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dbRIP: A Highly Integrated Database of Retrotransposon Insertion Polymorphisms in Humans†

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Abstract

Retrotransposons constitute over 40% of the human genome and play important roles in the evolution of the genome. Since certain types of retrotransposons, particularly members of the *Alu*, L1, and SVA families, are still active, their recent and ongoing propagation generates a unique and important class of human genomic diversity/polymorphism (for the presence and absence of an insertion) with some elements known to cause genetic diseases. So far, over 2,300, 500, and 80 *Alu*, L1, and SVA insertions, respectively, have been reported to be polymorphic and many more are yet to be discovered. We present here the Database of Retrotransposon Insertion Polymorphisms (dbRIP; <http://falcon.roswellpark.org:9090>), a highly integrated and interactive database of human retrotransposon insertion polymorphisms (RIPs). dbRIP currently contains a nonredundant list of 1,625, 407, and 63 polymorphic *Alu*, L1, and SVA elements, respectively, or a total of 2,095 RIPs. In dbRIP, we deploy the utilities and annotated data of the genome browser developed at the University of California at Santa Cruz (UCSC) for user-friendly queries and integrative browsing of RIPs along with all other genome annotation information. Users can query the database by a variety of means and have access to the detailed information related to a RIP, including detailed insertion sequences and genotype data. dbRIP represents the first database providing comprehensive, integrative, and interactive compilation of RIP data, and it will be a useful resource for researchers working in the area of human genetics.

Keywords

retrotransposition; polymorphism; mutation; L1; *Alu*; SVA; database

INTRODUCTION

The human genome, like those of most other eukaryotic organisms, is highly rich in repetitive elements derived from retrotransposons that amplify themselves in the genome through an

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RNA-mediated retrotransposition process. Most common among them are *Alu* elements, which are a class of short interspersed elements (SINEs), and LINE-1s (or L1s), which belong to the long interspersed elements (LINEs). *Alu* elements have over 1 million members covering ~11% of the human genome, while L1 elements account for ~21% of the genome with ~500,000 members; collectively, they constitute approximately one-third of the human genome [Lander et al., 2001]. While most of the retrotransposable elements in the human genome are considered to be dead fossils from past waves of mobile element amplification, some members belonging to young subfamilies of these elements are still actively mobilizing and continue to make new copies in the genome. The first of such active groups are L1 elements, the only active autonomous retrotransposons in the human genome, which are also responsible for the mobilization of nonautonomous retrotransposons [Boissinot et al., 2000, 2004; Brouha et al., 2003; Dewannieux et al., 2003]. Among the active nonautonomous groups are *Alu* elements and SVA elements, a composite type of retrotransposon formed of SINE-R, VNTR, and *Alu* [Boeke, 1997; Boeke and Chapman, 1991; Deininger and Batzer, 2002; Dewannieux et al., 2003; Ostertag et al., 2000, 2002, 2003; Sassaman et al., 1997; Shen et al., 1994; Wang et al., 2005; Wang et al., 2006]. Many of the insertions derived from these active retrotransposons occurred so recently that they are polymorphic with respect to the presence or absence of the insertion in different human populations, families, or even individuals [Batzer et al., 1994; Batzer and Deininger, 1991, 2002; Boissinot et al., 2000, 2004; Badge et al., 2003; Bamshad et al., 2003; Myers et al., 2002; Perna et al., 1992; Sheen et al., 2000; Watkins et al., 2001, 2003]. Newly integrated repetitive elements can cause genetic diseases by interrupting exons, generating aberrant RNA splicing, or altering gene expression [Deininger and Batzer, 1999; Miki, 1998; Ostertag and Kazazian, 2001; Wallace et al., 1991]. Due to their lack of homoplasy and known ancestral state, retrotransposon insertion polymorphisms (RIPs) also serve as excellent genetic markers for studies of human population genetics [Batzer et al., 1991, 1994; Batzer and Deininger, 1991, 2002; Bamshad et al., 2003; Perna et al., 1992; Salem et al., 2005a; Stoneking et al., 1997; Watkins et al., 2001, 2003].

Over the last two decades many studies have been carried out to detect genomic variation derived from retrotransposons using various approaches (see http://falcon.roswellpark.org:9090/dbRI-P_ref.html for a complete list of the studies). Earlier studies using genomic library screening or direct DNA sequencing of the suspected mutant gene alleles identified a number of individual *Alu* and L1 insertions, some of which are disease-related [Arcot et al., 1995; Batzer et al., 1995; Kazazian et al., 1988; Miki et al., 1992, 1996; Wallace et al., 1991]. The recent availability of the human genome draft sequence, and additional diverse human genomic sequence data, have accelerated the process of identifying newly integrated retrotransposons. One strategy that has been very successfully used is to identify members belonging to the young subfamilies of retrotransposons from the reference genome sequence via computational analysis followed by determining their insertion polymorphism status through screening of DNA samples from diverse human populations [Callinan et al., 2003; Carroll et al., 2001; Carter et al., 2004; Myers et al., 2002; Otieno et al., 2004; Salem et al., 2003; 2005b; Sheen et al., 2000; Vincent et al., 2003; Xing et al., 2003]. Furthermore, two recent studies, both employing *in silico* computational strategies that utilize the sequence data from sources representing different human individuals, have also shown great success. A total of 505 polymorphic *Alu*, 65 L1, and 39 SVA elements were recovered by comparing the trace sequences derived from different library sources [Bennett et al., 2004]. By comparing the two versions of the human genome sequences (public vs. Celera www.celera.com), we have recently identified over 800 polymorphic *Alu* elements and 150 L1 elements [Wang et al., 2006; authors' unpublished data].

Collectively, all these studies have reported, as of this writing, a total of over 3,000 (with redundancy) RIPs. Nevertheless, a database with systematically documented information about retrotransposon derived genomic variation is not in existence, although part of this information

has been scattered in several databases, including GenBank [Arcot et al., 1995; Batzer et al., 1995; Holmes et al., 1994; Kazazian et al., 1988; Miki et al., 1992, 1996; Narita et al., 1993; Schwahn et al., 1998; Wallace et al., 1991] and the SNP database (www.ncbi.nlm.nih.gov/SNP) [Bennett et al., 2004]. Here we report a new database called the Database of Retrotransposon Insertion Polymorphisms (dbRIP; <http://falcon.roswellpark.org:9090/>) to provide a comprehensive compilation of human genome variations derived from retrotransposon insertions.

DATA SOURCES, COLLECTION, AND CURATION

Data for polymorphic *Alu*, L1, and SVA elements was collected from all available published papers (see a complete list of cited original reports at http://falcon.roswellpark.org:9090/dbRIP_ref.html) and was compiled into XML files. For each reported RIP entry, we collected and compiled the following data items: original identifications (IDs), type of retrotransposon, family and subfamily designation, association with disease, DNA sequences of the elements, target site duplications (TSDs), 400 bp of flanking sequence regions, oligonucleotide primers and PCR conditions, expected PCR product sizes for both filled and empty alleles, ascertainment method(s), source of genome sequences, genotypic data, chromosome position, cytoband position, size of the insertion, and reference(s). The mapping of the exact location for each RIP in the current version of the human genome reference sequences (currently University of California at Santa Cruz [UCSC] hg17 assembly based on National Center for Biotechnology Information [NCBI] Human Genome Build 35) was based on the available sequence information for one or more items among the flanking regions, the primers, TSDs, and the retrotransposon. For each RIP, the raw genotypic data was summed and reported as three genotypes (insertion +/+, +/-, and -/-) for each examined human group.

DATABASE DESIGN AND STRUCTURE

In choosing a design for dbRIP, we reasoned that creating a standalone database with only the RIP data would impose a limitation on its use. By contrast, users would be able to get most out of the RIP data if we could integrate the data into a system such that the RIPs are displayed along with other genome information. For this reason, it was natural for us to choose a system that can display the RIP data in a genome browser style. Among the existing genome browsers that are portable, we found that the UCSC genome browser created by the Genome Bioinformatics Group of University of California at Santa Cruz best fit our purposes [Hsu et al., 2004; Kent et al., 2002]. The UCSC genome browser (hereafter referred to as “the browser”) has gained wide use because of its user-friendly web interface and comprehensive data. In addition, its code and web interface have been stabilized over the past few years, hence it requires very little effort to maintain and update.

To deploy the UCSC genome browser for our use, we first installed the UCSC mirror package and the latest version of the human genome database (hg17). We then added new codes and modified some existing codes for the browser to accommodate dbRIP data as its standard tracks. The dbRIP data is displayed as three separate tracks in the browser with each for polymorphic *Alu*, L1, and SVA elements, respectively; they are grouped under the title of “Retrotransposon Insertion Polymorphisms in Humans” in the browser and listed within the “Variation and Repeats” category on the display options panel of the browser. Two dbRIP-specific tables are created to contain RIP data: one for genotypic data and the other for all remaining RIP data. In addition, a third table was created to host the start and end genomic positions of all promoter, exon, intron, and intergenic regions in the entire genome based on the current version of NCBI RefGenes, and this table is used to query RIPs by their physical relationship to genes.

To accommodate queries unique to dbRIP, as well as to increase the speed of some commonly used query functions available from the browser, we implemented a special query interface called SearchdbRIP. SearchdbRIP is implemented as a PERL-based CGI program powered by the MySQL relational database engine (<http://dev.mysql.com/>). We integrated the SearchdbRIP function into the browser such that it is conveniently accessible within most of the browsing windows via a standard button in the browser. The relationship and data flow among dbRIP tables, human genome annotation tables, SearchdbRIP, and the browser is shown in Figure 1. The database is hosted on a Compaq ProLiant DL360 server machine (Palo Alto, CA; www.hp.com) running the RedHat Linux 8.0 operating system and Apache web server (www.apache.org), and is available freely at <http://falcon.roswellpark.org:9090/> and <http://batzerlab.lsu.edu/>.

DATABASE FUNCTIONS

Utility of SearchdbRIP

The query utilities of SearchdbRIP are divided into the “Quick Search” and “Advanced Search” sections. “Quick Search” allows users to search by IDs, including dbRIP ID and the original IDs, or by chromosome positions. These queries are also available from the Genome Gateway within the browser, but are much quicker in SearchdbRIP, as SearchdbRIP limits the search to the three dbRIP tables. Utilities under “Advanced Search” are largely designed for dbRIP. The available search criteria here include chromosome number, relationship to genes (gene context), genomic source containing the insertion, subfamily of the retrotransposon, the presence or absence within a diverse human group (from a predefined list based on the availability), allele frequency ranges, association with a disease or phenotype, and author name. Users can use these criteria individually or combine two or more criteria. For example, one can query all RIPs that locate inside exons and are known to associate with a disease phenotype and with insertion absent from hg17 by selecting “exon” in the gene context slot and “non-hg17” in the genomic source slot and inputting “all” in the disease slot. The gene context query is made available for users who are more interested in querying RIPs based on the potential effect on gene function, such as those locating inside exons or promoter regions. It is based on the physical relationship of retrotransposon insertions with the boundaries of annotated genes. When a RIP is overlapped with more than one region, an arbitrary priority order of “exon>promoter>intron>intergenic region” is used.

Detailed RIP Information in dbRIP Data Page

In dbRIP, it is our goal to provide all available related information in a detailed manner. All RIP-related data is displayed in the “RIP data page” that is accessible from the output of SearchdbRIP and from the browser, and it represents the most valuable and core part of dbRIP data. As the example in Figure 2 shows, for each RIP we provide 19 data items grouped into the following 10 categories: identification, classification, associated diseases/phenotype, detailed sequence data, PCR-related information, ascertainment methods, sources of RIP, genotypic data, genomic location information, and references. Below, we provide descriptions for a few of these categories and encourage users to explore the database website for the rest.

For RIP IDs, we provide a database ID and the original ID(s). A database ID contains three sections to indicate the type of RIP, the chromosome and position, and the number of the same type of RIPs in the region. For example, “RIP_Alu_chr7_003_01” indicates an *Alu* RIP on chromosome 7 in the third 3-Mb region starting from the telomere of the short arm. Database IDs are unique and thus represent a nonredundant list of RIPs, making it possible to keep track of the exact number of all compiled RIP loci and to compare the coverage of RIPs derived from different ascertainment methods. Conversely, we kept all original IDs used in the primary literature to facilitate identification of RIPs identified from multiple studies and query of RIPs

by any of the original IDs. For classification, we provide the class (i.e., SINE, LINE, etc.), type (such as *Alu*, L1, and SVA), family, and subfamily of the retrotransposon based on an updated list of consensus sequences and standard nomenclature [Batzer et al., 1996]. For example, we added several newly designated *AluY* subfamilies, including Yb11, Ya4b, Yf, Yg, Yh, Yj, and Yx [Garber et al., 2005; Salem et al., 2005b; Xing et al., 2003; Wang et al., 2006]. To track all disease-related RIPs, we provide the name of the disease or phenotype associated with each RIP. In the sequence data field, we provide detailed sequence information related to each RIP, which includes the insertion sequence, TSDs, and 400-bp flanking region on each side of the element. Each sequence section is clearly highlighted by a differently-colored font for easy recognition. For a small number of RIPs, we are unable to obtain the complete sequence information based on the data available from the original literature and/or the related GenBank entries. We use “nnnnn” to indicate unknown TSDs and “NNNNNNNNNN” to denote the unknown sequence of the entire or partial section (usually the polyA-tail) of the retrotransposon. Whenever available, we also provide detailed genotypic data for all screened geographic groups or sample sets, as well as the calculated allele frequencies, unbiased heterozygosity, and average allele frequencies. At this moment, due to the database design used, we are unable to include genotypic data for a small number of loci, for which the detailed genotypes were not reported. We encourage users to contact us if they have RIP genotype data not covered by dbRIP.

Browsing RIPs in Genome Context With the UCSC Browser

Since dbRIP is integrated as a part of the browser, the RIP data can be queried using the utilities available from the browser. Being able to browse RIPs alongside other available genome information offers a significant advantage by providing the users a graphic visualization of the genomic context of each RIP. For instance, as shown by the example in Figure 3, the user can easily visualize the fact that this breast cancer-related de novo *Alu* insertion [Miki et al., 1996] is located inside an exon of the *BRCA2* gene and it is flanked by several known SNPs. Users are advised to visit the UCSC genome website for detailed descriptions and tutorials of browser's utilities at <http://genome.ucsc.edu> [Kent, 2002; Kent et al., 2002], here we elaborate on a few important functions related to dbRIP. To examine the RIPs within a gene or a genomic region of particular interest, one can search dbRIP using the Genome Gateway by providing a genetic ID, such as a gene ID or an accession ID, or by specifying genomic positions. All RIPs that exist within the region will be displayed in the RIP tracks. Once a RIP is located, one can determine if the RIP contributes to an alternatively-spliced exon by expanding the Expressed Sequence Tag (EST) tracks. Using BLAST-like alignment tool (BLAT) with either DNA or protein sequences, the user can quickly find out if the related genomic region contains any known RIPs. Similarly, one can use BLAT to find out whether or not a newly identified sequence carrying a polymorphic retrotransposon represents a novel RIP.

Other Accessory Utilities

In addition to the main utilities described above, we also provide several other related resources on the dbRIP main page. These include a complete list of references used in dbRIP, genome-wide plots for all types and individual types of RIPs, and downloadable data in flat files, all of which are accessed via the menu bars at the top of the main page. Although most of the data for individual RIPs is available for downloading through the utilities of the browser, making the entire dbRIP data set available allows advanced users to perform systematic analysis of the large scale RIP data. On the “Help” page, we provide some special instructions for using dbRIP, which may not be so obvious to users. On the main page, a list of examples for utilizing the data in dbRIP is also provided.

DISCUSSION

Database Statistics and Genome Distribution of RIPs

As shown by the summary statistics of dbRIP data in Table 1, dbRIP, as of this writing, covers the data compiled from 2,300 *Alu*, 520 L1, and 80 SVA elements, respectively, from over 50 original reports. By determining their exact genome locations, we obtained a nonredundant set of 1,625 *Alu*, 407 L1, and 63 SVA elements or a total of 2,095 RIPs. For a small fraction of reported RIPs, we failed to map them to a genome location due to the lack of sufficient sequence information; therefore, we excluded them from dbRIP. Among the mapped RIPs, over 600 loci have been subjected to genotyping using DNA samples from diverse human groups. It would also be very useful to have the remaining RIPs that were largely identified via in silico comparative genomic approaches confirmed by the gold standard of genotyping a human diversity panel. Interestingly, a total of 531 loci (or 25%) among the compiled RIPs are elements that are absent from the reference genome sequences (hg17 or NCBI Human Genome Build 35). These RIPs were identified using methods that are either independent of the known reference genome sequences [Badge et al., 2003;Buzdin et al., 2003,2005;Roy et al., 1999;Mamedov et al., 2005;Sheen et al., 2000] or have utilized genomic sequences representing additional human individuals [Bennett et al., 2004;Wang et al., 2006]. The relatively high ratios of RIPs outside of reference genome sequences suggests to us that there are a large number of new RIPs yet to be identified. This notion is further supported by the fact that methods independent of known genomic sequences identify high ratios of novel RIPs, many of which fall into regions that have not been sequenced [Badge et al., 2003;Buzdin et al., 2003,2005;Roy et al., 1999;Sheen et al., 2000] and the fact that there is very low ratio of overlapping loci identified by different methods. Our data indicates that the minimal polymorphism rates (the number of RIPs vs. the total number of members in the class) for *Alu*, L1, and SVA are 0.14%, 0.10%, and 2.29%, respectively. The much higher polymorphism rate (greater than one order of magnitude) of SVA elements in comparison with that of the other two retrotransposon families may be indicative of a higher current rate of retrotransposition and/or a much younger evolutionary age for SVA elements.

Among the 2,100 RIPs, we have identified 51 cases of disease-related loci that are examples of the involvement of retrotransposon insertions in genetic diseases. The detection of such rare elements has been greatly hindered by the lack of sensitive techniques for identifying individual de novo retrotransposon insertions. We expect that with the advancement of these approaches it will be possible to identify many more such disease-related loci in the future and facilitate a more comprehensive understanding of the contribution that retrotransposons make to human genetic disorders.

Future Development

To increase the utility of dbRIP data, we will contact the UCSC Bioinformatics group to inquire about the possibility of adding a new track for the RIP data in their browser or modifying the existing "RepeatMasker" track to accommodate RIPs. We will also work with other experts in the genetic variation community, such as HGVS, to develop a nomenclature for this type of variation and to make the RIP data available for deposition into other related central databases, such as the ongoing international HUGO Mutation Central Database. Nevertheless, even with the integration of RIP data into central databases, we will continue to maintain dbRIP as an independent platform for purposes of raw data collection and validation, as well as for providing special queries that may not be available from the central databases. We will also implement a data input form for others to deposit their RIP data into dbRIP, and update the database on a regular basis.

CONCLUSION

A unique feature of dbRIP is the integration of RIP data with existing genome annotation data in a genome browser. This feature allows the graphic visualization of each RIP in context with all gene annotation in the regions, which can be extremely useful in understanding the potential functional effects of the variation. The utilities of the UCSC genome browser also provide users with many convenient tools for manipulation and retrieval of data. To our knowledge, dbRIP is the only currently available database that offers a comprehensive compilation of human genome variations/mutations related to retrotransposon insertions in a highly integrated and interactive manner. In this sense, dbRIP also represents a good example for utilizing existing genome browsing systems and genome annotation data to develop highly integrative and interactive specialized databases. We believe that dbRIP will be a very useful resource and tool for studying human genome variation, retrotransposition, human genome evolution, and population genetics, as well as forensic genomics.

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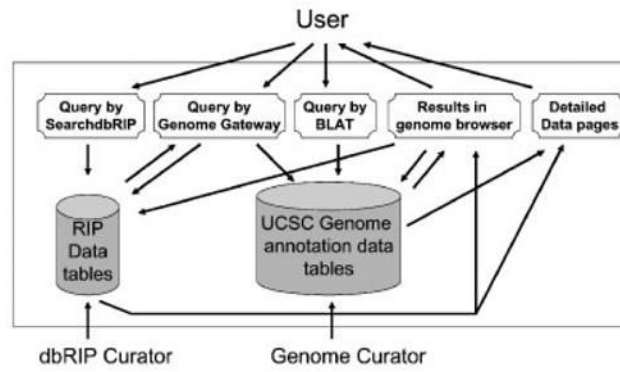


FIGURE 1. Overall design of dbRIP database. The schematic shows the relationship between dbRIP and the UCSC Genome Browser as well as the data flow and interactions among users, curators, browser, and SearchdbRIP. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

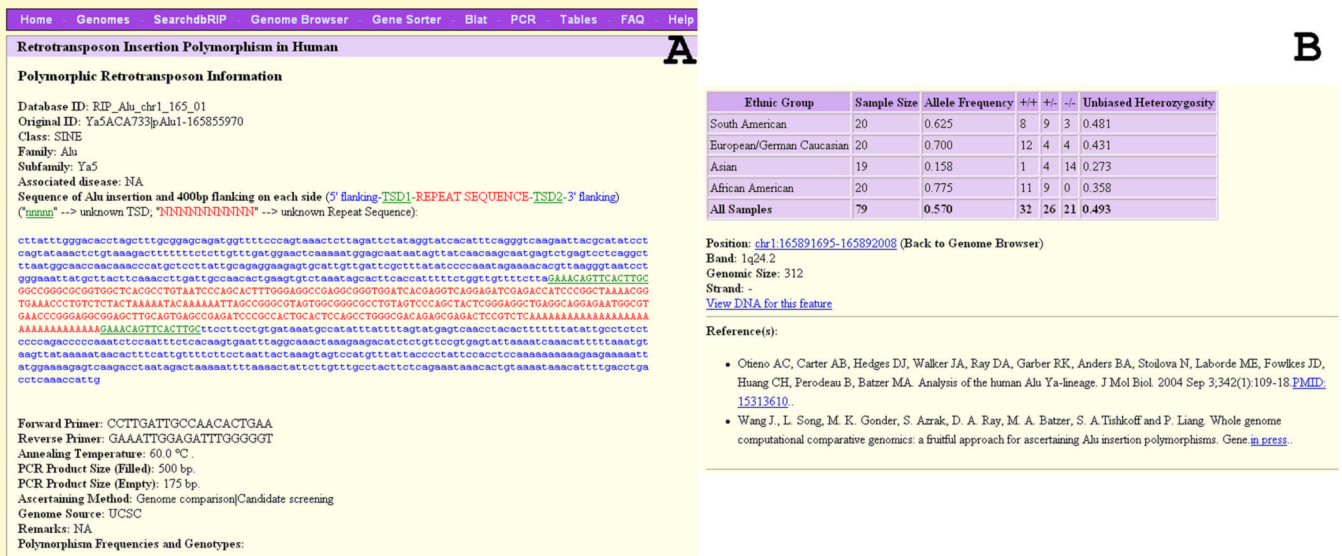


FIGURE 2. A typical RIP data page. The data page shows the detailed information of locus RIP_Alu_chr1_165_01. **A:** Information from database ID to genome source. **B:** Information from genotypic data to reference. This locus was originally identified in two studies as shown by the number of original IDs and the references. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

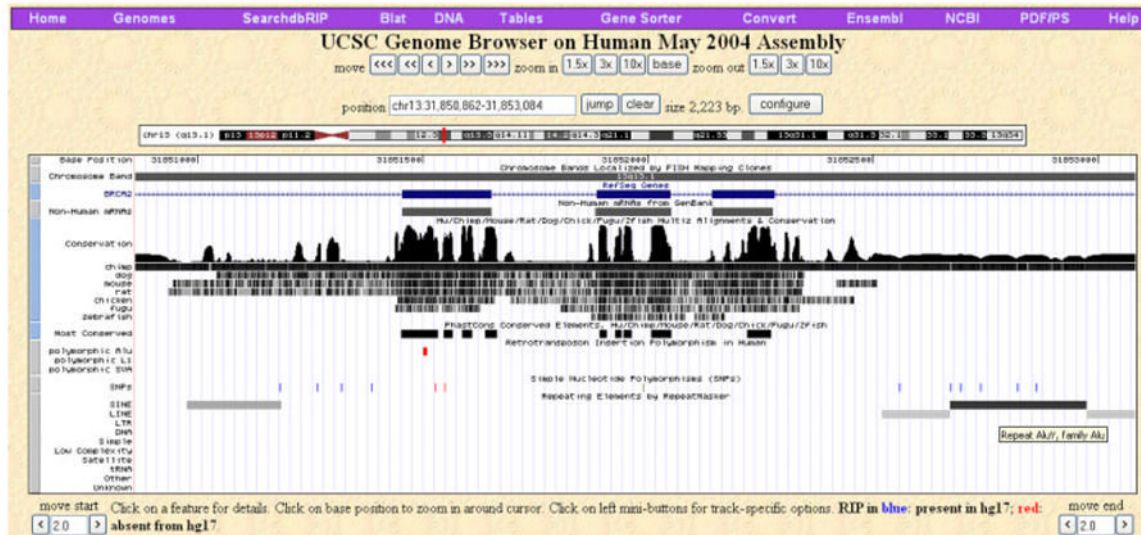


FIGURE 3.

Integrative display of a RIP in the UCSC Genome Browser. In the example shows a RIP that is located within one of the exons of *BRCA2*. This RIP is absent from the reference genome as indicated by the red color of the RIP tick, as well as the small size of the bar representing the insertion. Within this 2.2-kb genomic region (window), there are multiple SNPs, an *Alu* repeat, and several other repetitive elements. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE 1

dbRIP Summary Statistics

RIP type	RIP counts (unique/ total)	RIPs outside hg17	RIP with genotype ^a	Loci gene context (5 kb promotor/ exon/intron/ intergenic)	Disease- related loci
<i>Alu</i>	1625/2299	395	528	41/18/623/943	33
L1	407/524	132	81	7/9/130/261	15
SVA	63/74	4	31	7/3/22/31	3
Total	2095/2897	531	640	55/30/775/1235	51

^aExcluding those with only calculated allele frequency.