino et al. [29].

| Species                        | Chromosome morphology | Chr. # | Human chromosome association | Reference | Method |
|-------------------------------|-----------------------|--------|------------------------------|-----------|--------|
|                               |                       |        |                              |           |        |
| **MAMMALIA**                  |                       |        |                              |           |        |
| **EUTHERIA**                  |                       |        |                              |           |        |
| **BOROEUTHERIA**             |                       |        |                              |           |        |
| **EUARCHONTOGLIERES**        |                       |        |                              |           |        |
| **PRIMATES**                 |                       |        |                              |           |        |
| Catarrhini                    |                       |        |                              |           |        |
| *Homo sapiens*                | A                     | 13     |                              | [7]       | CP     |
| *Pan troglodytes*             | A                     | 14     |                              | [7]       | CP     |
| *Gorilla gorilla*             | A                     | 14     |                              | [7]       | CP     |
| *Pongo pygmaeus*              | A                     | 14     |                              | [7]       | CP     |
| *Hylobates concolor*          | M                     | 5, 9   | 1/13; 1/4/10/13              | [33]      | CP     |
| *Hylobates klossii*           | 4q                    | 3/13   |                              | [34]      | CP     |
| *Hylobates moloch*            | 4q                    | 3/13   |                              | [34]      | CP     |
| *Hylobates lar*               | 4q                    | 3/13   |                              | [7]       | CP     |
| *Symphalangus syndactylus*   | M                     | 15     |                              | [7]       | CP     |
| *Pygathris nemaeus*           | SM                    | 17     |                              | [35]      | CP     |
| *Nasalis larvatus*            | M                     | 15     |                              | [36]      | CP     |
| *Semnopithecus francoisi*     | M                     | 9      |                              | [37]      | CP     |
| *Semnopithecus phyreii*       | M                     | 9      |                              | [34]      | CP     |
| *Presbytis cristata*          | M                     | 19     |                              | [38]      | CP     |
| *Colobus guereza*             | M                     | 19     |                              | [39]      | CP     |
| *Erythrocebus patas*          | SM                    | 15     |                              | [40]      | RP     |
| *Chlorocebus aeriopi*         | M                     | 3      |                              | [41]      | CP     |
| *Cercopithecus erythrogaster* | SM                    | 12     |                              | [42]      | Z-F    |
| *Cercopithecus stampfii*      | SM                    | 13     |                              | [42]      | Z-F    |
| *Cercopithecus neglectus*     | M                     | 19     |                              | [40]      | RP     |
| *Macaca fuscata*              | SM                    | 16     |                              | [43]      | CP     |
| **Platyrrhini**               |                       |        |                              |           |        |
| *Cebuella pygmaea*            | SMs                   | 1, 4   | 13/9/22, 20/17/13            | [44,48]   | CP, RP |
| *Callithrix argentata*        | SMs                   | 2, 1   | 13/9/22, 20/17/13            |           |        |
| *Callithrix jacchus*          | SMs                   | 1, 5   | 13/9/22, 20/17/13            |           |        |
| *Callimico goeldii*           | As                    | 19, 17 | 13/9/22, 13/17              |           |        |
| *Saguinus oedipus*            | SMs                   | 1, 2   | 9/13/22, 20/17/13            |           |        |
| *Leontopithecus chrysomelas*  | SMs                   | 1, 2   | 9/13/22, 13/17/20            | [45]      | CP     |
| *Aotus nancymaeae*            | A                     | 19     |                              | [46]      | CP     |
| *Aotus infulatus*             | A                     | 14     |                              | [47]      | CP     |
| *Aotus lemurinus*             | A                     | 17     |                              | [46,48,49]| CP     |
| *griseimembra*                | A                     | 16     |                              | [8,50]    | CP     |
| *Saimiri sciureus*            | A                     | 17     |                              | [51]      | CP     |
| *Cebus (Sapajus) apella*      | A                     | 17     |                              | [52]      | Z-F    |
| *Sapajus a. paraguaianus*     | A                     | 17     |                              | [52]      | CP     |
| *Sapajus a. robustus*         | A                     | 17     |                              |           |        |
| *Cebus capucinus*             | A                     | 11     |                              |           |        |
| *Cebus nigrivittatus*         | A                     | 17     |                              | [53]      | CP     |
| Species             | Size | Chromosome | Notes |
|---------------------|------|------------|-------|
| Lagothrix lagotricha | SM   | 8          | [54]  |
| Brachyteles arachnoides | A   | 20         | [55]  |
| Ateles paniscus paniscus | M   | 4          | 13a/13b/3c/7b/1a |
| Ateles belzebuth marginatus | SM | 12         |       |
| Ateles geoffroyi | SM   | 12         |       |
| Ateles belzebuth hybridus | A  | 12         |       |
| Alouatta belzebuth | A    | 14         |       |
| Alouatta seniculus sara | 16 | 12         | [57]  |
| Alouatta seniculus arctoidea | A  | 15 (20*)  | (* [48]; [58]) |
| Alouatta caraya | A    | 4q         | [57]  |
| Alouatta guariba guariba | SM | 14         | [48,49] |
| Cacajao calvus rubicundus | A  | 13         | [59]  |
| Chiropotes israelita | A   | 15         | [46]  |
| Chiropotes utahicki | A    | 15         | [46]  |
| Pithecia irrorata | SM   | 8          | [59]  |
| Plecturocebus (Callicebus) donacophilus pallescens | A | 15       | [60]  |
| Plecturocebus (Callicebus) cupreus | SM | 7, 17     | 3/21/13, 13/17 |
| Plecturocebus (Callicebus) palesscens | A | 18, 21 | 13/17, 13 |
| Cheracebus (Callicebus) lugens | SM | 1     | 1/13 - 12/13 |
| Callicebus moloch | A    | 21         | [50]  |
| Callicebus personatus | M   | 1          | 13/20  |
| Callicebus nigrifrons | A   | 4, 17      | 13/20, 13/17 |
| Strepsirrhini       |      |            |       |
| Lemur catta | A    | 13         | [65]  |
| Hapalemur griseus griseus |   | 15        | [66]  |
| Eulemur fulvus | A     | 12         | [66]  |
| Microcebus murinus | SM   | 13         | [67]  |
| Lepilemur edwardsi | 6p   |            | [67]  |
| Lepilemur ankaranensis | 14 |            | [67]  |
| Lepilemur jamesi | 5q ter |            | [67]  |
| Lepilemur leucopus | 1q ter |            | [67]  |
| Lepilemur microdon | 5p   |            | [67]  |
| Lepilemur mittermeieri | 7p |            | [67]  |
| Lepilemur dorsalis | 6p   |            | [66]  |
| Lepilemur muselinus | 8 ter |            | [67]  |
| Lepilemur ruficaudatus | 5q prox |            | [67]  |
| Lepilemur septentrionalis |    | 14        | [67]  |
| Lepilemur dorsalis | 6p   |            | [66]  |
| Lepilemur muselinus | 8 ter |            | [67]  |
| Lepilemur ruficaudatus | 5q prox |            | [66]  |
| Lepilemur septentrionalis |    | 14        | [66]  |
| Indri indri | SM   | 3p         | 13/17 |
| Propithecus verreauxi | 6q | 5/13      | [66]  |
| Avahi laniger | 12   |            | [66]  |
| Daubentonia madagascariensis | 8p | 10/13     | [66]  |
| Nycticebus coucang | SM   | 18         | [68]  |
| Galago moholi | M     | 5          | [69]  |
| Taxon                           | Chromosomal Location | References |
|--------------------------------|----------------------|------------|
| Otolemur garnettii             | SM 14                | [68] RP    |
| Otolemur crassicaudatus        | A 14                 | [70] CP    |
| DERMOPTERA                     |                      |            |
| Galeopterus variegatus         | A 13                 | [71] RP    |
| SCANDENTIA                     |                      |            |
| Tupai a belangeri              | A 17                 | [72] CP    |
| Tupai a minor                  | A 16                 | [73] CP    |
| LAGOMORPHA                     |                      |            |
| Oryctolagus cuniculus          | SM 8                 | 13/12 [74] RP |
|                                |                      | [75] SA    |
| RODENTIA                       |                      |            |
| Mus musculus                   | 3, 5, 8, 14, 12, 15, 16 | [20], [21], [75], [23] SA |
| Rattus norvegicus              |                     |            |
| Pedetes capensis               | SM 6                 | 13/12/22 [76] CP |
| Sicista betulina               | M, SM 1, 9          | 13/4/10/11/9/10, 3/6/13/19 [76] CP |
| Castor fiber                   | SM 4                 | 8/13 [76] CP |
| Sciur us carolinensis          | SM 6, 10            | 10/13 [77], [78] RP |
| Petaurista albiventer          | M 11                | 10/13 [78] CP |
| Tamias sibiricus               | M 10                | 10/13 [78] CP |
| LAURASIATHERIA                 |                      |            |
| Manis javanica                 | SM 1, 9q            | 13/5/2p, 18/13 [79] CP |
|                                | M                    |            |
| Manis pentadactyla             | SM 1q, 17           | 13/5/2, 13 [80] CP |
| CARNIVORA                      |                      |            |
| Canis familiaris               | As (25*), 22, 28     | (*[81]), [82], [83], [75], [23] Z-F CP |
| Vulpes vulpes                  | SMs 6, 9            | 13/12/14, 2/8/13/3/19 [82] RP |
| Mustela putorius               | SM 8                 | [84] CP    |
| Procyon lotor                  | M 3                 | 13/2 [85] CP |
| Mephitis mephitis              | SM 19                |            |
| Felis catus                    | A1p 13/5             | [19], [20], [75] CP |
| PERISSODACTYLA                 |                      |            |
| Tapirus indicus                | A 18                 | [9] Z-F    |
| Diceros bicornis               | A 10                 | [9] Z-F    |
| Ceratotherium simum            | 10                   | [9] Z-F    |
| Equus caballus                 | A 17                 | [20], [23] SA |
|                                |                      | [27] BAC   |
| Equus burchelli                | SM 6q                | 13/9 [9] Z-F |
| Equus asinus                   | 11                   | [9] Z-F    |
| Equus grevyi                   | SM 6q                | 13/9 [9] Z-F |
| Equus zebra hartmannae         | 15                   | [9] Z-F    |
| Equus hemionus onager          | 5q                   | 12/13/22 [9] Z-F |
| Equus przewalskii              | 16                   | [9] Z-F    |
| CETARTIODACTYLA                |                      |            |
| Bos taurus                     | A 12                 | [19] SA    |
| Moschus moschiferus            | A 17                 | [23], [87] RP |
| Okapia johnstonii              | A 11                 | [88] Z-F   |
| Giraffa camelopardalis         | M 12                 | 14/15/13 [88] Z-F |
| Globicephala melas             | M 15                 | [88] Z-F   |
| Hippopotamus amphibius         | M 15                 | [88] Z-F   |
| Sus scrofa                     | M 11                 | [19] SA    |
| Genus                           | Species                  | Chromosome Counts | Reference Notes |
|--------------------------------|--------------------------|-------------------|-----------------|
| **Camelidae**                  | **Camelus dromedarius**  | M 14              | [23] [87] RP    |
| **CHIROPTERA**                 | **Mormopterus planiceps**| M M7              | [89] CP         |
|                                | **Myotis myotis**        | M V5/6            | [89] CP         |
|                                | **Taphozous melanopogon**| SM 1              | [90] CP         |
|                                | **Megaderma spasma**     | M 12              | [90] CP         |
|                                | **Rhinolophus mehelyi**  | A R6              | [89] CP         |
|                                | **Aselliscus stoliczkanus**| M 1              | [91] CP         |
|                                | **Hipposideros larvatus**| M H1              | [89] CP         |
|                                | **Eonycteris spelaea**   | SM E11            | [89] CP         |
| **EULIPOTYPHLA**               | **Hemiechinus auritus**  | SMs 5q, 6         | [79] CP         |
|                                | **Neotetracus sinensis** | SM A 3, 10        | [92] CP         |
|                                | **Sorex araneus**        | M bc              | [92,23] CP, SA  |
|                                | **Blarinella griselda**  | SM 3              | [92] CP         |
|                                | **Talpa europaea**       | M 6               | [93] CP         |
| **ATLANTOGENATA**              |                          |                   |                 |
| **AFROTHERIA**                 |                          |                   |                 |
| **PROBOSCIDEA**                |                          |                   |                 |
|                                | **Loxodonta africana**   | A, SM 16, 26      | [94],[19] CP    |
|                                | **Elephas maximus**      | A, SM 16, 26      | [94] CP         |
| **SIRENIA**                    | **Trichechus manatus**   | M 19              | [95] CP         |
| **TUBULIDENTATA**              | **Orycteropus afer**     | SM 1              | [94],[96] CP, SA|
| **MACROSCELIDEA**              |                          |                   |                 |
|                                | **Elephantulus rupestris**| SM 2              | [97] CP         |
|                                | **Elephantulus edwardii**| SM 2              | [96] SA         |
|                                | **Macroscelides proboscidus**| SM 2          | [98] CP         |
| **AFROSORICIDA**               |                          |                   |                 |
|                                | **Chrysochloris asiatica**| M 8              | [97],[96] RP, SA|
| **XENARTHRA**                  |                          |                   |                 |
| **CINGULATA**                  | **Dasypus novemcinctus** | SM 19             | [99] CP         |
| **PILOSA**                     |                          |                   |                 |
|                                | **Tamandua tetradactyla**| M 4, (2*)        | [79],[99] CP    |
|                                | **Choloepus didactylus** | A 17             | [79] CP         |
|                                | **Choloepus hoffmanni**  | A 12             | [99] CP         |
|                                | **Bradypus torquatus**   | A 12             | [99] CP         |
|                                | **Bradypus variegatus**  | A 17             | [100] CP        |
| **METATHERIA**                 |                          |                   |                 |
| **MARSUPIALIA**                |                          |                   |                 |
| **DIDELPHIMORPHIA**            | **Monodelphis domestica**| SMs 4, 7         | [101],[102] SA  |
| **PROTOTHERIA**                |                          |                   |                 |
| **MONOTREMATA**                | **Ornithorhyncus anatinus**| SM Ms 2, 10, 20  | [101] SA        |
| **AVES**                       | **Gallus gallus**        | 1                | [101,102] SA    |

Chromosome morphology legend: Green–acrocentric, light green–submetacentric.
Figure 1. The mammalian phylogenetic tree shows the orthologous blocks that correspond to human chromosome 13 (in yellow) in representative eutherian species for which reciprocal painting data is available; the tree presents data from Table 2. Chromosome ideograms on which human synteny 13 is found are reported for each species, and the species’ chromosome number is shown on the left of the ideograms and HSA syntenies on the right. When HSA13 synteny, yellow, is rearranged with just a few human syntenies, these are represented in different colours and are reported on the right of the ideogram (for example, in indri, chromosome 3, synteny 13 (yellow), is fused with synteny 17 (red)), while when HSA 13 (yellow) is rearranged with many other human syntenies, these are represented by white segments for logistic reasons (for example, on chicken chromosome 1). For some species, DNA sequence alignments have been done previously, see Table 2 for citations. On the tree, the ancestral synteny 13 form (chromosome 14) described by painting data analysis is reported, and the eutherian ancestral chromosome 13 (EUT 1) alternative reconstruction, obtained through sequence data, from table 2, is shown in the upon box on the right of the tree underlined with an asterisk * [23]. Platypus (Monotremata), opossum (Marsupialia) and chicken (Aves) chromosome homologues are reported in the box at the lower right; these species are representative outgroups. Synteny homologues to human chromosome 13 are on chromosomes 2, 10 and 20 in the platypus, chromosomes 4 and 7 in the opossum and chromosome 1 in the chicken. Black areas indicate the centromere. The tree topology constructed according to previous data [31], and also considering results from [23] was modified from Scardino et al. [29].

Bright signals of the BAC probes on the chromosomes of the analysed species are shown (Figure 2); human synteny 13 homologues were two chromosomes in both *Saginus oedipus* (chr 1, 2) and *Callithrix argentata* (chr 1, 2) and a single synteny in *Alouatta belzebul* (chr 14), in accordance with previous chromosome painting data [44,49]; these chromosomes have been identified using inverted DAPI banding or G-banding.

BAC types and mapping results are summarised in Table 3.
Figure 2. Examples of fluorescent in situ hybridisation of mapped BACs onto CAR (a), ABE (b), SOE (c, d) metaphases. Note that BAC A7 on SOE chr 1p (d) shows triple band signals.
Table 3. The list of Bacterial Artificial Chromosome (BAC) clones used with their chromosome start coordinates and mapping position in the human genome from the UCSC genome browser (GRCH 37/Dec 2004) and the mapping position obtained on the three species analysed: S. oedipus (SOE), C. argentata (CAR), A. belzebul (ABE).

| BAC clone                  | Start coordinates | HSA      | SOE       | ABE       | CAR       |
|----------------------------|-------------------|----------|-----------|-----------|-----------|
| A6 CHORI RP11-35m5         | 27534229          | 13 tel   | 1p tel/ three bands | 14 tel   | 1p tel   |
| A7 CHORI RP11-85p8         | 27475788          |          |           |           |           |
| A11 CHORI RP11-14a4        | 39027477          | 13 tel   | 1p tel    | 14 tel    | 1p tel    |
| B8 CHORI RP11-30n18        | 48823331          | 13 cen   | 2q tel    | 4 interstitial below dark band | 2q tel    |
| B11 CHORI RP11-54g17       | 44481779          | 13 cen   | 2q tel    | 14 interstitial below dark band | 2q tel    |

These results were compared with other species previously analysed using the same approach [27]. The painting data (Table 2) and BAC mapping signals on synteny HSA13 are reported on the platyrrhine phylogenetic tree (Figure 3), here drawn in accordance with a previous reconstruction [4], but with some modifications using the Mesquite program v.2.75 [32].

Furthermore, we analysed disease loci (365) reported for HSA13 in the OMIM database and many cancer breakpoints (519) involving this chromosome from the Mitelman database. The analysis permitted us to construct a histogram to study the distribution of the disease loci (Figure 4) considering only representative ones with phenotype (109 among 365) (Table S1), and all cancer breakpoints ordered on chromosomal bands along human chromosome 13 (Table S2).

Figure 3. The platyrrhine phylogenetic tree showing the ideograms of the chromosome homologous to HSA13 synteny in representative New World monkeys (NWM). BAC probe mapping (red and green signals) are reported on the right side of banded chromosomes. The species’ chromosome numbers are reported under the ideograms, and HSA synteny associations are on the right. Note that some species previously recognised among the Callicebus genus have now been placed among the new Plecturocebus genus in recent molecular phylogeny [103]. PA—primate ancestor, OWM—Old World monkeys. The tree topology has been here reconstructed and modified according to previous analyses and reconstructions [4,104].
Figure 4. Distribution by band (x-axis) of 109 disease loci (orange) and 519 cancer breakpoints (blue), described in the OMIM and Mitelman databases, respectively (Tables S1 and S2). (Note that q12-q14 bands are particularly involved, not just in medical aspects but also in inter-chromosomal rearrangements occurring during evolution, as in Platyrhini).

4. Discussion

In this work, we have delineated the main steps regarding the evolutionary history of human chromosome 13 synteny in mammals. This chromosome history was traced based on comparative chromosome painting and mapping data. Furthermore, we performed comparative cytogenomic analysis and BAC mapping by FISH, with particular attention to platyrrhine species (Primates). These latter data were compared with those for other mammal species, in particular other primates, which had been previously analysed using the same approaches.

We also show chromosome 13 implicated in many human tumour formations and diseases; furthermore, we show that studies of chromosomes in an evolutionary perspective could shed light on the pattern of changes in correlation with cancer breakpoints or peculiar sequences that may be responsible for disease occurrence. In particular, we show that the region chr13q12-q14 is involved in both evolutionary changes and disease events.

4.1. Evolutionary History of HSA13 Synteny in Eutherian Mammals

The main steps of the evolution of human chromosome 13 synteny have been reconstructed and upgraded, considering previous molecular cytogenetic data obtained by painting and sequence analysis (Table 2), [29]; the steps are illustrated in a graphical reconstruction of the mammalian phylogenetic tree (Figure 1); this mammalian phylogenetic tree reconstructed in agreement with previous ones [23,29,31], has been drawn using Mesquite 2.75 [32].

Mammals are categorised into three major groups: monotremes (Prototheria, platypus), marsupials (Metatheria, opossum) and placental mammals (Eutheria), with these last two known as Theria; among placental mammals, Afrotheria, Xerathra and Boreoeutheria are recognised, with the latter comprising Laurasiatheria and Euarchontoglires (or Supraprimates) [31]. Synteny 13 orthologues are reported in the mammalian phylogenetic tree for representative eutherian species for which RP is available; molecular sequence alignments are also reported for some of them, when available (Table 2). Chromosome painting data let us propose that synteny 13 is conserved in mammalian orders as a single chromosome, as seen in Dermoptera, Pilosa, Carnivora, Perissodactyla and Cetartiodactyla but with exceptions in each group; for example, in cow—Bos taurus, chr 12 and pig—Sus scrofa, chr 11; in pigs, however, the synteny is on the metacentric chromosome due to the formation of a new centromere. Many rearrangements can be seen in other groups: Afrotheria (Tubulidentata, Afroscopicida, Macroscelidea, Sirenia), Eulipotyphla, Pholidota, Chiroptera, Rodentia where synteny 13 is associated with one or more human syntenies due to translocation; for example, among Chiroptera, in the greater mouse-eared bat Myotis myotis, human synteny 13 is present on chromosome 5/6, associated with many other human syntenies (8/4/13/12/22), and among Rodentia, in the eastern grey squirrel Sciurus carolinensis, human synteny 13 is present on chromosome 6, associated with other human syntenies (reported in white in Figure 1) and in Lagomorpha with the
rabbit—Oryctolagus cuniculus, chr 8 covered by the human association 12/13. Furthermore, human synteny 13 can be fragmented into two or more segments and associated with other HSA syntenies; for example, in carnivores (dog—Canis familiaris, chr 22, 28), Proboscidea (elephant—Loxodonta africana, chr 16, 26) and Rodentia species such as the birch mouse (Sicista betulina, chr 1, 9).

Analysing sequence alignments available from genomic browsers, chromosome 13 homologues are conserved in many mammals such as pigs, horses and cats [20], in agreement with painting data, and it is very fragmented in mice (Mus musculus, chr 3, 5, 8, 14) [21]; however, in outgroups such as the opossum (Monodelphis domestica, ch 4, 7), the chicken (Gallus gallus, chr 1) [101,102] and the platypus (Ornithorhynchus anatinus, chr 2, 10, 20) [100], through SA it has also been shown to be fragmented (Table 2, Figure 1). Indeed, recently, the analysis of many placental mammals has allowed researchers to hypothesise that the eutherian ancestral chromosome HSA13 was fused with other human syntenies (HSA4, and parts of HSA 2 and 8) [23]; in the latter reconstruction in Figure 1, synteny 13 on eutherian mammals (EUT) chromosome 1 is associated with other HSA syntenies (HSA4/8/2/13) and is in agreement with previous SA data [23]. Our chromosome painting analysis shows, on the other hand, these kind of human associations (13/2/8/4) involving human synteny 13 only on the greater mouse-eared bat’s chromosome 5/6, (HSA 4/8/13/12/22) [89]; thus, the molecular reconstruction of this ancestral form does not find support through painting. Consequently, the two reconstructions of ancestral synteny 13 in eutherians, by painting and sequence analysis, are not consistent. To better clarify this complex origin would require using appropriate outgroups and filling the gap in the incomplete set of taxa analysed so far. In particular, the lack of comparative chromosome painting between eutherians, monotremes and marsupials, and the lack of genomic data, do not permit a better reconstruction [23,29,98].

At a finer level, through BAC mapping applied to some representative mammals, common small intrachromosomal rearrangements have been shown along human chromosome 13 homologues in non-primate mammals [27], in agreement with SA data [23]. Moreover, evolutionarily new centromeres potentially linkable to neocentromeres are common, such as those shown in pig and Lagothrix lagothricha chr 8 (Platyrrhini).

4.2. Evolutionary History of HSA 13 Synteny in Primates

The first reconstruction of human chromosome 13 synteny was proposed using classical cytogenetics applied to Anthropoidea [1,26,105]; it is an acrocentric chromosome in great apes, with a paracentric inversion only in Gorilla gorilla [105]. In prosimians, the human chromosome 13 homologue is present as a single conserved synteny, but possibly metacentric, presumably due to an inversion or, alternatively, to the presence of a new centromere, as in Microcebus murinus (chromosome 13). On the other hand, it could be rearranged, as in Indri indri (chromosome 3), where it is associated with human synteny 17 (Figure 1). In catarrhines, a new centromere changed morphology from acrocentric to metacentric, as in Chlorocebus aethiops. While it is relatively conserved in these species, it is much more rearranged in platyrrhines.

4.3. Evolutionary History of HSA13 Synteny in Platyrrhines

The main evolutionary steps indicated by chromosome painting data on Platyrrhini regarding synteny HSA 13 (Table 2) are illustrated in a graphical reconstruction of the platyrrhine phylogenetic tree, drawn here using Mesquite (Figure 3). Even though human chromosome 13 is presumably conserved in the ancestors of platyrrhines, HSA 13 homologues have undergone many rearrangements in New World monkeys. Among platyrrhines, three families are recognised: Pitheciidae, Atelidae and Cebidae (Figure 3). Among Pitheciidae (Figure 3a) in Calllicebus (also known as Plecturocebus [103]), we found conservation of synteny HSA 13, as demonstrated in C./P. donacophilus, chromosome 15 [60], while it is split in some others species, for example, C./P. pallescens, on chromosomes 18 and 21 [61]. Furthermore, on chromosome 18, synteny HSA 13 is associated with human synteny 17. In this latter species, breakpoints have also been evaluated, occurring in position q12.3 [61]. A similar organisation is found in Titi monkeys (C./P. cupreus) on chromosomes 7 and 17 (covered, respectively, by HSA 3/21/13 and 13/17 [61]). Among Atelidae (Figure 3b), synteny 13
appears to be conserved, as in *Alouatta belzebul* chromosome 14 [57] and *L. lagothricha* chromosome 8 [27]; however, in the latter species, the chromosome is metacentric and a new centromere has been shown by BAC probe mapping [27]. Among Cebidae (Figure 3c), synteny 13 is conserved in a single chromosome, for example, on *Cebus capucinus* chromosome 11 [52] and *Saimiri sciureus* chromosome 16 [50], or fissioned, with subsequent translocation to other HSA syntenies. This latter arrangement is found, for example, in common marmosets (*Callithrix jacchus*), resulting in the formation of chromosomes 1 and 5 (covered respectively by HSA 13/9/22 and 13/17/20, Figure 1a) [44]. In addition, in *Callimico goeldii*, synteny 13 is fragmented into two segments forming chromosomes 17 and 19, with chromosome 17 covered by the syntenic association 13/17 and chromosome 19 by synteny 13 with little parts of synteny 9 [8,44].

In the species analysed in the present work, human synteny 13 homologues have also been split into two fragments on chromosomes 1 and 2 of both SOE and CAR (Cebidae); on SOE, the breakpoint has been evaluated by RP in position 13q13 [8,44]. On the metacentric SOE 1 and CAR 2, human synteny 13 is associated with human synteny 9 (13/9/22), and on chromosomes SOE 2 and CAR 1, synteny 13 is associated with human synteny 17 (20/17/13); this organisation is the same as that found in *Callithrix jacchus* chromosome 1 and 5. The mapping of our BAC probes was in agreement with the painting data (Figure 3c), in particular, probe A6/A11 on the terminal position of p arm of chromosome SOE 1 and CAR 2, and probes B8 and B11 on SOE 2 and CAR 1 on the q arm in a terminal position (Figure 2, Figure 3c). In ABE (Atelidae), all four probes hybridised onto chromosome 14, with B8 and B11 interstitial underneath the black band below the centromere and A11 and A6 at the terminal position; this same position was found for the probes that were applied onto HSA metaphases as control. Those data have been compared with the BAC probes of the same coordinates applied in a previous work on other platyrrhine species, such as *Callithrix jacchus, Saimiri sciureus* (Cebidae), *L. lagothricha* (Atelidae) and *Callicebus moloch* (Pithecidae) [27]. Human association data reported in the latter work on *Callithrix jacchus* needed to be revised due to the fact that synteny 13 is fissioned into two fragments on CJA chromosomes 1 and 5, which are covered, respectively, by human syntenic associations 13/9/22 and 20/17/13, in agreement with the painting data [44]; moreover, *Callicebus moloch* should instead be considered as *C. pallescens* due to the fact that this latter species’ synteny is fissioned into two fragments: one covering chromosome 21 and one on chromosome 18, where it is in association with HSA synteny 17 [61], as correctly reported in Figure 3c for further comparisons.

Our analysis showed marker order conservation of the BAC probes considered in all species compared, even where synteny 13 had been split during evolution; but we found an exception for probe A7 that had been mapped on SOE, where it showed three mapping signals on chromosome 1 (Figure 2, Figure 3c), in agreement with previous BAC mapping in *Callithrix jacchus* chromosome 1p [27]. These data indicate that a complex rearrangement in SOE chromosome 1p occurred, probably an inversion or duplication. This small rearrangement, demonstrable only through BAC mapping, is also present on CJA chromosome 1 as it possible to see when the same probe position is considered [27]. Further analysis is needed to show whether the small and not easily detectable rearrangement is shared with others Cebidae.

Our analysis of the organisation of synteny 13 in platyrrhine species shows that it is not as conserved as previously shown. Indeed, in the three families, we show both ancestral and derived organisation of human synteny 13. The derived form of synteny 13 often has breakpoints occurring between q12.2 and q14. Furthermore, probe mapping shows marker order conservation with exceptions. In light of these results, better analyses at a finer level are needed in order to better understand the evolution of synteny 13 and to help define homologies useful for phylogenetic and adaptive interpretation [23].

4.4. Distribution of Cancer Breakpoints and Loci Implicated in Human Diseases

The distribution of the loci considered, representative ones with phenotype (109 among 365) (Table S1), and all cancer breakpoints ordered by chromosomal bands along human chromosome 13 (Table S2), does not appear to be uniform. Indeed, there are some bands (13q12 and 13q14) that are
clearly more affected than others, as it is possible to observe in the frequency histograms we have produced (Figure 4). These data are in agreement with evolutionary synteny 13 changes occurring in the same region in Platyrrhini. In general, it has been shown that the most frequent cancer-associated chromosomal aberrations affecting tumour genes are close (at less than 0.4 MB) to reuse breakpoint regions identified through multispecies genome comparison [20]. This evidence is in agreement with other frequent human cancer-associated breakpoints that are co-localised with evolutionary breakpoints more frequently than other, less common, neoplasms. The coincidence of frequently occurring cancer breakpoints with evolutionary breakpoints indicates that some of the features that induce fragility in certain evolutionary breakpoints in germ lines are still retained in the human genome [22]. On chromosome 13, the most frequent cancer-associated chromosomal aberration close to reuse breakpoints identified from multispecies genome comparisons are the ones involving: gene ZNF198 (ZMYM2) translocation t(8;13) (p11;q12), which is linked to chronic myeloproliferative disorder and stem cell leukaemia lymphoma syndrome (SCLL); and gene FOXO1 translocation t(2;13)(q36;q14), linked to alveolar rhabdomyosarcoma. Furthermore, many other disease loci have been described. Indeed, chromosome 13 contains genes involved in other chromosomal aberrations, such as those involving the LCP1 gene translocation t(3;13)(q27;q14), linked to follicular lymphoma, BCL6 translocation t(3;13)(q27;q14), linked to B-cell non-Hodgkin lymphomas (B-cell NHL). Moreover, it is rearranged with the deletion del(13)(q13q14) in B-cell chronic lymphocytic leukaemia (CLL), the translocations t(12;13)(p13;q12) and t(12;15)(13p;q25) are common in acute myeloid leukaemia (AML), translocation t(12;13)(p13q14) in acute lymphoblastic leukaemia (ALL) and deletion del(13)(q13q14) in retinoblastoma (RB1). Chromosome 13 is also responsible for type 2 breast cancer (BRCA2) and contains the DAOA locus associated with bipolar disorder and schizophrenia, among many other genetic diseases (Table S1). Since it has been shown that some genetic diseases or cancer breakpoints occur in correspondence with the same peculiar region along the chromosomal arms linked to the presence of repeated sequences or segmental duplications [25], or in correspondence with reuse breakpoints which arose during evolution [20,22], the study of the distribution of the loci along the chromosome and the features that could induce fragility in the sequence would be a promising path to pursue.

5. Conclusion

Our analysis of human chromosome 13 synteny, updating a previous data report [29], permits us to define conserved segments but also to show that it is less conserved than previously thought. In particular, we have reviewed previous data regarding inter-chromosomal rearrangements detectable through painting, and intra-chromosomal rearrangements detected by BAC mapping, on synteny HSA 13. We have focused our attention on primates, in particular on platyrrhines, where we show a highly inter-chromosomal and intra-chromosomal dynamic. Furthermore, we show chromosome 13 as an autosome that is commonly implicated in human tumour formation and diseases; the study of chromosomes in an evolutionary perspective shed light on the pattern of changes in correlation with cancer breakpoints or particular sequences that may be responsible for disease occurrence. In particular, we show that the region between q12–q14 is involved both in evolutionary changes and disease events, and for this reason it deserves special attention.

Supplementary Materials: The following are available online at www.mdpi.com/2073-4425/11/4/383/s1, Table S1: List of disease loci from the OMIM database, considering only representative ones with phenotype (109 among 365), ordered by chromosomal bands along human chromosome 13, Table S2: List of cancer breakpoints (519) from the Mitelman database, ordered by chromosomal bands along human chromosome 13.

Author Contributions: Conceptualization, F.D.; methodology, V.M. and A.A.P.; software, R.S., V.M. and F.D.; validation, N.A.S., A.A.P., V.M. and F.D.; formal analysis, R.S., V.M. and F.D.; investigation, V.M. and N.A.S.; resources, F.D. and P.P.; data curation, R.S.; writing—original draft preparation, F.D.; writing—review and editing, F.D., P.P. and A.A.P.; visualization, A.A.P., R.S. and F.D.; supervision, F.D.; project administration, F.D.; funding acquisition, F.D. and P.P. All authors have read and agreed to the published version of the manuscript.
**Funding:** This research was funded by “Fondazione Intesa San Paolo Onlus”, grant number 2016-NAZ-0012, CUP: B72F16001300005. The grant covered cost of F.D.’s project “Evoluzione genomica in Primates” covering also two fellowships to R.S. and V.M. P.P. and A.P.’s work was supported by RSF 19-14-00034.

**Acknowledgments:** Special thanks to Melody Roelke (Frederick National Laboratory of Cancer Research, Leidos Biomedical Research, Frederick, MD, USA), June Bellizzi and Director Richard Hann (Catoctin Wildlife Park and Zoo, Thurmont, MD, USA), Stephen J. O’Brien (Laboratory of Genomic Diversity, National Cancer Institute, Frederick, MD, USA) and Hector Seuánez (Departamento de Genética, Instituto de Biologia, Universidade Federal do Rio de Janeiro, Brazil) who provided samples or cell lines used in this study.

**Conflicts of Interest:** The authors declare no conflicts of interest. The funders had no role in the design of the study, the collection, analyses, or interpretation of the data, the writing of the manuscript, or the decision to publish the results.

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