**Supplementary files**

**Table S1** : **Parental origin showing the paternal origin of the deletion and duplication regions**

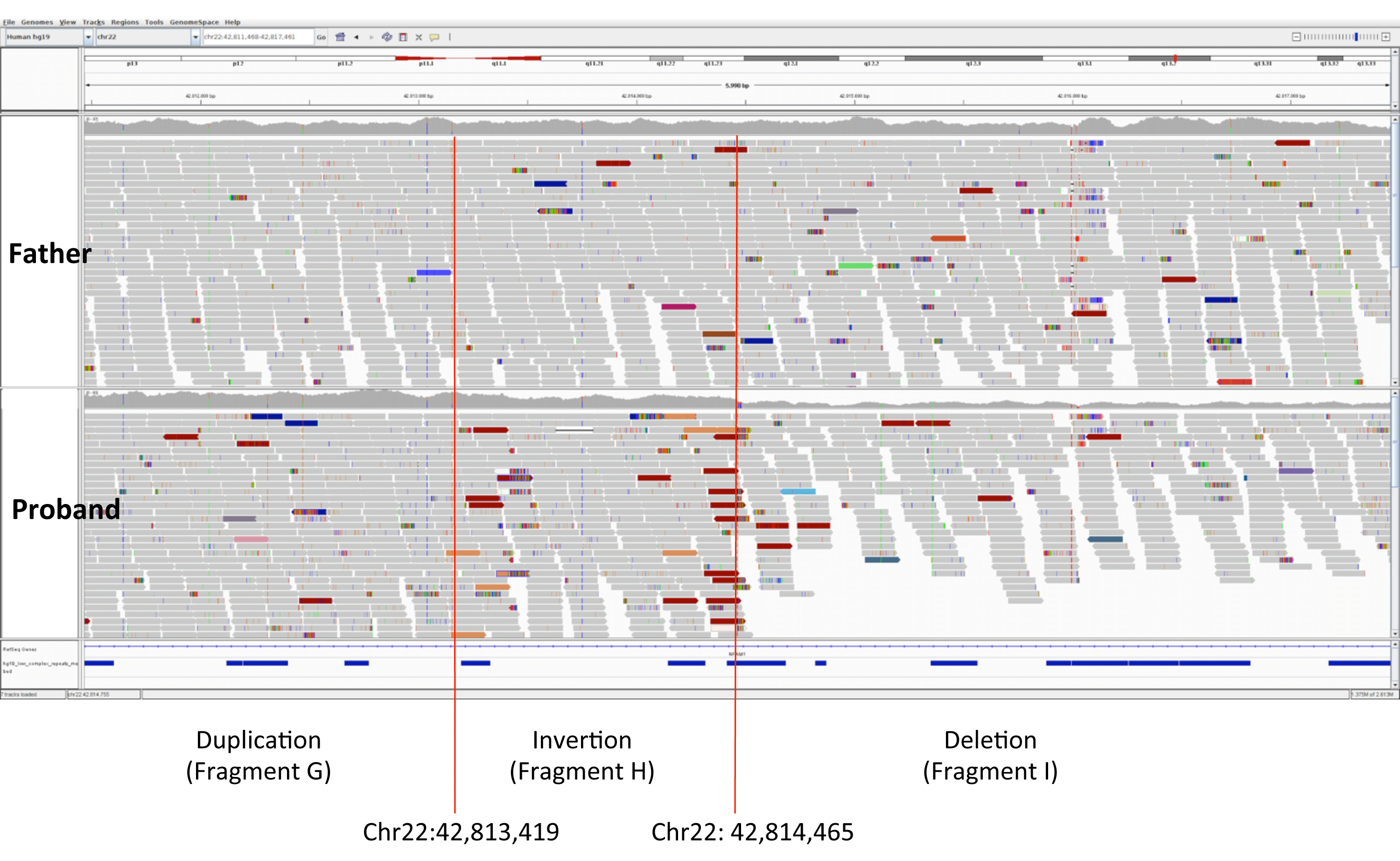
a) Highly polymorphic Sequence Tagged Sites (STSs) were selected using the STS Markers track on the UCSC Genome Browser, Human Feb. 2009 (GRCh37/hg19) Assembly. Asterisks (\*) indicate duplicated alleles.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Locus** | **Position (hg19)** | **Proband** | **Father** | **Mother** | **Status** |
| D22S284 | 40316896 | 84\*/100 | 84/96 | 94/100 | Dup(Pat) |
| D22S423 | 40382186 | 217\*/219 | 217/232 | 219/230 | Dup(Pat) |
| D22S1160 | 46429162 | 210 | 186/200 | 186/210 | Del(Pat) |

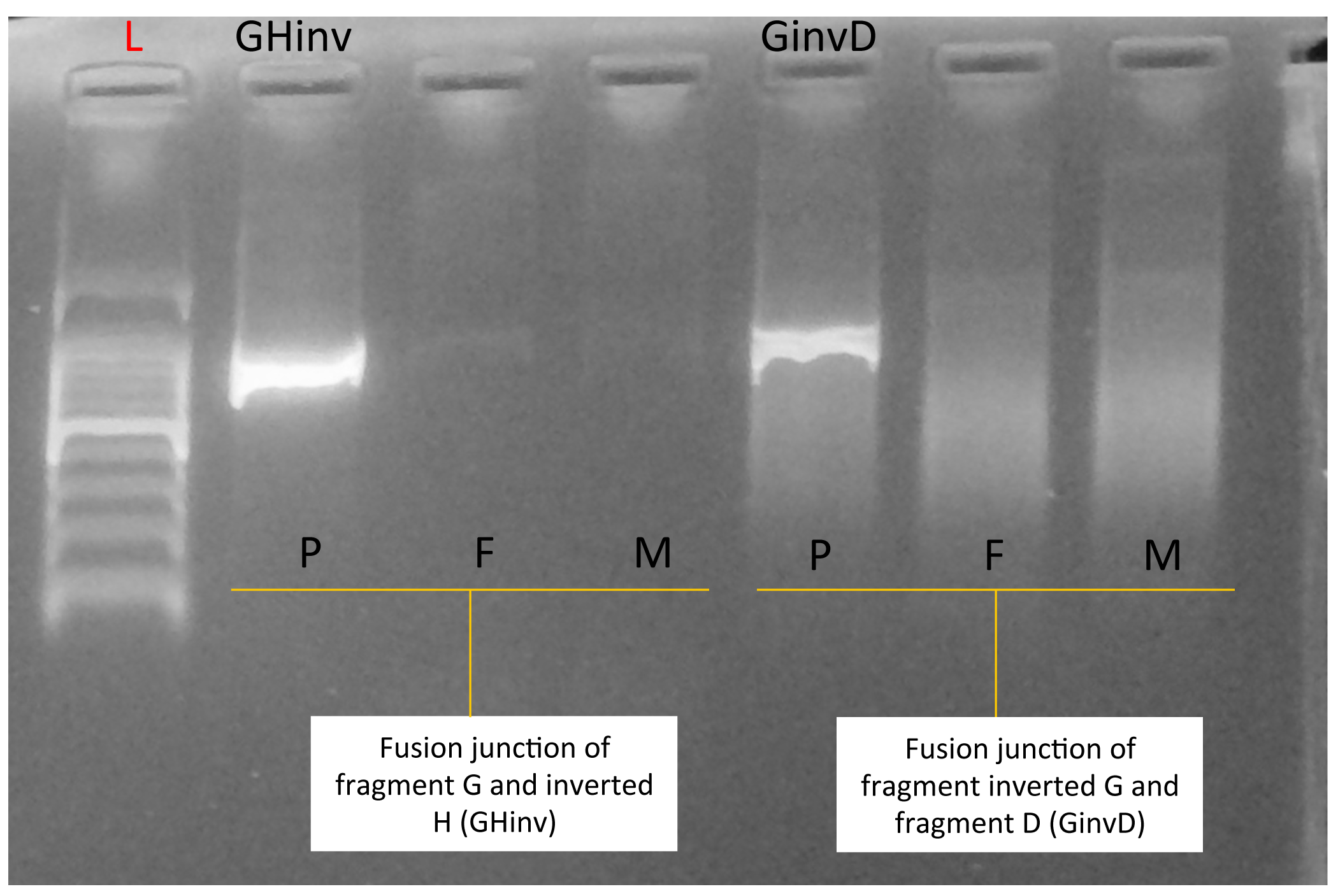
**b)** Informative SNPsobtained by the use of 180K CGH+SNP array platform (G4890A, Agilent Technologies)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **SN­P ID** | **Chr** | **SNP Position** | **Proband** | **Mother** | **Father** | **Interpretation** |
| rs2267423 | chr22 | 40.364.415 | AGG | AA | AG | Dup(Pat) |
| rs130388 | chr22 | 43.082.826 | G | GG | TT | Del(Pat) |
| rs2092212 | chr22 | 43.318.948 | G | CG | CC | Del(Pat) |
| rs738386 | chr22 | 43.328.419 | G | AG | AA | Del(Pat) |
| rs5751458 | chr22 | 43.655.526 | G | GG | AA | Del(Pat) |
| rs10453447 | chr22 | 46.334.133 | T | TT | GG | Del(Pat) |
| rs5769162 | chr22 | 47.195.274 | C | CC | TT | Del(Pat) |
| rs139581 | chr22 | 47.209.900 | T | TT | CC | Del(Pat) |
| rs9626954 | chr22 | 47.560.432 | C | CC | GG | Del(Pat) |
| rs5767669 | chr22 | 47.707.793 | C | GC | GG | Del(Pat) |
| rs732493 | chr22 | 47.729.347 | T | TA | AA | Del(Pat) |
| rs6008558 | chr22 | 48.516.695 | A | AG | GG | Del(Pat) |
| rs6007867 | chr22 | 48.889.170 | G | TG | TT | Del(Pat) |
| rs9616484 | chr22 | 49.580.069 | C | CT | TT | Del(Pat) |
| rs134465 | chr22 | 49.913.238 | T | TT | CC | Del(Pat) |
| rs137887 | chr22 | 50.464.439 | C | CC | GG | Del(Pat) |

**Figure S1**: WGS data showing the 1kb invertion event between duplicated and deleted segments on chromosome 22 of proband.



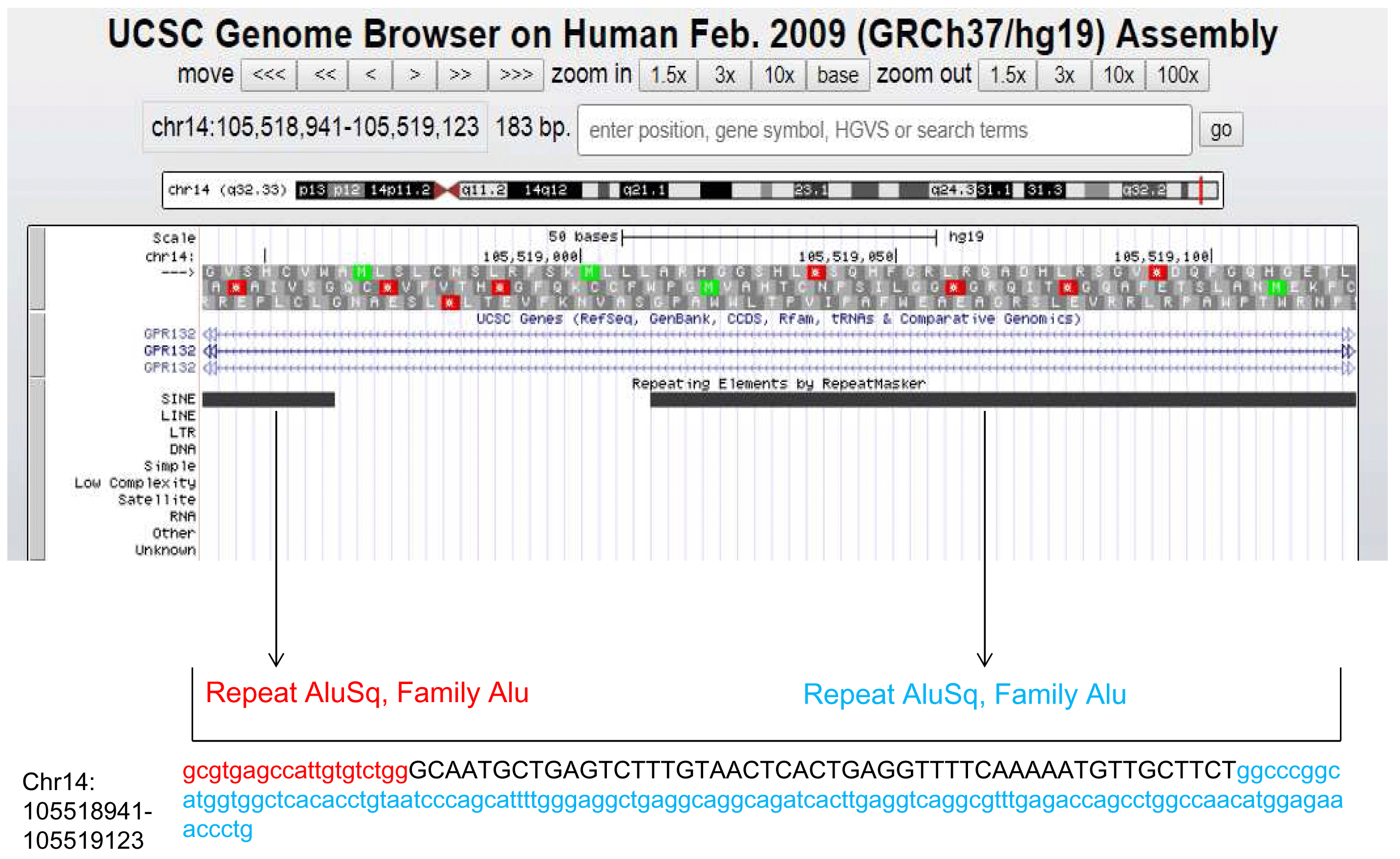
**Figure S2**: PCR confirmation of fusion junctions on proband; fragment G-inverted fragment H (GHinv) and inverted fragment G-fragment D. (P: proband; F: father; M: mother; L: ladder)



**Table S2:** Primers used for Sanger Sequencing Confirmation of Breakpoints

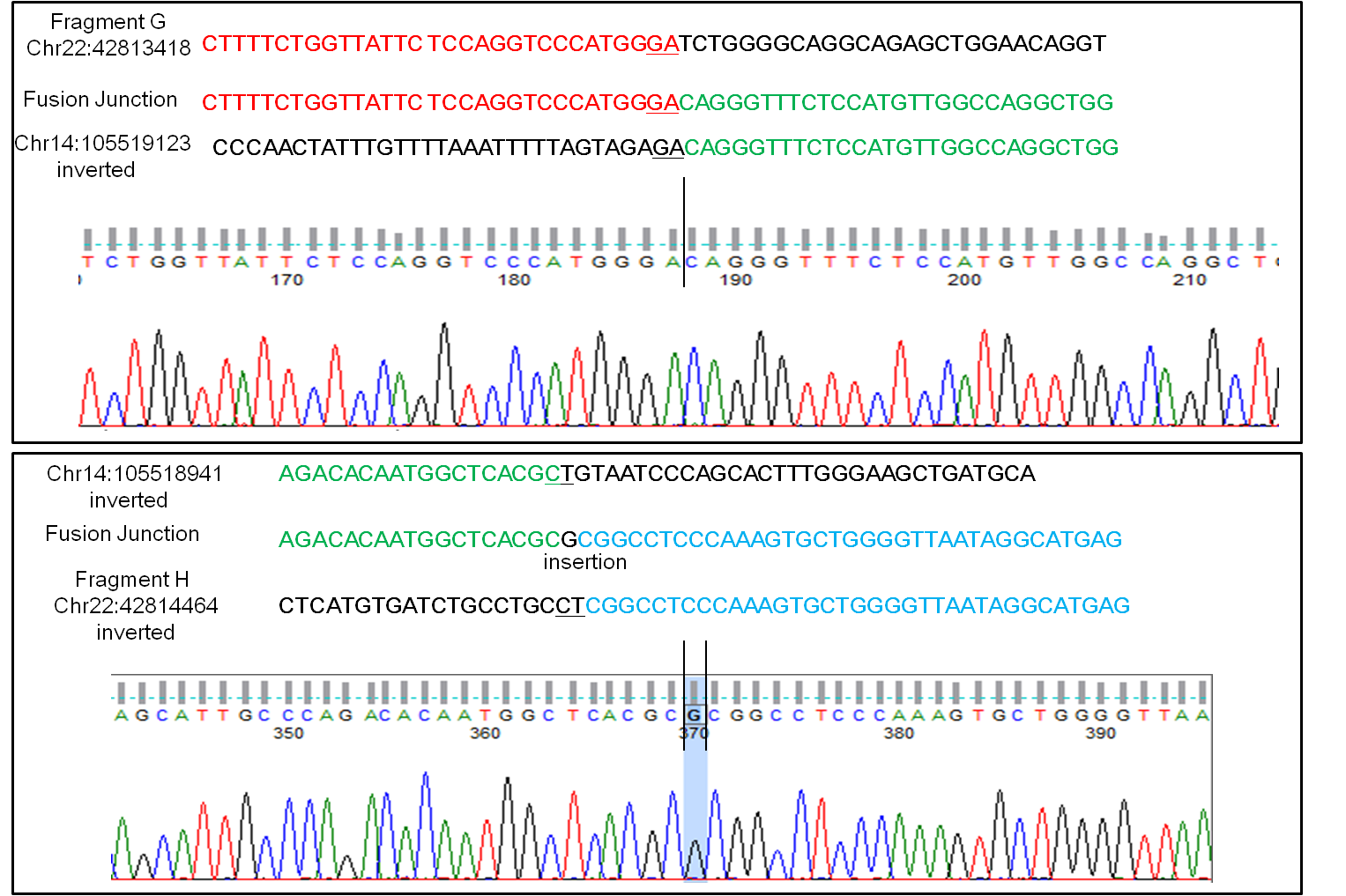
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Primer ID | Direction | Sequence | Product Size (bp) | Ta |
| BP\_GHinv\_F | Forward | GGGGAACCACTTCAGCTTTA | 708 | 62 |
| BP\_GHinv\_R | Reverse | TGGATCCCTGCTTAGTCTGC |
| BP\_GinvD \_F | Forward | TGGTGTTGAAGATGCAGGAG | 832 | 62 |
| BP\_GinvD \_R | Reverse | GTTAGCCAGGATGGTCTCCA |

**Figure S3:** AluSq sequence of chromosome 14 represented by the UCSC RepeatMasker track (<https://genome.ucsc.edu/>)

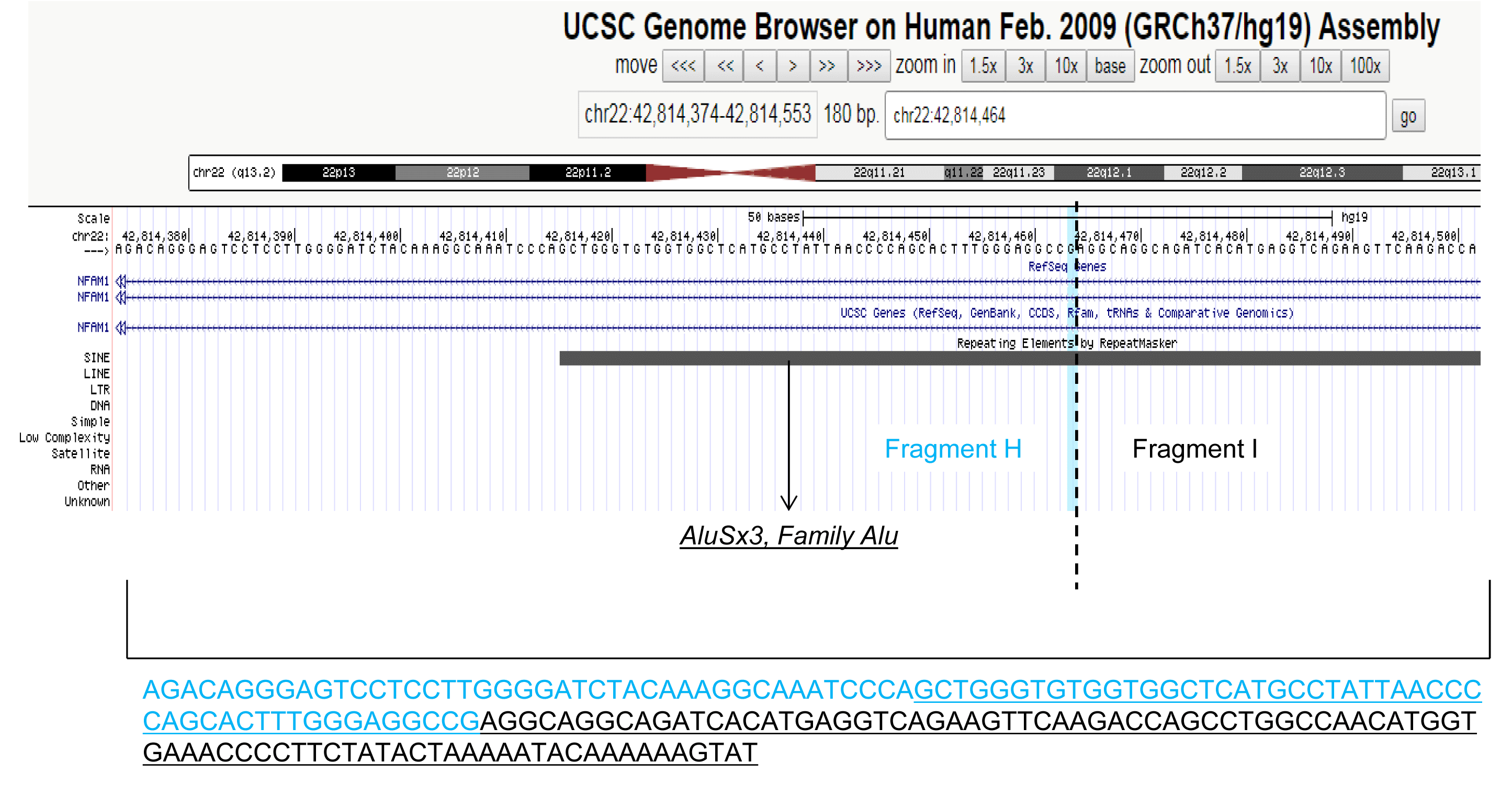
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**Figure S4** : **Breakpoint Junction G-chr14(inv)-H(inv)**

Sanger Sequencing result of fusion junction between,: (upper) Fragment G (red) and inverted sequence of chromosome 14 (green), (bottom) inverted sequence of chromosome 14 and Fragment H. Microhomology at the breakpoints is underlined.

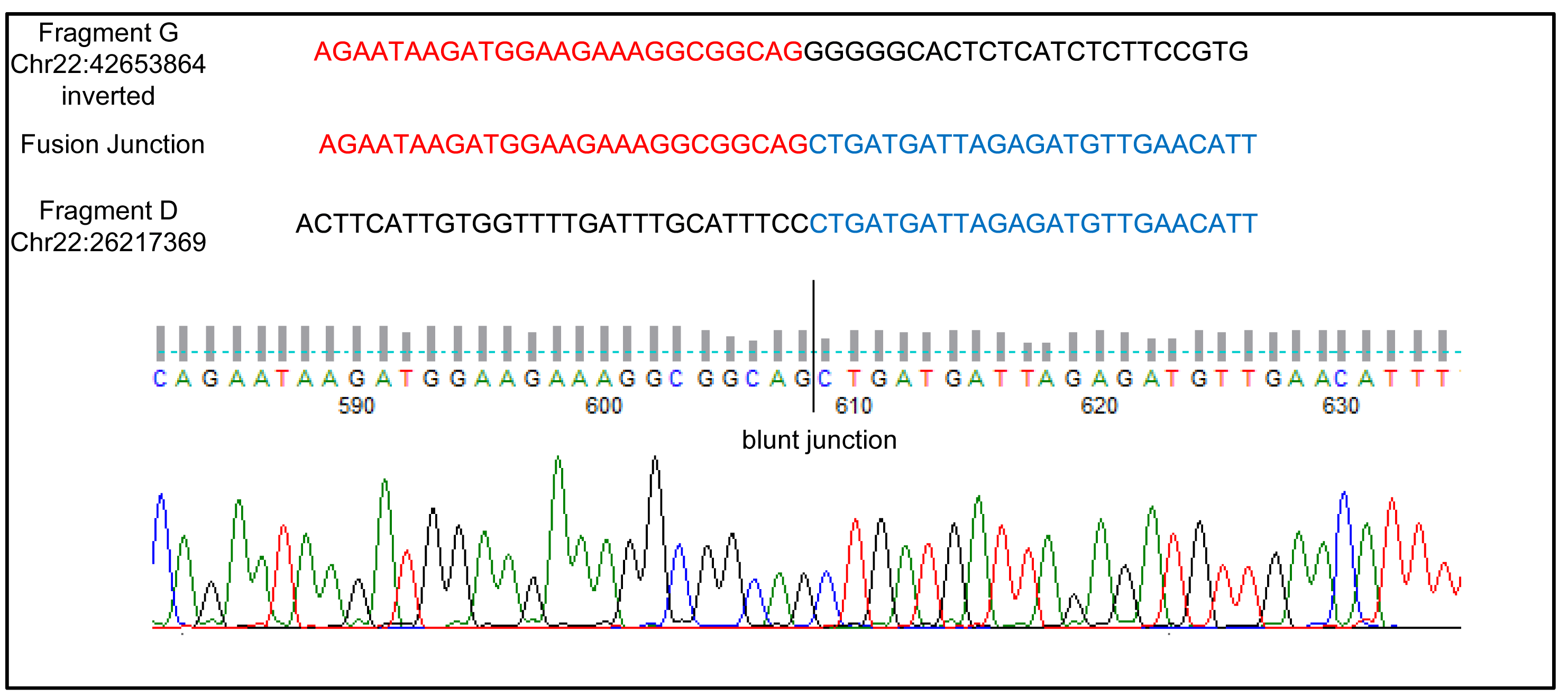


**Figure S5:** *AluSx3* sequence (underlined in the text) at the H-I breakpoint junction represented by the UCSC RepeatMasker track (https://genome.ucsc.edu/). Breakpoint between fragment H (blue) and fragment I is shown with a dashed line.

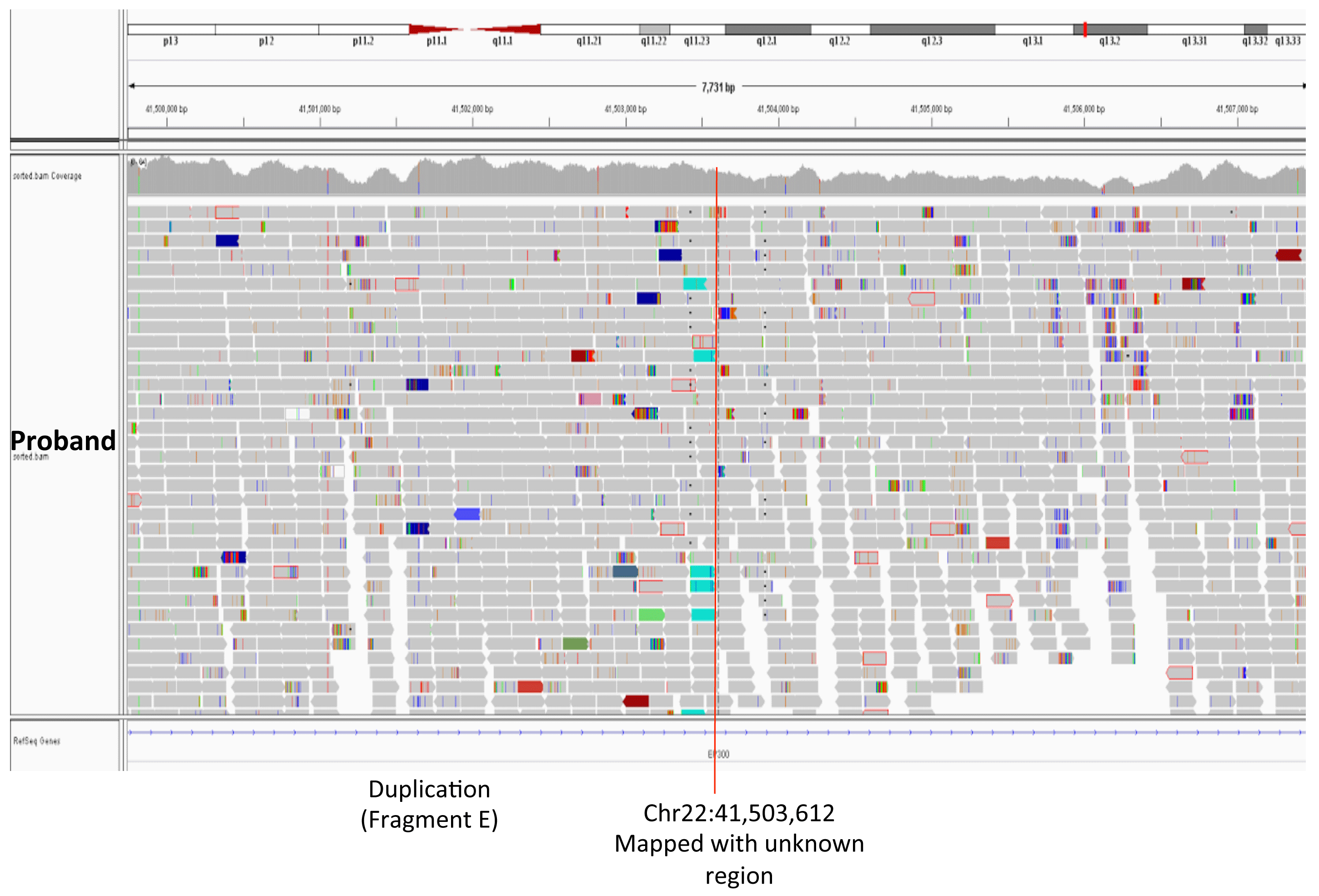
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**Figure S6: Breakpoint Junction G(inv)-D**

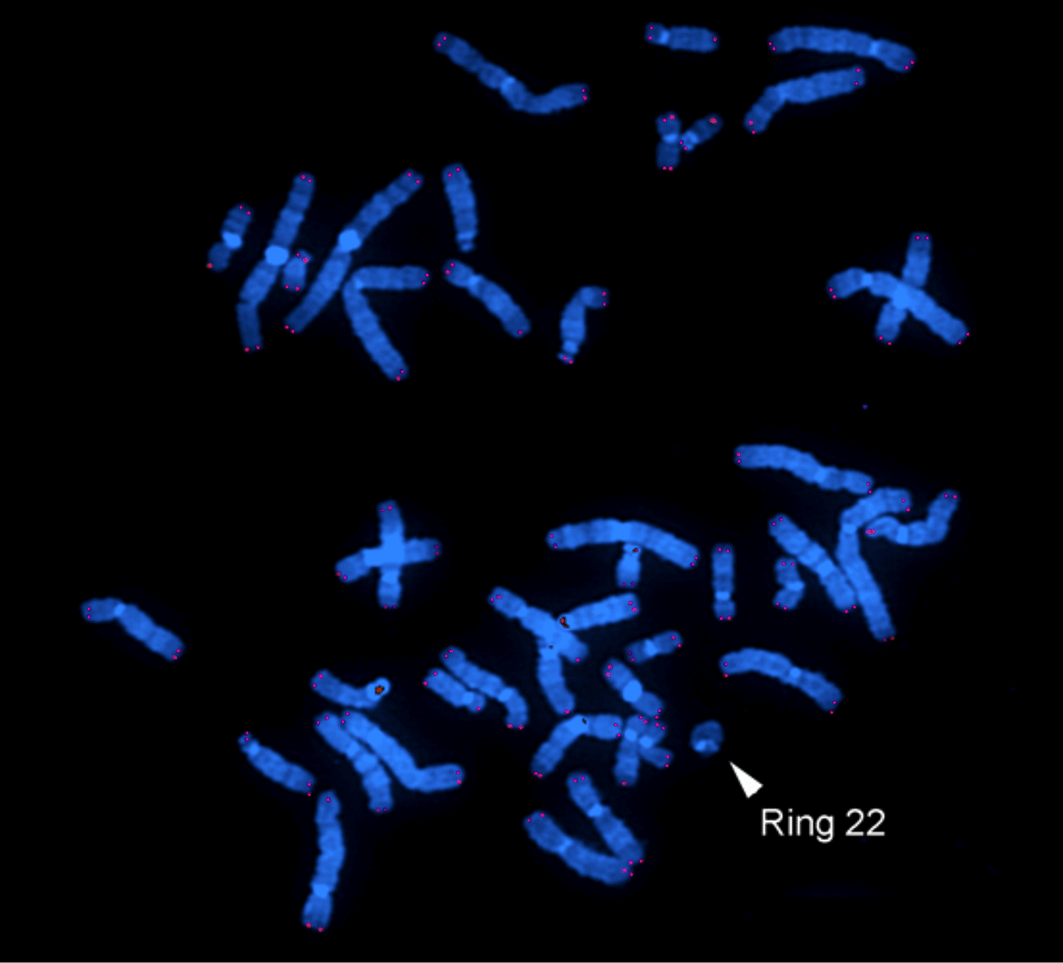
Sanger confirmation of breakpoint junction between inverted fragment G and fragment D

****

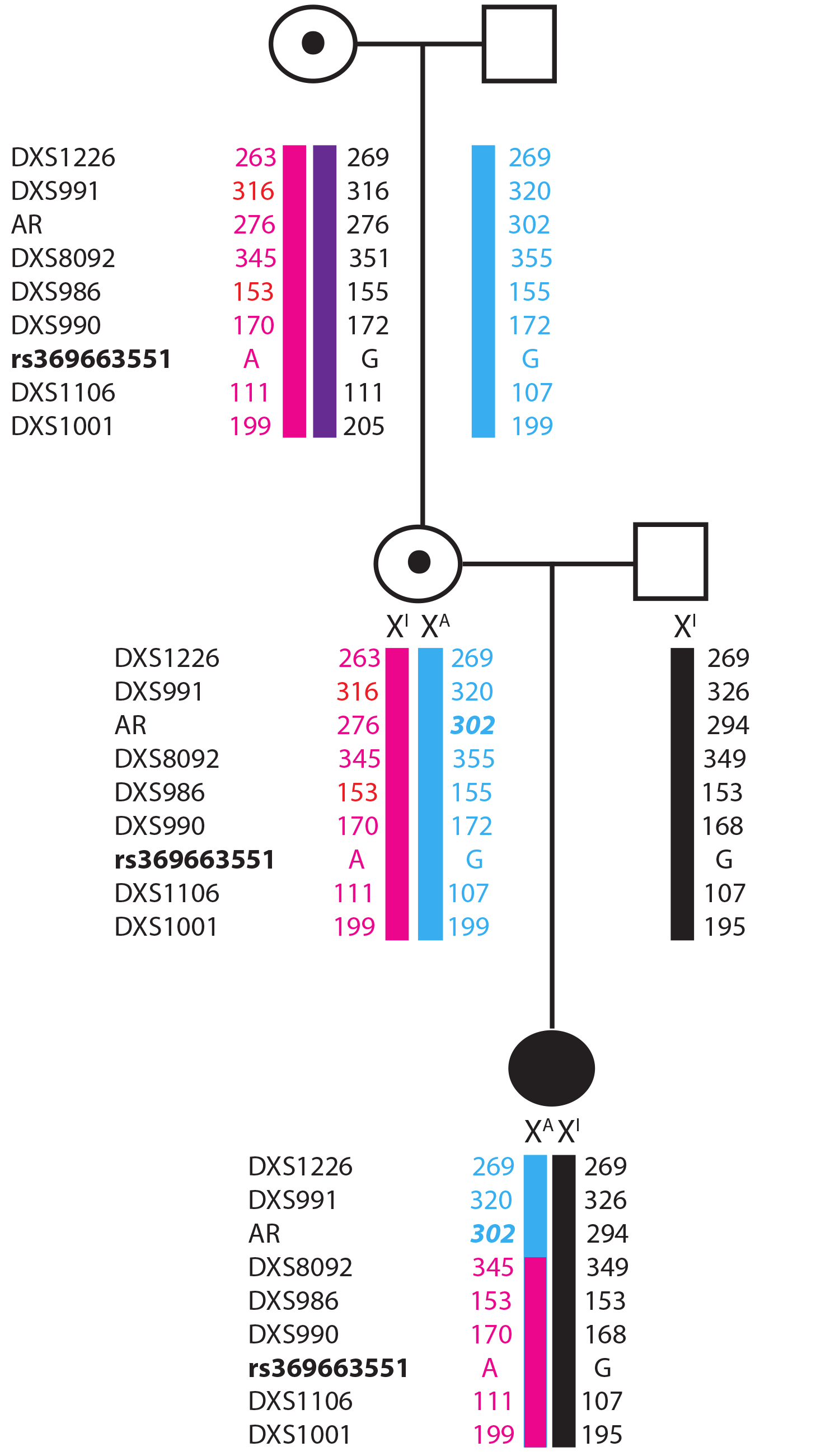
**Figure S7**: WGS data showing breakpoint on Fragment E (chr22:41,503,612) mapped with unknown region (reads mapped with unknown region represented with cyanine blue).

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**Figure S8**: FISH analysis using pan-telomeric peptide nucleic acid (PNA) probe (PNA FISH kit/Cy3, Dako Denmark A/S, red signals). Ring chromosome 22 (arrowhead) showed the absence of the consensus sequence (TTAGGG)n of human telomeres



**Figure S9**: Three-generation family pedigree showing the segregation for *SRPX2* variant and X-inactivation pattern.



**Chromosome X inactivation** analysis was performed as described (Allen et al. 1992) on a highly polymorphic microsatellite repeat of the androgen receptor (AR) gene.

The analysis showed complete (>98%) inactivation of the paternal X chromosome in the proband. Her mother had >80% inactivation of her maternally-inherited X chromosome, containing the SRPX2 variant, but she did not pass on to her daughter the AR allele she had inherited from the maternal grandmother. In fact, microsatellite analysis demonstrated a meiotic crossover between AR (chrX: 66765056) and DXS8092 (chrX: 74122919) on the X chromosome transmitted to the patient from her mother (Supplementary Figure S10). Therefore the SRPX2 variant is located on the active X chromosome in the proband and on the inactive one in her mother. The maternal grandmother was homozygous for AR and therefore not informative.

**REFERENCES** Allen RC, Zoghbi HY, Moseley AB, Rosenblatt HM, Belmont JW. Methylation of HpaII and HhaI sites near the polymorphic CAG repeat in the human androgen-receptor gene correlates with X chromosome inactivation. Am J Hum Genet 1992;51:1229-1239.