Supplementary Information

Refining analyses of copy number variation identifies specific genes associated with developmental delay

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Contents

Supplementary Note

Interpretation of q-values

In CNV-based analysis, the number of independent comparisons is far lower than the number of genes and/or windows examined due to the large size and variable breakpoints of many pathogenic CNVs leading to complex spatial autocorrelation effects. In addition, the general concept of multiple testing corrections is most applicable in the context of multiple naïve tests that have a low prior probability of being relevant to disease[1] (e.g. testing association of a large number of single-nucleotide polymorphisms (SNPs) with low odds ratios (OR)). In the case of large CNVs, we have a significant prior (Supplementary Figure 2) implied by the presence of a large CNV regardless of frequency; (an extreme example is a 10 Mbp deletion that is highly likely to be pathogenic regardless of frequency. In addition, the magnitude of effect must be considered as a risk factor (low OR), and completely penetrant pathogenic CNVs (very high to infinite OR) need to be treated very differently in a diagnostic setting (i.e., a highly significant risk factor is less clinically relevant than a less significant but completely penetrant event). An optimal correction methodology would incorporate differential independence, CNV size, magnitude of effect, phenotypic commonalities, and *de novo* rates. An additional challenge is based in the assumptions upon which the Benjamini Hochberg FDR is defined[2]. The calculation of FDR is based on assuming that the number of true null hypotheses (m0) is equal to the number of hypotheses tested (m), which is overly conservative in many situations. The specific definition of the false discovery rate is $FDR \leq \frac{m_0}{m} q$, where m is the number of hypotheses tested and m_0 is the number of true negatives. In genome-wide screens where there is little prior evidence of significance, and the variable under examination is random, assuming $m_0 = m$ yields a robust FDR estimate that is guaranteed to not exceed q. However, when $\frac{m_0}{m} \ll 1$, the FDR estimate is, by definition, overly conservative. For the genomic disorders (Supplemental Tables 2 and 3 combined) we assume that a significant fraction of these loci are pathogenic ($\frac{m}{m_o}$ is 50% to 80%) giving a reasonable q-value cut-off between 0.1 and 0.25. In the case of genes with loss-of-function hits in exomes this prior likely approaches 50%[3] giving a reasonable q-value cut-off of 0.1 to maintain a 5% FDR. Similarly, for our MIP screen we assume a similar prior and q-value cut-off, which includes 5 of 6 positive control genes in our significant fraction. Given these challenges, we have chosen to calculate nominal significance and q-values for this study and suggest that the reader infer clinical significance from the likelihood ratios.

Identification of New Pathogenic CNVs in Intellectual Disability (ID) / Developmental Delay (DD)

To identify novel loci, we calculated enrichment in probands using both a windowed approach (Online Methods, Supplementary Figure 1, Supplementary Figure 3) and counts of CNVs intersecting the exons of RefSeq genes (Online Methods, Supplementary Table 4).

In addition to known genomic disorders, we identified 14 newly significant regions that are either novel or previously discussed in the context of case reports (Table 1). In addition to our cases, we investigated 5,531 previously published cases[4] for supporting *de novo* variants.

Region (Table 1)	State	Supporting *de novo* CNV (Vulto-Van Silfhout *et al*[4])
2p16.1 (NRXN1)	del	chr2:50,703,229-50,939,853
3q13 (GAP43)	del	chr3:112,960,465-120,202,706
10q23.1 (NRG3)	del	chr10:81,562,779-88,946,867
10q23.1 (NRG3)	del	chr10:86,446,444-89,783,066
12p13 (SCNN1A to PIANP)	dup	chr12:50,447-11,939,631
12p13 (SCNN1A to PIANP)	dup	chr12:50,447-132,287,718*
12p13 (SCNN1A to PIANP)	dup	chr12:3,689,536-8,080,230
12p13 (SCNN1A to PIANP)	dup	chr12:5,954,585-6,375,790

*Trisomy not included in *de novo* counts.

Here, we discuss the potential implication of a select subset of these CNVs.

We observed several peaks of significance within the 1q24q25 microdeletion syndrome. In addition to the locus extending from *DNM3* to *CENPL*[5], we observed overlapping proximal deletions with significance extending proximally to *SELE* with a minimal region highlighting a cluster of flavin-containing monooxygenase (*FMO*) genes (*FMO1,2,3*) (Table 1, Supplementary Figure 1). *FMO* genes are primarily expressed in the liver and kidneys, are associated with trimethylaminuria, and function as drug metabolizing enzymes with specific temporal expression patterns[6-10]. *FMO1* is primarily expressed prenatally and is significantly downregulated at birth where *FMO3* expression increases. One compound targeted by *FMO1* of particular relevance to neurological function is 1,2,3,4-tetrahydroisoquinoline (TIQ) (9076656). TIQ has been linked to the pathogenesis of Parkinson's disease[11] and the modulation of dopaminergic and glutamatergic neurotransmission[12,13]. Although preliminary, we believe that these data are suggestive of a potential role for haploinsufficiency of these genes in neurodevelopmental disorders. Notably, a similar critical region was recently highlighted in a study of congenital heart disease by Thorsson et al[14].

Duplications on 12p13 have been associated with dysmorphic features and neurodevelopmental anomalies[15-17]. Here, we observe a significant enrichment of the 12p13.3 region with a focal CNV highlighting a ~360 kbp minimal region containing 19 genes (*SCNN1A* to *PIANP*) and a further focal CNV highlighting a 96 kbp subregion peak containing 5 genes, including *CHD4*, which has been shown to inhibit astroglial cell differentiation and act as a Wnt antagonist[18] (Supplementary Figure 4m, Table 1).

Deletions at 3q13.31 have been linked to developmental delay. Here, we observe a significant enrichment at *GAP43* with three deletions arising *de novo* (Supplementary Figure 4f, Table 1)[20,21]. *GAP43* is a critical gene in the establishment of synaptic connections; rare variants in *GAP43* have been linked to schizophrenia[19].

A previous report noted that small deletions focal to *SATB2* demonstrate a phenotype similar to the 2q33.1 microdeletion syndrome[20,21]. We observe a statistically significant enrichment of deletions with a peak at *SATB2* (Supplementary Figure 4a, Table 1). Additionally, we observe a significant enrichment for deletions at *MEF2C*, which has been associated with intellectual disability by Paciorkowski *et al*[22] (Supplementary Figure 4i, Table 1).

In addition to pathogenic CNV loci, we examined our data set for potential protective loci and identified one genic duplication with a moderate protective likelihood ratio of 0.519 (95% C.I. 0.324 to 0.831) at chr19:56,965,069-57,309,202. This locus is present in 35/19,584 controls and 27/29,085 cases and is nominally significant (p = 0.024, q = 0.203, simulation p = 0.0011).

Expanded Clinical Reports and Additional Patient Photographs

Nijmegen DNA-00335

SETBP1 Chr18(GRCh37):g.42531769del

This 14-year-old boy was born with APGAR scores of 1/6/8 and a congenital facialis paresis.

His speech development was delayed, first words at the age of 18 months with little progression. Until the age of 5 years he used only a few words and at the age of 14, his speech was still delayed. His Full IQ scale was measured at 76, but was disharmonic. He was diagnosed with ADHD, for which he was treated with methylphenidate.

At the age of 14 years he had a height of 156.8 cm (-1 SD), a weight of 57.5 kg (+2 SD) and a head circumference of 56 cm (+0.5 SD). He had mild facial dysmorphisms, flattened crux superior of the ears, straight eyebrows, blepharophimosis, high palate with broad dental ridges, and clinodactyly of fifth fingers and 3rd, 4th, 5th toes and inverted nipples and one café-au-lait spot.

MRI of the brain did not show any abnormalities.

Nijmegen DNA-008897

SETBP1 Chr18(GRCh37):g.42530536_42530537del

This 54-year-old male patient was the sixth of nine children of non-consanguineous Caucasian parents. There was no family history of developmental delay.

He was born after an uncomplicated pregnancy. The testes were not descended. His development was delayed with sitting at the age of 12 months and walking at the age of 3 years. There was still a lack of speech at the age of 54 years. Psychological assessment at the age of 25 years showed a severe intellectual disability with an IQ score of 30. During his life, he developed a skin disease which resembled psoriasis or eczema. At the age of 52 years he was diagnosed with hearing loss of 70 dB of the left ear.

Physical examination at the age of 54 years showed a height of 175.5 cm (-1 SD), a weight of 60.1 kg (+0 SD) and a head circumference of 58.1 cm (+0 SD). His facial dysmorphisms included a long shaped head, large ears, a high hair line in the neck and brittle hairs, sparse eyebrows and flat midface. Moreover, he had long hands/fingers, a kyphosis, pes cavus and a spastic walk pattern. The man was in general very anxious.

Previous investigations consisting of karyotyping, FMR1 repeat expansion analysis and screening metabolic urine tests were normal.

Nijmegen DNA11-21308Z

SETBP1 Chr18(GRCh37):g.42531178C>T

This 36-year-old female patient is a child of non-consanguineous Caucasian parents. There was no family history of developmental delay, except one sister of the mother.

The index patient was born after an uncomplicated pregnancy and delivery. She had hip dysplasia bilaterally. The motor and language development were delayed. She attended special education. Her behavior was compulsive and she had signs within the autism spectrum and ADHD, but examination by a psychologist and psychiatrist resulted in insufficient evidence for a formal ASD or ADHD diagnosis. During observation in pediatrics, dysphasia was diagnosed, possibly caused by encephalopathy. However, a MRI of the cerebrum was normal.

Physical examination at the age of 36 years she had a height of 176 cm (-0.5 SD), a weight of 58.3 kg (+1 SD) and a head circumference of 53.5 cm (-1 SD). Facial dysmorphisms included short palpebral fissures, full nasal tip, small mouth with a high palate. She had an increased lumbal lordosis and pes cavus. She had multiple naevi on her skin.

Previous investigations consisting of FMR1 repeat expansion analysis and 250k SNP array were normal.

Nijmegen DNA11-19324Z

SETBP1 Chr18(GRCh37):g.42531181C>T

This 9-year-old female patient is the fifth of six children of non-consanguineous Arabic parents. There was no evident family history of intellectual disability. Both the patient, her father and two sisters were diagnosed with neurofibromatosis type 1 (NF1).

The index patient was born after an uncomplicated pregnancy and delivery. Her development was delayed with sitting at the age of 18 months, walking at the age of 2 years and speaking the first words at the age of 20 months. However, at the age of 9 years, there was no speech and she couldn't write and read. Her social-emotional development was estimated at a level of 24-30 months at the age of 9 years.

At the age of 9 years, she had a height of 129 cm (-2 SD), a weight of 25.4 kg (0 SD) and a head circumference of 52.0 cm (0 SD). Facial dysmorphisms included a long shaped head, high forehead, large low-set ears, hypertelorism, synophrys, deep set eyes with ptosis, a full nasal tip, long philtrum and full lips with open mouth appearance. She had a sandal gap on both feet. Her skin contained multiple café-au-lait spots, freckling in line with her NF1 diagnosis and hirsutism.

Previous investigations consisting of karyotyping, MLPA of subtelomeric regions, 250k SNP array and FISH of 22q11 were normal.

Nijmegen DNA-008272

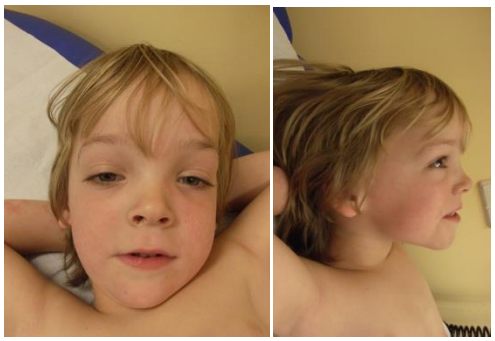
SETBP1 Chr18(GRCh37):g.42281350_42281351del

This 10-year-old boy is the second of two children of non-consanguineous Caucasian parents. There was no family history of developmental delay.

The patient was born after an uncomplicated pregnancy and delivery at 40 weeks of gestation with a birth weight of 3500 gram (0 SD). His language development was delayed with a lack of speech at the age of 10 years. His IQ was 55. He had hypermetropia (+7 dpt) of both eyes and had a sleeping disorder with hyperactivity. He used Depakine because of epilepsy. He had often bruising. MRI of the brain and EEG were normal.

At the age of 5 years, he had a height of 110.3 cm (0 SD), a weight of 20.6 kg (+ 1 SD) and a head circumference of 52.0 cm (+0.5 SD). Facial dysmorphisms included mild frontal bossing with a high hair line, low set ears, mild synophrys, mild down slanting palpebral fissures, hypertelorism, mild ptosis, broad nose, flat and long philtrum, thin upper lip and a pointed chin. He had short, broad halluxes, a short 4th and 5th toes left and clinodactyly 2nd toe. The skin had one naevus flammeus on the right lower arm and 2 café-au-lait spots.

Previous investigations consisting of karyotyping, MLPA of the subtelomeric regions, 250k SNP array, and metabolic screening were normal.



Troina 3097

SETBP1 Chr18(GRCh37):g.42281738del

Female, born 1972

Severe ID, Epilepsy and Diabetes

Her pedigree shows ID in cousins of her parents. Her developmental milestones were normal, but the speech, which was significantly delayed. Two febrile seizures reported at age 18 and 22 months, respectively. At age 22 years she showed a generalized seizure and since 2005 she showed generalized seizures with motor automatisms.
She's currently on antiepileptic treatment with Lamotrigine.

First evaluation at age 34 years (see Figure 1d) showed obesity, hirsutism, low-set hairline, long face, large low-set ears, dental crowding, high narrow palate, brachydactyly, Dubois sign and interdigital webbing on the hands, wide halluces. Her hypotonic appearance is highlighted by an apparent palpebral ptosis, anteverted shoulders, lumbar hyperlordosis, awkward gait.

Glucose oral load results are compatible with type 2 diabetes

Nijmegen DNA05-04370

ZMYND11 Chr10(GRCh37):g.294294_294295del

This 32-year-old male is the second of 2 children of non-consanguineous Caucasian parents. There was no family history of developmental delay.

He was born after an uncomplicated pregnancy and delivery at 40 weeks of gestation with a birth weight of 3320 g. As baby he was operated on a pyloric stenosis and was hypotonic.

He developed no speech and had difficulties making contact.

He had epilepsy, a movement disorder (choreoathetotic), severe obstipation and signs of a cerebral visual impairment. A CT scan of the brain revealed mild atrophy.

At the age of 32 years, he had a height of 156 cm (- 2.5 SD), and a head circumference of 52.5 cm (- 2.5 SD). Facial dysmorphisms included asymmetric skull, deep set eyes, hypertelorism, an overfolded upper helix left ear, long philtrum. Small hands and flat feet

Previous investigations consisting of karyotyping, FMR1 repeat expansion analysis, MLPA of the subtelomeric regions, metabolic screening, MECP2 sequencing, SMEI, Array CGH were normal.

Adelaide 3553

ZMYND11 Chr10(GRCh37):g.282793_282794insC

Last seen 26/12/1992, clinical features updated by phone with mother 21/03/2014 and following review of hospital medical records

The patient is a 22-year-old male, the third child of non-consanguineous Caucasian Australian parents. The pregnancy was normal apart from a short-lived rash at 6 months gestation. He was born at term after an augmented spontaneous labour and normal delivery with Apgar scores of 6 at 1 minute and 9 at 5 minutes, birth weight 2,840g (10^{th} percentile, -1.3SD) and birth head circumference 32 cm (<10^{th} percentile). He fed well at the breast but was slow to gain weight.

His mother had concerns about him from the first weeks of life because he was a sleepy/placid baby, seemed to have abnormalities of tone (either floppy or stiff), had an exaggerated Moro response when lifted, startled easily at sounds and did not appear to see well.

At 5 months of age he had small head size (less than 2^{nd} percentile), developmental delay, severe head lag, excess extensor tone with head retraction, stiffness of the limbs, fisting, persistence of primitive reflexes, poor visual behaviour and strabismus. Cerebral ultrasound showed the ventricles to be prominent with the right

being larger than the left and, given the small head size, the interpretation was of possible cerebral atrophy. Electroencephalogram, chromosomes, urine amino/organic acids, CMV culture and the serology for intrauterine infection (TORCH screen) gave normal results.

Cutaneous electroretinograms were present for both eyes with the amplitude of the response mildly reduced for the right eye compared to the left eye; mid-occipital flash visual evoked responses were present for both eyes but were of higher amplitude for the left eye compared with those for the right eye; no identifiable pattern visual evoked responses could be recorded with binocular stimulation using large checks. Examination under anaesthesia at 7 months of age showed a macular scar with vitreous opacity overlying it in the right eye and bilateral optic atrophy.

At 8 months of age, a neurologist found him to have developmental delay, small head size, poor vision, bilateral convergent strabismus, three café au lait patches, a supernumerary nipple and brisk reflexes in the lower limbs. A cerebral CT scan showed curvilinear calcification adjacent to the ventricles and confirmed the ventricular enlargement and asymmetry shown on the earlier cerebral ultrasound.

On examination at 9 months of age, head circumference was 42.4 cm (3rd percentile). He was not dysmorphic. There were left esotropia, three café au lait patches (two on the right thigh and one on the left temple) and a left supernumerary nipple. His development was around the 4 month level. Tone appeared normal and reflexes were normal to brisk.

At 11 months of age, there was evidence of an evolving left hemiparesis. He was a tiptoe walker on the left and had lengthening of his left tendo Achilles at 9 years of age.

Brain MRI which he at 19 months of age showed dilatation of the lateral ventricles and periventricular leukomalacia with immature myelination.

He walked at 4 years of age. He had a small number of words at 2 years of age but then seemed to lose them, began to speak again at around 5 years of age, was speaking well at 6 years of age at the end of his first year at school. He was toilet trained by 6 years.

Surgery to correct strabismus was performed around 9 years of age.

He developed epilepsy, with generalised tonic-clonic seizures, at 9 years of age and treatment was started with sodium valproate. His last seizure was at around 19-20 years of age.

Review of motor function during childhood and teenage confirmed left hemiplegic cerebral palsy, associated with a small left foot and pes cavus, and head circumference tracking along the 2nd percentile. Ophthalmologist review at 16 years of age showed bilaterally pale and small optic discs and mild myopia with a right divergent strabismus and no central fixation on that side.

He attended a special school until 15 years of age and then transferred to a special class in a regular school for the final years of his education, which was largely focused on life skills.

Now at 22 years of age, he speaks well, can hold a conversation and has a good sense of humour. He spends considerable time at a computer, with computer games as a major interest. Most of his reading occurs at the computer. He continues to have difficulties with activities of daily living because of a combination of motor and visual impairment – while he can shower and toilet independently, he needs help with dressing, is unable

to hold a writing implement and eats with a spoon or with fingers. Open mouth posture with drooling has been a lifelong problem and benztropine has been prescribed. He sleeps well. He has a quick temper and can be aggressive, which his family puts down to frustration. He dislikes changes in routine and is obsessive about certain things e.g. punctuality and staying slim. He needs help with mobility outside the home mainly because of his visual impairment. Constipation has never been a problem. Puberty occurred at the normal time. His teeth are healthy and erupted the normal time. Height is 177 cm (50^{th} percentile), weight is 65 kg (25^{th}-50^{th} percentile) and general health is good. He continues with life skills training and will soon move into supported accommodation.

Family history: his brother, sister and maternal half-sister developed normally, as did his mother, her sister and four of her brothers; however, the fifth of her brothers had borderline intellectual abilities and poor eyesight.

Adelaide 20124

ZMYND11 Chr10(GRCh37):g.298360_298362del

The female patient was the second child of non-consanguineous Caucasian parents. Her brother has normal intellectual abilities, a cousin is described as having developmental delay with learning difficulties, but there is no other known family history of intellectual disability.

She was born at 37 weeks gestation by elective Caesarean section (for breech presentation and previous Caesarean section) after a normal pregnancy and was well at birth, with birth weight 2.9 kg (50^{th} percentile). There were difficulties with breastfeeding and she was bottle fed from two months of age.

She was recognized from an early age to be hypotonic and to have global developmental delay, with speech and language most severely affected. She was described as happy, sociable and having a short attention span. She had an intermittent strabismus. Hearing was normal.

Psychological assessment at 4 years of age using the Adaptive Behaviour Assessment System showed her to be functioning within the Extremely Low range of adaptive behaviour, with delays across the areas of conceptual, social and practical behaviours. Her abilities ranged from 12-24 months below her chronological age.

At 4 years 4 months, she was described as having brachycephaly, up-slanting palpebral fissures, a wide mouth, a bowed upper lip and wide gaps between her teeth. She had an ectopic left lacrimal punctum and generalised joint laxity. She was an active girl with frequent arm flapping.

When reviewed at 9 years 2 months, she was attending a special school. An ophthalmologist had assessed the strabismus and prescribed glasses because of refractive error. Weight was 37.3 kg (75^{th}-90^{th} percentile), height was 142 cm (90^{th} percentile) and head circumference was 52.5 cm (50^{th} percentile). She was considered to have fleshy earlobes in addition to the facial characteristics described previously.

Previous investigations included array CGH (both oligonucleotide and SNP); methylation studies for Angelman syndrome; UBE3A sequencing;, MECP2 sequencing; molecular testing for fragile X syndrome, MRI brain; full blood examination; blood electrolytes, urea, creatinine, lactate, lead, liver function tests, thyroid function and creatine kinase; urine amino acids, organic acids and mucopolysaccharides.

Nijmegen DNA-017151

ZMYND11 Chr10(GRCh37):g.255918dup

This female patient was the fourth child of non-consanguineous Caucasian parents. There is no family history of developmental delay.

She was born at 41 weeks of gestation by Caesarean section after an uncomplicated pregnancy with a birth weight of 3250 grams (-1 SD). Her Apgar scores were 6/8/9 after 1/5/10 minutes respectively. She was noted to be hypotonic and her development appeared delayed. She was able to roll over at the age of 8 months, sit at the age of 12 months, and walk at the age of 21 months. She said her first words at the age of 23 months. Psychological assessment (WISC-RN) at the age of 8 years revealed a Full Scale IQ of 73 with a Verbal IQ of 80 and a Nonverbal of 68, especially perceptual organisation was poor (IQ 62) as well as her social emotional development. She attended special education. Her behaviour showed signs within the autistic spectrum, including difficulties playing together with peers, distinguishing reality and fantasy, and disturbed information processing. She is also avoiding contact and has irrational fears. Examination by a psychologist and psychiatrist at the age of 9 years showed insufficient evidence for a formal ASD diagnosis.

There was a suspicion of a connective tissue disorder, because of joint laxity for which she received physiotherapy. In addition, she had ichthyosis, recurrent infections, failure to thrive, constipation (treated with lactulose), sleeping problems (treated with melatonin), and enamel hypoplasia of her primary teeth. A CT scan of the brain performed at age 21 months showed no abnormalities.

Physical examination at the age of 17 years showed a height of 158.2 cm (-1.7 SD), a weight of 51.1 kg (-0.5 SD), and a head circumference of 56.6 cm (+0.8 SD). Facial dysmorphisms included small ears with overfolded upper helices and prominent antihelices, mild ptosis, and a wide mouth. She had mild hyperlaxity of the fingers and elbows, but not of the lower extremities. Her hands showed clinodactyly of the 5^{th} fingers. She wore special shoes because she was easily fatigued when walking. She had a hallux valgus and long 2^{nd}-4^{th} toes. Her skin was dry with fragmented palmar and plantar creases and ichthyosiform eruptions on the neck and back.

Previous investigations consisting of karyotyping, FISH 22q11, FMR1 repeat expansion analysis, and DMPK repeat expansion analysis, gave normal results.

Nijmegen DNA-002424

ZMYND11 Chr10 (GRCh37):g.292731C>T

The male patient was the first of three children of non-consanguineous Caucasian parents. There was no family history of developmental delay.

His speech development was delayed for which he attended lower special education where he learned to read and write. His Full scale IQ was measured at 65 (Verbal IQ 61, Non verbal IQ 76) using the WAIS. He was diagnosed with rapid cycling bipolar disorder, borderline personality disorder and pervasive developmental disorder, with psychosis and alcohol and drugs abuse.

At the age of 41 years, he had a height of 180 cm (-0.6 SD), a weight of 71 kg (+0.2 SD), and a head circumference of 57 cm (-0.5 SD). Physical examination was normal except for hypertelorism and cubiti valgi.

Previous investigations consisting of karyotyping, FISH 22q11 and FMR1 repeat expansion analysis were normal.

Nijmegen DNA-013587

ZMYND11 Chr10(GRCh37):g.283569del

The male patient was the only child of non-consanguineous Caucasian parents, who both have children from other partners as well. The father, who had the *ZMYND11* mutation as well, also had a developmental delay. He was said to have walked around the age of 3-4 years. He did lower professional education because of learning problems and worked in a factory. He can read, write and calculate and he has a driving license. He had behavioral problems including aggression in childhood with mood swings, but he never received medication for this. His other three children all had a developmental delay and/or behavioral problems.

The index patient was born after an uncomplicated pregnancy and delivery at 41 weeks of gestation with a birth weight of 2750 gram (-2.2 SD). His development was delayed with sitting at the age of 10 months, walking at the age of nearly 2 years, and speaking at the age of 3.5 years. He attended special education where he learned to read and write. Psychological assessment (WAIS IV) at the age of 25 years showed a mild intellectual disability (Full scale IQ 55, verbal comprehension 62, perceptual organization 51, processing speed 66, working memory 65). Previous tests at the age of 9 years showed a Full scale IQ of 63 (WISC-RN) and 71 (RAKIT) and at the age of 18 years a Full scale IQ 66, Verbal IQ 63, Nonverbal IQ 75 (WISC III). His social-emotional development was estimated at 18-36 months at the age of 22 years. His behavior was characterized by a low frustration tolerance with aggression, impulsivity and provocative behavior and temper tantrums for which he was treated with Risperidone. He lived in a residential setting.

In addition, he had an open lumbar arcus vertebrae and constipation in childhood.

Physical examination at the age of 25 years showed a height of 188.5 cm (+0.7 SD), a weight of 114.2 kg (+3 SD), and a head circumference of 61.0 cm (+1.8 SD). Facial dysmorphisms included synophrys, ptosis, and hypertelorism. He had gynaecomastia. His fingers were tapering and his feet had long toes with sandal gaps and lateral deviation of the halluces. His facial appearance showed similarities to his father.

Previous investigations consisting of karyotyping and FMR1 repeat expansion analysis were normal.

Supplementary Table 1 – Control SNP Array Cohorts

Cohort	Array Platform	Number of Samples	Description	Raw Data Source	CNV Call Source
HGDP	HumanHap650Yv3_A	984	The HGDP consists of 1064 individuals sampled from 51 different world populations. N = 984 after sample quality control.	PMID:18292342	dbVar: nstd54
NINDS (Coriell 550K)	HumanHap550v3_A	441	Genotype data from NINDS were derived from two sets of neurological disease controls totaling 790 people and consist of individuals of European descent with no family history of or any first-degree relative with amyotrophic lateral sclerosis, ataxia, autism, brain aneurysm, dystonia, Parkinson disease, or schizophrenia.	dbGaP Accession: phs000089	dbVar: nstd54
NINDS (317K+240K)	Illumina 317K+240K	227	Genotype data from NINDS were derived from two sets of neurological disease controls totaling 790 people and consist of individuals of European descent with no family history of or any first-degree relative with amyotrophic lateral sclerosis, ataxia, autism, brain aneurysm, dystonia, Parkinson disease, or schizophrenia.	dbGaP Accession: phs000089	dbVar: nstd54
PARC (CAP and PRINCE)	Illumina 317K	936	The PARC samples are a subset of the cohorts used in two statin trials, CAP and PRINCE and consist of 960 middle-age (40-70 years) individuals of European descent living in the United States with moderately high levels of total cholesterol.	PMIDs: 11434828, 16516587	dbVar: nstd54
London (Parents)	Illumina 550K	760	The London samples represent parents of asthmatic children from Mexico City.	PMID: 19714205	dbVar: nstd54
PARC2 (CAP2)	Human610-Quadv1_B	232	The PARC samples are a subset of the cohorts used in two statin trials, CAP2 and PRINCE2, and consist of middle-age (40-70 years) individuals of European descent living in the United States with moderately high levels of total cholesterol	PMIDs: 11434828, 16516587	dbVar: nstd54
PARC2 (PRINCE2)	Illumina 610K Quad	534	The PARC samples are a subset of the cohorts used in two statin trials, CAP2 and PRINCE2, and consist of middle-age (40-70 years) individuals of European descent living in the United States with moderately high levels of total cholesterol.	PMIDs: 11434828, 16516587	dbVar: nstd54
FHCRC	Human610-Quadv1_B	1430	The FHCRC set are part of an ongoing Genome-wide Association Study to Identify Genetic Components of Hip Fracture in the Women's Health Initiative. Samples represent post-menopausal (50-79 years) female controls for pancreatic cancer, colon cancer, and cases and controls for a hip fracture study.	FHCRC	dbVar: nstd54
inChianti	HumanHap550v3_a	695	Population-based study of older persons living in the Chianti geographic area.	http://www.inchiantistudy.net/	dbVar: nstd54

WTCCC2(NBS)	Custom Illumina 1.2M	2090	UK Blood Service Control Group (blood donors, age range 18-69 years). Custom Illumina 1.2M Data.	http://www.wtccc.org.uk/	dbVar: nstd54
ARIC	SNP6	8733	The Atherosclerosis Risk in Communities (ARIC) Cohort Component samples are from a prospective epidemiologic study conducted in four U.S. communities, designed to investigate the etiology and natural history of atherosclerosis, the etiology of clinical atherosclerotic diseases, and variation in cardiovascular risk factors, medical care and disease by race, gender, location, and date.	dbGaP Accession: phs000090	Affymetrix GTC 4.1 + Filtering
WTCCC2(58C)	SNP6	2523	1958 British Birth Cohort	http://www.wtccc.org.uk/	Affymetrix GTC 4.1 + Filtering

Supplementary Table 2 – Newly Significant Genomic Disorders

				Deletions						Duplications					
Chr	Start (hg18 Mbp)	End (hg18 Mbp)	Type[a]	Deletion Syndrome	Cases	Controls	p-value	q-value	Likelihood Ratio	Duplication Syndrome	Cases	Controls	p-value	q-value	Likelihood Ratio
1	144	144.34	HS	TAR deletion[23 b]	25	2	1.63E-04	5.27E-04	8.42 (2.49 to 38.3)	None[24 b,c]	56	11	2.37E-05	1.86E-04	3.43 (1.94 to 6.22)
2	96.09	97.04	HS	2q11.2 deletion[25 b,c]	6	0	0.0455	0.0758	Inf (1 to Inf)	2q11.2 duplication[25]	4	0	0.1280	0.261	Inf (0.559 to Inf)
2	111.1	112.81	HS	2q13 deletion[25 b]	20	3	0.00483	0.0102	4.49 (1.53 to 15.5)	2q13 duplication[25 b]	7	0	0.027	0.0928	Inf (1.23 to Inf)
3	197.2	198.84	HS	3q29 deletion[26 b]	11	0	0.0035	0.00837	Inf (2.21 to Inf)	3q29 duplication[26]	6	2	0.3100	0.474	2.02 (0.425 to 12.2)
4	1.84	1.98	MB	Wolf-Hirschhorn deletion[27]	24	0	4.29E-06	1.97E-05	Inf (5.61 to Inf)	None[28 b]	11	0	0.0035	0.0193	Inf (2.21-Inf)
8	8.13	11.93	HS	8p23.1 deletion[29 b]	8	0	0.0163	0.032	Inf (1.47 to Inf)	8p23.1 duplication[30 b,c]	6	0	0.0455	0.125	Inf (1 to Inf)
9	137	140.2	MB	9q34 deletion[31]	5	0	0.0762	0.12	Inf (0.78 to Inf)	9q34 duplication[32,33 b]	6	0	0.0455	0.125	Inf (1 to Inf)
11	43.94	46.02	MB	Potocki-Shaffer syndrome[34,35 b]	6	0	0.0455	0.0758	Inf (1 to Inf)	None	2	0	0.3580	0.492	Inf (0.174-Inf)
15	70.75	73.32	HS	15q24 A to C deletion[36,37 b,c]	7	0	0.027	0.0495	Inf (1.23 to Inf)	None[36,38,39]	3	0	0.2130	0.378	Inf (0.356 to Inf)
15	71.8	73.32	HS	15q24 Covers B to C deletion[36,37 b,c]	13	0	0.0012	0.00314	Inf (2.71 to Inf)	None[36,38,39 b,c]	7	0	0.027	0.0928	Inf (1.23 to Inf)
15	97.18	100.34	MB	15q26 deletion[40,41 b]	11	1	0.0188	0.0357	7.41 (1.29 to 92.7)	15q26 overgrowth syndrome[42]	4	0	0.1280	0.261	Inf (0.559 to Inf)
16	15.41	16.2	HS	16p13.11 deletion[43]	36	7	0.0007	0.00193	3.45 (1.68-7.45)	16p13.11 duplication[43 b,c]	68	27	0.0112	0.0513	1.7 (1.13-2.56)
17	0.05	2.54	MB	17p13.3 deletion (both YWHAE and PAFAH1B1)[44-46 b]	16	0	2.64E-04	7.64E-04	Inf (3.49 to Inf)	17p13.3 duplication (both YWHAE and PAFAH1B1)[44,47 b]	6	0	0.0455	0.125	Inf (1 to Inf)
17	0.5	1.3	MB	17p13.3 deletion (including YWHAE)[44-46]	17	0	1.58E-04	5.43E-04	Inf (3.75 to Inf)	17p13.3 duplication (including YWHAE [44,47 b]	11	1	0.0188	0.0689	7.41 (1.29 to 92.7)
17	2.31	2.87	MB	17p13.3 deletion (including PAFAH1B1)[44-46 b]	11	0	0.0035	0.00837	Inf (2.21 to Inf)	17p13.3 duplication (including PAFAH1B1)[44,47]	8	1	0.0686	0.164043478	5.39 (0.859 to 72.4)
17	26.19	27.24	HS	NF1 microdeletion syndrome[48,49 b]	7	0	0.027	0.0495	Inf (1.23 to Inf)	None[50 b,c]	7	0	0.027	0.0928	Inf (1.23 to Inf)
17	31.89	33.28	HS	17q12 deletion (ACACA)[51 b]	20	2	0.00145	0.00363	6.73 (1.93 to 31.6)	17q12 duplication (ACACA)[51 b]	23	3	0.00147	0.00898	5.16 (1.80 to 17.50)
22	20.24	21.98	HS	22q11.2 distal deletion[52-54]	20	0	1.25E-05	4.58E-05	Inf (5.05-Inf)	22q11.2 distal duplication[54 b]	7	0	0.027	0.0928	Inf (1.23 to Inf)

22	49.46	49.52	MB	Phelan-McDermid syndrome deletion[55]	43	0	2.4E-10	1.89E-09	Inf (10.8-Inf)	None[55 b]	11	0	0.0035	0.0193	Inf (2.21 to Inf)

[a] Hotspot (HS) or multiple breakpoint (MB) locus, [1 ab] Newly Case-Control Significant, [c] Newly Significant and discussed in three large-scale studies[56-58]

Supplementary Table 3 – Refined Estimates of Significance for Genomic Disorders

				Deletions						Duplications					
Chr	Start (Mbp)	End (Mbp)	Type[a]	Deletion Syndrome	Cases	Controls	p-value	q-value	Likelihood Ratio	Duplication Syndrome	Cases	Controls	p-value	q-value	Likelihood Ratio
1	0	10	MB	1p36 deletion syndrome	77	0	5.84E-18	1.07E-16	Inf (20.4 to Inf)	None	28	1	6.70E-06	6.15E-05	18.9 (3.91 to 203)
1	145.04	145.86	HS	1q21.1 deletion	68	6	5.50E-10	3.78E-09	7.63 (3.8 to 16.4)	1q21.1 duplication	48	5	6.50E-07	7.15E-06	6.46 (2.95 to 15.4)
2	57.6	61.59	HS	2p15-16.1 microdeletion syndrome	0	0	1.0000	1	NA (0 to Inf)	None	0	0	1.0000	1	NA (0 to Inf)
2	100.06	107.81	HS	2q11.2q13 deletion	0	0	1.0000	1	NA (0 to Inf)	None	1	0	0.5980	0.8	Inf (0.0364 to Inf)
2	239.37	242.12	MB	2q37 deletion	33	0	4.16E-08	2.29E-07	Inf (8.05 to Inf)	None	1	0	0.5980	0.802	Inf (0.0364 to Inf)
5	0	11.78	MB	Cri du Chat syndrome	4	0	0.1270	0.189	Inf (0.559 to Inf)	None	1	0	0.5980	0.802	Inf (0.0364 to Inf)
5	175.65	176.99	HS	Sotos syndrome deletion	10	0	0.0058	0.0118	Inf (1.96 to Inf)	None	3	0	0.2130	0.378	Inf (0.356 to Inf)
6	100.92	101.05	MB	6q16 deletion	1	0	0.5980	0.7	Inf (0.0364 to Inf)	None	1	1	0.8380	0.96	0.673 (0.0213 to 21.3)
7	66.12	71.91	HS	Wms-prox deletion	0	0	1.0000	1	NA (0 to Inf)	Wms-prox duplication	1	0	0.5980	0.802	Inf (0.0364 to Inf)
7	72.38	73.78	HS	Williams syndrome deletion	61	0	2.24E-14	2.05E-13	Inf (15.9 to Inf)	WBS duplication	28	0	5.46E-07	7.51E-06	Inf (6.69 to Inf)
7	74.8	76.5	HS	Wms-distal deletion	5	0	0.0762	0.12	Inf (0.775 to Inf)	Wms-distal duplication	1	0	0.5980	0.802	Inf (0.0364 to Inf)
10	81.95	88.79	HS	10q23 deletion	11	0	0.0035	0.00837	Inf (2.21 to Inf)	None	4	0	0.1280	0.261	Inf (0.559 to Inf)
11	67.51	70.96	HS	SHANK2 FGFs deletion	1	0	0.5980	0.7	Inf (0.0364 to Inf)	None	0	0	1.0000	1	NA (0 to Inf)
12	63.36	66.93	MB	12q14 microdeletion syndrome	3	0	0.2130	0.293	Inf (0.356 to Inf)	None	0	0	1.0000	1	NA (0 to Inf)
13	19.71	19.91	MB	13q12 deletion	34	17	0.1950	0.275	1.35 (0.784 to 2.34)	None	5	1	0.2300	0.361	3.37 (0.453 to 51.5)
15	20.35	20.64	HS	15q11.2 deletion	200	27	3.19E-21	8.77E-20	4.99 (3.57 to 7.04)	None	128	60	0.0112	0.0513	1.44 (1.09 to 1.9)
15	22.37	26.1	HS	Prader-Willi/Angelman	40	0	1.13E-09	6.91E-09	Inf (9.99 to Inf)	PWS duplication	48	0	1.82E-11	5.01E-10	Inf (12.2 to Inf)
15	28.92	30.27	HS	15q13.3 deletion	65	0	2.85E-15	3.14E-14	Inf (17 to Inf)	15q13.3 duplication	28	11	0.0834	0.176	1.71 (0.898 to 3.35)
15	70.75	73.8	HS	15q24 A to D deletion	2	0	0.3570	0.457	Inf (0.175 to Inf)	None	3	0	0.2130	0.378	Inf (0.356 to Inf)

15	71.8	73.32	HS	15q24 B to C deletion	0	0	1.0000	1	NA (0 to Inf)	None	0	0	1.0000	1	NA (0 to Inf)
15	71.8	73.8	HS	15q24 B to D deletion	2	0	0.3570	0.457	Inf (0.175 to Inf)	None	1	0	0.5980	0.802	Inf (0.0364 to Inf)
15	71.8	75.92	HS	15q24 B to E deletion	2	0	0.3570	0.457	Inf (0.175 to Inf)	None	0	0	1.0000	1	NA (0 to Inf)
15	80.98	82.53	HS	15q25.2 deletion	1	0	0.5980	0.7	Inf (0.0364 to Inf)	None	1	0	0.5980	0.802	Inf (0.0364 to Inf)
15	82.94	83.5	HS	Cooper 15q25.2	7	0	0.0272	0.0468	Inf (1.23 to Inf)	None	2	0	0.3570	0.531	Inf (0.175 to Inf)
16	3.72	3.8	MB	Rubinstein-Taybi syndrome	4	0	0.1280	0.185	Inf (0.559 to Inf)	None	8	1	0.0686	0.164	5.39 (0.859 to 72.4)
16	21.26	29.35	HS	Shaffer locus deletion	3	0	0.2130	0.293	Inf (0.356 to Inf)	None	2	0	0.3570	0.531	Inf (0.175 to Inf)
16	21.52	28.95	HS	16p11.2-p11.2 microdeletion syndrome	3	0	0.2130	0.293	Inf (0.356 to Inf)	None	2	0	0.3570	0.531	Inf (0.175 to Inf)
16	21.85	22.37	HS	16p12.1 deletion	50	11	1.77E-04	5.41E-04	3.06 (1.72 to 5.61)	None	11	4	0.2120	0.389	1.85 (0.62 to 6.04)
16	28.68	29.02	HS	16p11.2 distal deletion	27	1	1.09E-05	4.28E-05	18.2 (3.75 to 196)	None	29	8	0.0137	0.0538	2.44 (1.2 to 5.18)
16	29.56	30.11	HS	16p11.2 deletion	101	6	2.07E-16	2.85E-15	11.3 (5.81 to 23.7)	16p11.2 duplication	62	9	3.50E-07	6.42E-06	4.64 (2.54 to 8.8)
17	14.01	15.44	HS	HNPP	13	8	0.5150	0.616	1.09 (0.466 to 2.63)	CMT1A	17	5	0.0691	0.15202	2.29 (0.905 to 6.21)
17	16.65	20.42	HS,MB	Smith-Magenis syndrome deletion	24	0	4.29E-06	1.97E-05	Inf (5.61 to Inf)	Potocki-Lupski syndrome duplication	19	0	5.63E-05	3.87E-04	Inf (4.27 to Inf)
17	41.06	41.54	HS	17q21.31 deletion	31	0	1.16E-07	5.80E-07	Inf (7.51 to Inf)	17q21.31 duplication	3	0	0.2130	0.378	Inf (0.356 to Inf)
17	55.01	55.43	HS	17q23 deletion	0	0	1.0000	1	NA (0 to Inf)	None	0	0	1.0000	1	NA (0 to Inf)
17	55.42	57.66	HS	17q23.1q23.2 deletion	1	0	0.5980	0.7	Inf (0.0364 to Inf)	None	0	0	1.0000	1	NA (0 to Inf)
22	17.4	18.67	HS	DiGeorge/VCFS deletion	158	0	3.97E-36	2.18E-34	Inf (43.9 to Inf)	22q11.2 duplication	97	12	1.35E-11	7.43E-10	5.44 (3.28 to 9.27)

[a] Hotspot (HS) or multiple breakpoint (MB) locus.

Supplementary Table 4 – Enrichment of RefSeq Genes by CNVs in ID/DD

See Excel Document

Supplementary Table 5 – Truncating and Splice Variants Discovered by MIP resequencing

Gene	Accession	Genomic Variant	Coding Effect	Protein Annotation	Sample	Validation
ACACA	NM_198834.1	Chr17(GRCh37):g.35564585del	Frameshift	p.Phe1242Leufs*11	Leuven_293186	Valid
ACACA	NM_198834.1	Chr17(GRCh37):g.35620683_35620686del	Frameshift	p.Phe411Valfs*35	Ssib_8000209830	Valid
ACACA	NM_198834.1	Chr17(GRCh37):g.35632944dup	splice	p.? (splice)	Adelaide3446	Valid
ADNP	NM_015339.2	Chr20(GRCh37):g.49508443del	Frameshift	p.Tyr936*	NijmegenDNA07-06960	Valid, *de novo*
ADNP	NM_015339.2	Chr20(GRCh37):g.49508752_49508755del	Frameshift	p.Asn832Lysfs*81	NijmegenDNA-024061	Valid
ADNP	NM_015339.2	Chr20(GRCh37):g.49508757_49508760del	Frameshift	p.Leu831Ilefs*82	Troina2376	Valid, *de novo*
ADNP	NM_015339.2	Chr20(GRCh37):g.49520470dup	Frameshift	p.Ile22Asnfs*3	NijmegenDNA-023820	Valid
ADNP	NM_015339.2	Chr20(GRCh37):g.49507972_49507973dup	Frameshift	p.Gly1094Profs*5	Ssib_16033147	Valid
ADNP	NM_015339.2	Chr20(GRCh37):g.49509046_49509048del	In-frame	p.Asp735del	Leuven_371130	Valid
ADNP	NM_015339.2	Chr20(GRCh37):g.49508699_49508701del	In-Frame	p.Asp850del	Ssib_15990823	Valid
ADNP	NM_015339.2	Chr20(GRCh37):g.49509046_49509048del	In-frame	p.Asp735del	Adelaide687	Valid
ADNP	NM_015339.2	Chr20(GRCh37):g.49509321G>A	nonsense	p.Arg644*	Troina2533	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157522197dup	Frameshift	p.Tyr1477*	Adelaide12350	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157528567del	Frameshift	p.Leu2085*	Adelaide16465	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157527498_157527500del	In-Frame	p.Asp1728del	Leuven_256277	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157527498_157527500del	In-Frame	p.Asp1728del	Ssib_15970079	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157527498_157527500del	In-Frame	p.Asp1728del	Ssib_15970724	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157527498_157527500del	In-Frame	p.Asp1728del	Ssib_8000209654	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157406006C>T	nonsense	p.Arg737*	NijmegenDNA-024311	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157406006C>T	nonsense	p.Arg737*	NijmegenDNA03-04634Z	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157469856G>T	nonsense	p.Gly871*	NijmegenDNA-012786	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157469898C>T	nonsense	p.Arg885*	Sage4048	Valid, *de novo*
ARID1B	NM_017519.2	Chr6(GRCh37):g.157519957T>G	nonsense	p.Tyr1329*	NijmegenDNA06-01159	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157528786C>T	nonsense	p.Gln2158*	Nijmegen18-78	Valid
ARID1B	NM_017519.2	Chr6(GRCh37):g.157522598C>T	nonsense	p.Arg1611*	Nijmgenan17-56	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146714385del	Frameshift	p.Gly11Alafs*31	Adelaide24398	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146757068_146757069del	Frameshift	p.Glu641Glyfs*28	NijmegenDNA03-00027	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146757068_146757069del	Frameshift	p.Glu641Glyfs*28	NijmegenDNA03-00283	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146757131_146757133del	In-frame	p.Lys662del	Troina2129	Valid, Maternal
CHD1L	NM_004284.3	Chr1(GRCh37):g.146743873G>T	nonsense	p.Glu401*	Adelaide12167	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146757076C>T	nonsense	p.Gln644*	Adelaide958	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146757076C>T	nonsense	p.Gln644*	Adelaide963	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146757076C>T	nonsense	p.Gln644*	Adelaide973	Valid

CHD1L	NM_004284.3	Chr1(GRCh37):g.146742591A>C	splice	p.? (splice)	Adelaide24966	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146747766A>G	splice	p.? (splice)	Adelaide12576	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146747766A>G	splice	p.? (splice)	Leuven_346287	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146747766A>G	splice	p.? (splice)	NijmegenDNA-007437	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146747766A>G	splice	p.? (splice)	NijmegenDNA08-03719	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146747766A>G	splice	p.? (splice)	Troina1188	Valid
CHD1L	NM_004284.3	Chr1(GRCh37):g.146751866T>G	splice	p.? (splice)	NijmegenDNA06-04307	Valid
CYFIP1	NM_014608.2	Chr15(GRCh37):g.22969308G>A	nonsense	p.Trp845*	APP_108378-100	Valid
DIP2A	NM_015151.3	Chr21(GRCh37):g.47931416C>T	nonsense	p.Arg331*	NijmegenDNA05-02744	Valid
DIP2A	NM_015151.3	Chr21(GRCh37):g.47957453G>A	splice	p.? (splice)	Murdoch_ASD_1022-1	Valid
DIP2A	NM_015151.3	Chr21(GRCh37):g.47983832C>G	splice	p.Ser1384*	Ssib_8001979012	Valid
DNM3	NM_015569.3	Chr1(GRCh37):g.172376970_172376971del	Frameshift	p.Leu861Valfs*14	Troina1407	Valid, Maternal
DNM3	NM_015569.3	Chr1(GRCh37):g.172348278C>T	nonsense	p.Arg672*	NijmegenDNA-017175	Valid
DNM3	NM_015569.3	Chr1(GRCh37):g.172277980G>A	splice	p.? (splice)	Leuven_138808	Valid
DYRK1A	NM_001396.3	Chr21(GRCh37):g.38853130T>C	splice	p.? (splice)	Troina1818	Valid, *de novo*
DYRK1A	NM_001396.3	Chr21(GRCh37):g.38850482G>A	splice	p.? (splice)	Murdoch_ASD_1157-1	Valid
DYRK1A	NM_001396.3	Chr21(GRCh37):g.38877584A>G	splice	p.? (splice)	Nijmgenan17-74	Valid
FOXP1	NM_032682.5	Chr3(GRCh37):g.71019936dup	Frameshift	p.Asn558Lysfs*22	NijmegenDNA-014621	Valid
GRIN2B	NM_000834.3	Chr12(GRCh37):g.13716114_13716116del	In-frame	p.Asn1352del	Ssib_17326674	Valid
GRIN2B	NM_000834.3	Chr12(GRCh37):g.13761570A>T	nonsense	p.Tyr659*	NijmegenDNA-007987	Valid
GRIN2B	NM_000834.3	Chr12(GRCh37):g.14018885A>T	nonsense	p.Cys86*	Troina2106	Valid
GRIN2B	NM_000834.3	Chr12(GRCh37):g.13764658C>T	splice	p.? (splice)	Leuven_185718	Valid
GRIN2B	NM_000834.3	Chr12(GRCh37):g.13906250C>T	splice	p.? (splice)	Leuven_150281	Valid
KANSL1	NM_001193466.1	Chr17(GRCh37):g.44144921_44144928del	Frameshift	p.Gly547*	Adelaide20978	Valid, Not Maternal
KANSL1	NM_001193466.1	Chr17(GRCh37):g.44249272dup	Frameshift	p.Ala80Glyfs*7	Adelaide3714	Valid
KANSL1	NM_001193466.1	Chr17(GRCh37):g.44248783G>A	nonsense	p.Gln243*	NijmegenDNA-010062	Valid
KANSL1	NM_001193466.1	Chr17(GRCh37):g.44248783G>A	nonsense	p.Gln243*	NijmegenDNA-010564	Valid
KANSL1	NM_001193466.1	Chr17(GRCh37):g.44248783G>A	nonsense	p.Gln243*	Leuven_388846	Valid
KANSL1	NM_001193466.1	Chr17(GRCh37):g.44248783G>A	nonsense	p.Gln243*	Leuven_388852	Valid
KANSL1	NM_001193466.1	Chr17(GRCh37):g.44108985G>A	nonsense	p.Arg1059*	Ssib_17327376	Valid
MAPT	NM_016835.4	Chr17(GRCh37):g.44060786dup	Frameshift	p.Ala206Glyfs*15	NijmegenDNA04-01345	Valid
MAPT	NM_016835.4	Chr17(GRCh37):g.44087687_44087690del	Frameshift	p.Asn596Argfs*29	NijmegenDNA-011188	Valid
MBD5	NM_018328.4	Chr2(GRCh37):g.149226838dup	Frameshift	p.Val443Argfs*12	NijmegenDNA04-05467	Valid
NRG3	NM_001165973.1	Chr10(GRCh37):g.84745337_84745338del	Frameshift	p.Asp494Leufs*8	Troina1619	Valid
NRG3	NM_001165973.1	Chr10(GRCh37):g.84745302C>T	nonsense	p.Arg481*	Troina3449	Valid, Maternal
NRG3	NM_001165973.1	Chr10(GRCh37):g.83637777G>A	splice	p.? (splice)	Leuven_242207	Valid
NRXN1	NM_001135659.1	Chr2(GRCh37):g.50779724C>T	splice	p.? (splice)	Leuven_402553	Valid
PTEN	NM_000314.4	Chr10(GRCh37):g.89717672C>T	nonsense	p.Arg233*	NijmegenDNA-013917	Valid
SCN1A	NM_001165963.1	Chr2(GRCh37):g.166897842del	Frameshift	p.Leu772Trpfs*9	Troina3366	Valid, *de novo*
SCN1A	NM_001165963.1	Chr2(GRCh37):g.166903375C>A	nonsense	p.Glu428*	Troina422	Valid

SCN2A	NM_021007.2	Chr2(GRCh37):g.166211129del	Frameshift	p.Asn1116Ilefs*2	Troina2326	Valid
SCN2A	NM_021007.2	Chr2(GRCh37):g.166201068C>T	nonsense	p.Arg856*	Leuven_308280	Valid
SCN2A	NM_021007.2	Chr2(GRCh37):g.166231415G>A	nonsense	p.Trp1398*	NijmegenDNA04-04625	Valid
SCN2A	NM_021007.2	Chr2(GRCh37):g.166231477G>A	splice	p.? (splice)	NijmegenDNA08-01694	Valid
SETBP1	NM_015559.2	Chr18(GRCh37):g.42530536_42530537del	Frameshift	p.Leu411Glyfs*6	NijmegenDNA-008897	Valid
SETBP1	NM_015559.2	Chr18(GRCh37):g.42531769del	Frameshift	p.Ile822Tyrfs*13	NijmegenDNA03-00335	Valid, *de novo*
SETBP1	NM_015559.2	Chr18(GRCh37):g.42281738del	Frameshift	p.Arg143Valfs*64	Troina3097	Valid
SETBP1	NM_015559.2	Chr18(GRCh37):g.42530901G>A	nonsense	p.Trp532*	Troina1274	Valid, *de novo*
SETBP1	NM_015559.2	Chr18(GRCh37):g.42532337C>G	nonsense	p.Ser1011*	Troina1512	Valid, *de novo*
SOX5	NM_006940.4	Chr12(GRCh37):g.23757468C>T	splice	p.? (splice)	Murdoch_ASD_1256-1	Valid
TTC21B	NM_024753.4	Chr2(GRCh37):g.166731330del	Frameshift	p.His1296Ilefs*19	NijmegenDNA-023328	Valid
ZMYND11	NM_006624.5	Chr10(GRCh37):g.255918dup	Frameshift	p.Thr70Asnfs*12	NijmegenDNA-017151	Valid, *de novo*
ZMYND11	NM_006624.5	Chr10(GRCh37):g.283569del	Frameshift	p.Met187Ilefs*19	NijmegenDNA-013587	Valid, Inherited
ZMYND11	NM_006624.5	Chr10(GRCh37):g.294294_294295del	Frameshift	p.Glu416Serfs*5	NijmegenDNA05-04370	Valid
ZMYND11	NM_006624.5	Chr10(GRCh37):g.282793_282794insC	Frameshift	p.Asn152Thrfs*26	Adelaide3553	Valid
ZMYND11	NM_006624.5	Chr10(GRCh37):g.298360_298362del	In-frame	p.Gln587del	Adelaide20124	Valid, *de novo*
ZMYND11	NM_006624.5	Chr10(GRCh37):g.292731C>T	nonsense	p.Gln326*	NijmegenDNA04-02424	Valid

Supplementary Table 6 – Phenotypes of Cases with *SETBP1* Loss-of-Function Variants

See Excel Document

Supplementary Table 7 – Phenotypes of Cases with *ZMYND11* Loss-of-Function Variants

See Excel Document

Supplementary Table 8 – Signature Array Platforms

Platform	Samples	Probes (tens of thousands)
SignatureChip PN v2.0 12-plex	169	34
Agilent NICHD 44	367	43
SignatureChip PN v1.1 12-plex	863	54
SignatureChip OS v1.1	4296	97
SignatureChip OS v1.1 Rev. B	4557	97
SignatureChip OS v1.0	314	104
SignatureChip OS v2.0 12-plex	16754	135
SignatureChip OS v3.0 12-plex	1765	137

Supplementary Table 9 – Regions Prone to Artifacts on Signature Arrays

Chromosome	Bp Start (hg18)	Bp End (hg18)
chr1	196776236	197322372
chr1	205394967	205710784
chr1	232815653	233051555
chr2	37706786	37867932
chr2	48405825	48472728
chr2	144844478	145027567
chr2	157896283	158091183
chr2	176642951	176737453
chr2	207666932	207749750
chr3	30560012	30762182
chr3	46668266	47023170
chr3	46694521	46932097
chr3	127518563	127581045
chr3	153372786	153820605
chr3	185528026	185609839
chr4	15737006	15984885
chr4	68832243	69742453
chr4	174685638	174705733
chr4	185875253	186107309
chr5	98240090	98327546
chr5	118582959	118798388
chr5	130616845	130789163
chr5	131628670	131954993
chr5	169556900	169777365
chr5	172637729	173355061
chr6	15342654	15734068

chr6	143150726	143401791
chr7	50262711	50512979
chr7	105462120	105889591
chr7	130234670	130448525
chr8	21953740	21972837
chr9	79672565	79809500
chr10	3752639	3872872
chr10	5098345	5274334
chr10	11183670	11453047
chr10	64571508	64762739
chr11	4577772	4625919
chr11	34978512	35253990
chr11	64873963	65185928
chr12	64834236	64926090
chr12	90847497	91213233
chr12	114960544	115226869
chr13	40406085	40527590
chr13	98616144	98908087
chr14	20729184	20841424
chr14	21505230	22119754
chr14	51363321	51518388
chr14	60780839	61271148
chr15	67935857	68374442
chr15	91141932	91382338
chr16	22301139	22683209
chr16	56193598	56285084
chr17	25028825	25113673
chr19	15246205	15392044
chr19	21503451	2156653
chr19	50949472	51032302
chr19	60567620	60650434
chr20	33693322	33838225
chr20	38943097	39222636
chr21	37626981	37742004
chr22	21730739	21808354

Supplementary Table 10 – MIP Sequences and Performance

See Excel Document

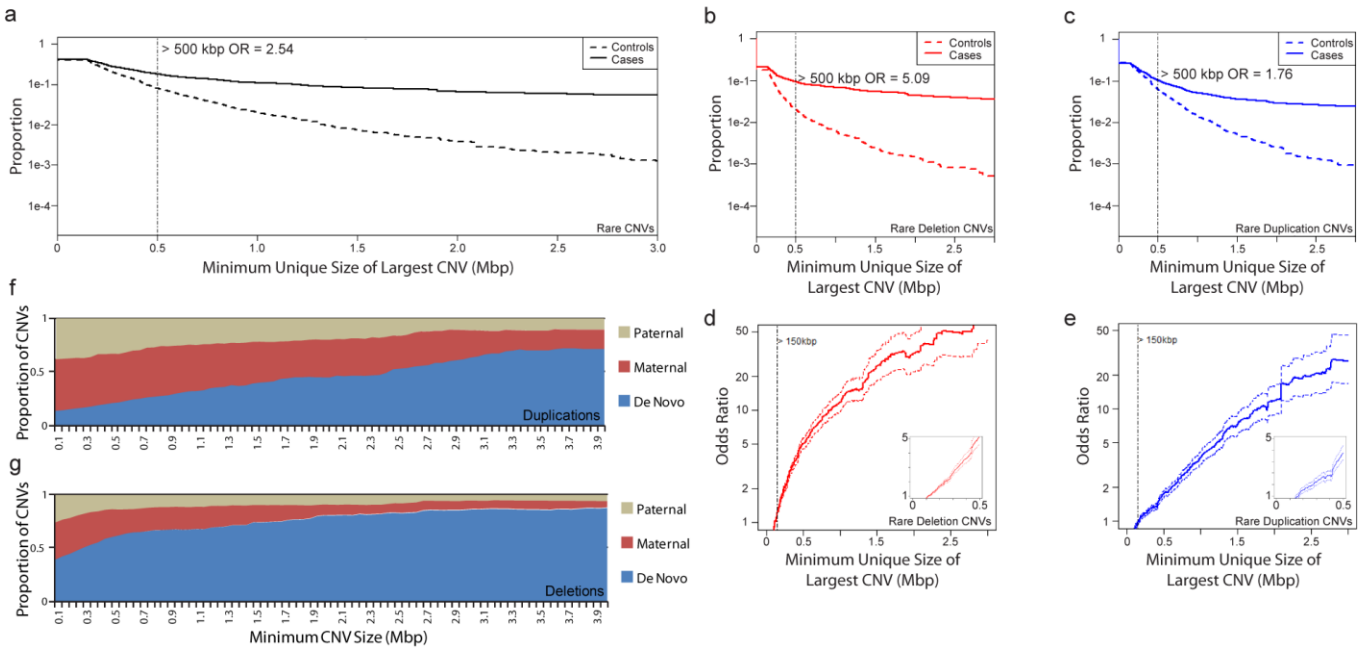
Supplementary Table 11 – MIP Resequencing Cohorts

Cohort (Source) and Ascertainment	Phenotypes	QC-Passing Samples
APP (David Amaral, UC Davis) www.ucdmc.ucdavis.edu/mindinstitute/research/app	ASD	217
Leuven (Hilde Peeters, University Hospitals Leuven) Patients were diagnosed with ASD, and cases with clinically recognizable diagnosis were excluded (Fragile X, NF1, TSC, known microduplication / microdeletion syndromes). Most cases were screened by array CGH or SNP arrays, those that were not screened have normal physical examination.	ASD	837
Murdoch (Ingrid E Scheffer, Murdoch Children's research Institute) ASD patients were diagnosed by a community-based multidisciplinary team (trio of developmental pediatrician or child psychiatrist, speech pathologist, psychologist) reflecting current community standard practice in Australia. Approximately 50% have had a formal cognitive assessment, with approximately 50% of those demonstrating intellectual disability (25% of the entire cohort). ADI and ADOS are utilised during these community-based assessments, but specific ADI/ADOS data is not available for individual patients.	ASD	275
Adelaide (Jozef Gécz, University of Adelaide) Developmental delay and intellectual disability were determined using age-appropriate assessment tools by the affected individual's pediatrician or a child development team. Autism spectrum disorders were diagnosed using the Childhood Autism Rating Scale or DSM IV.	ID/DD	1242
Nijmegen (Bert B.A. de Vries, Radboud university medical center) All patients from the Nijmegen cohort, have been evaluated by a clinical geneticist and, in most cases, received a routine genetic diagnostic assessment and psychological assessment (WISC and/or WAIS), leading to an accurate ascertainment of the level of intellectual disability.	ID/DD	1315
SAGE (Raphael Bernier, University of Washington)	ID/DD	112

Parents were asked if their children have a diagnosis of ASD or Developmental Delay or are suspected of having ASD or Developmental Delay		
Troina (Corrado Romano, Associazione Oasi Maria Santissima) ID and ASD patients were diagnosed according to current DSM criteria. DD patients had a delay in psychomotor development. All patients were evaluated by a clinical geneticist who ruled out any genetic syndrome suggested on phenotypic ground. Array CGH was performed as a first step genetic test.	ID/DD	718
Simons Siblings (SSC) This collection includes unaffected siblings from the Simons Simplex Collection (SSC). Probands and siblings were screened for adaptive function, behavior, emotional problems and symptoms of autism using ADOS, ADI-R, SRS, and vineland measurements.	Unaffected Siblings from the SSC	2193

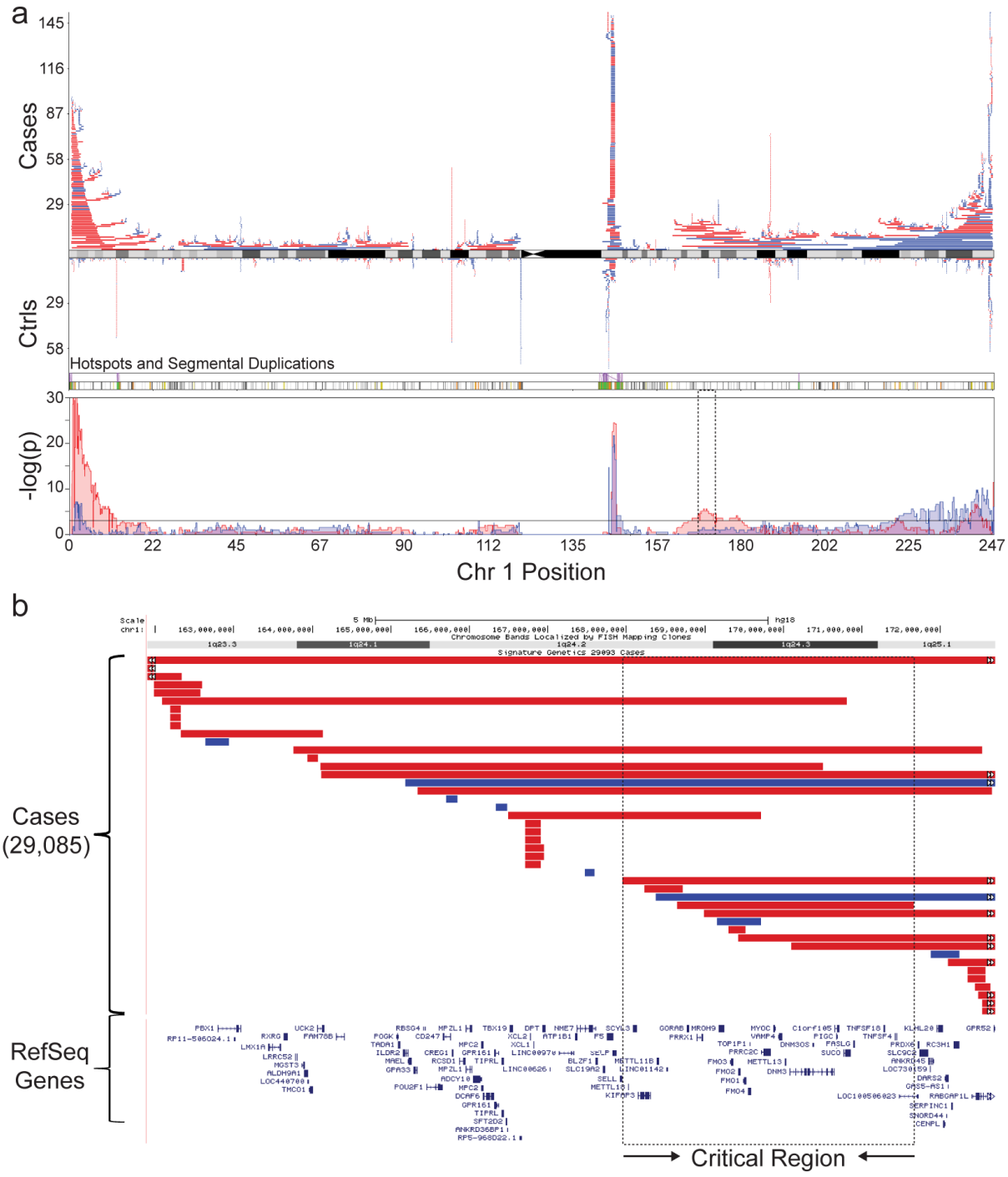
Supplementary Figure 1 – Population Incidence of Large CNVs

A comparison of cases and controls in terms of the population incidence of large CNVs demonstrates a significant increase in the frequency of large CNVs (greater than 150 kbp to account for differences in array coverage) in cases with ID/DD consistent with previous observations with deviation in population frequencies beginning around 250 kbp and an OR of 2.54 for CNVs of 500 kbp or larger (**a**). Stratifying CNVs by deletions (**b,d**) and duplications (**c,e**) supports the increased pathogenicity of deletions by their increased enrichment in cases with an OR of 5.09 over 500 kbp compared to an OR of 1.76 (odds ratios at 250 kbp are 2.07 and 1.18 for deletions and duplications, respectively). Further supporting the pathogenicity implied by large CNVs, examination of *de novo* CNVs demonstrated that larger CNVs are overwhelmingly *de novo* in origin (**f-g**). Strikingly, likely deleterious inherited CNVs are transmitted preferentially from mothers 58% (**f-g**).



Supplementary Figure 2 –CNV Regions on Chromosome 1

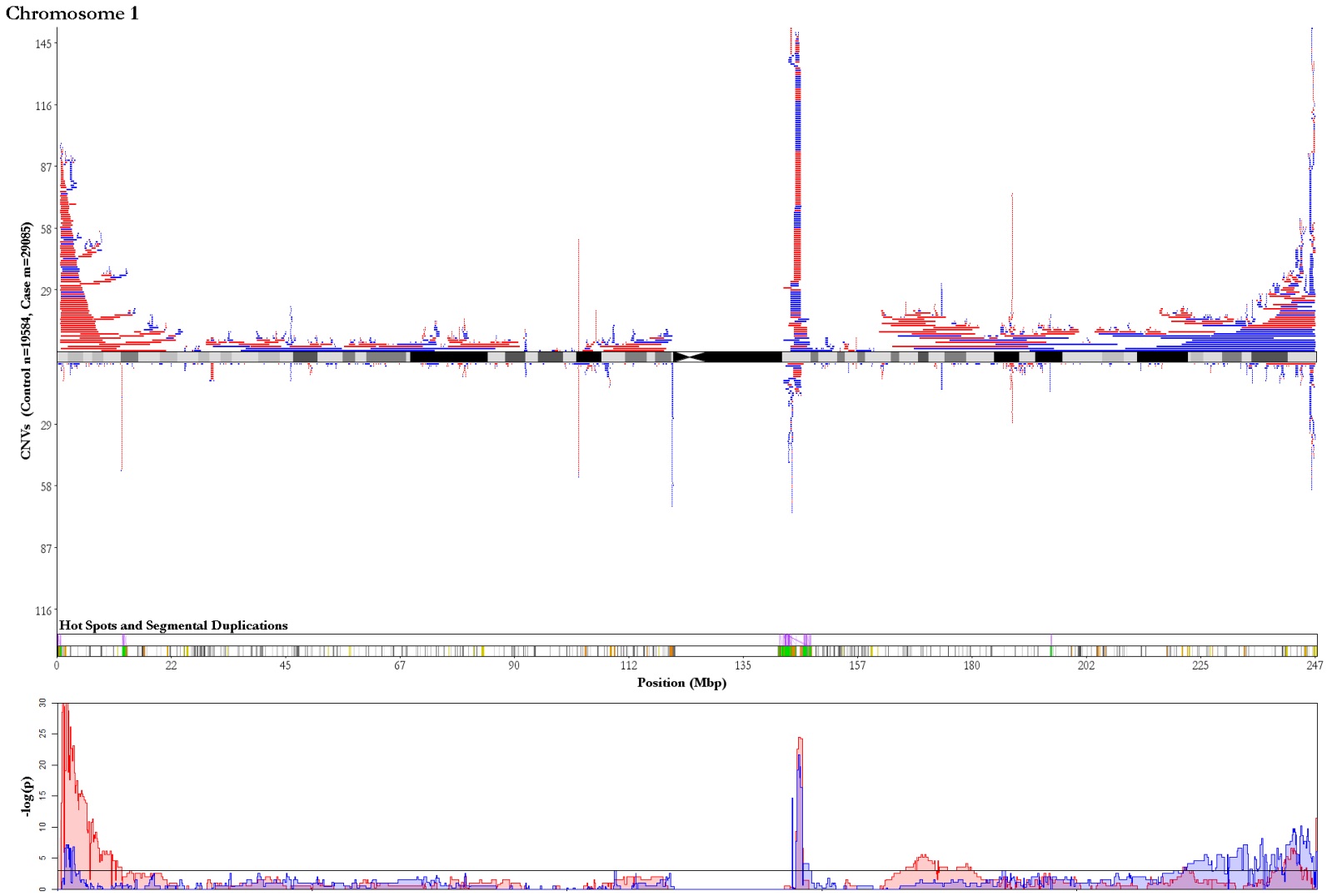
(**a**) Shown are CNV deletions (red bars) and duplications (blue bars) for 29,085 cases of ID and DD (top) and 19,584 adult controls (bottom). Small recurrent CNVs specific to controls are indicative of increased resolution of SNP microarrays for controls at those loci. Segmental duplications predisposing to deletions and duplications are indicated by purple lines, and segmental duplications are shaded according to their percent identity (orange to black for 90% to 100% identity). Sliding window based Fisher's exact test p-values across chromosome 1 are indicated by red- and blue-shaded areas (see Methods). The critical region of the 1q24 microdeletion locus (**b**) is indicated by a dashed outline. The critical region contains multiple peaks of significance, including *FMO1/2* and *DNM3*.



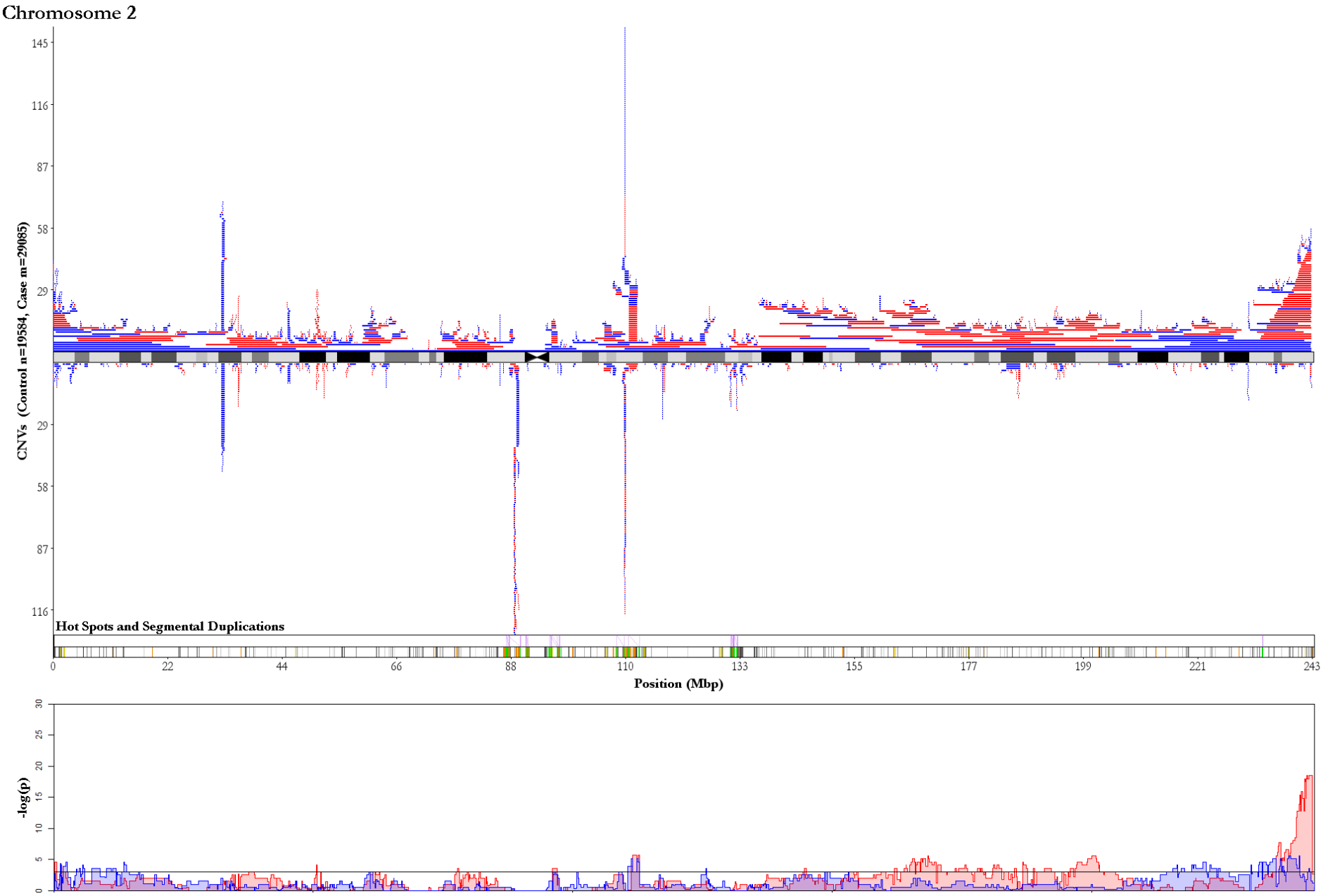
Supplementary Figure 3 - A CNV Morbidity Map of DD

CNVs in 29,085 cases are shown above each chromosome ideogram with control CNVs from 19,584 controls below the ideogram. Directly oriented segmental duplications promoting non-allelic homologous recombination are indicated by connected purple line segments. Segmental duplications are shaded according to percent identity (**a - x**). The bottom plot represents enrichment significance for cases by windowed analysis. The underlying data for the counts and p-values are available in Supplementary Data Set 1.

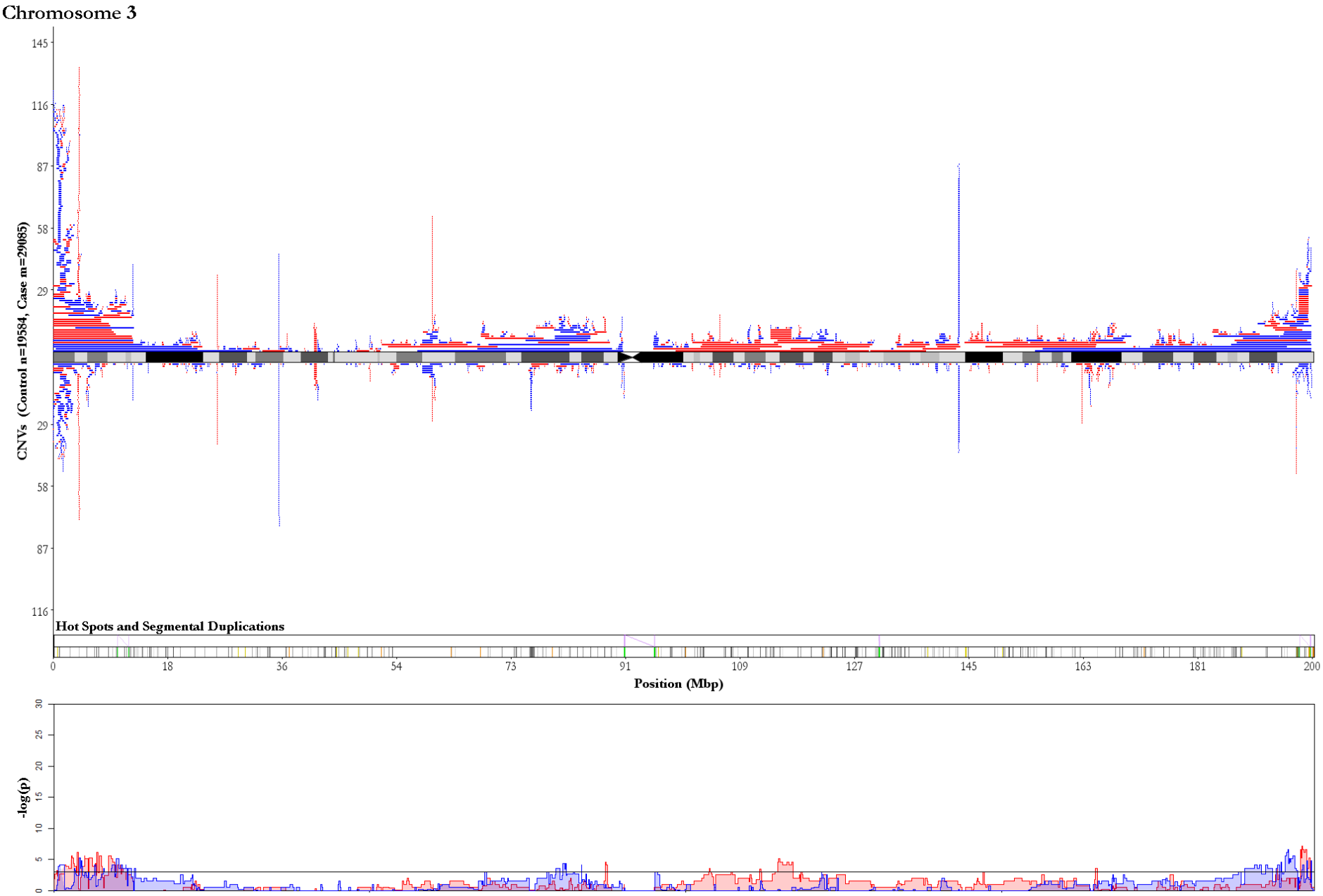
Supplementary Figure 3a



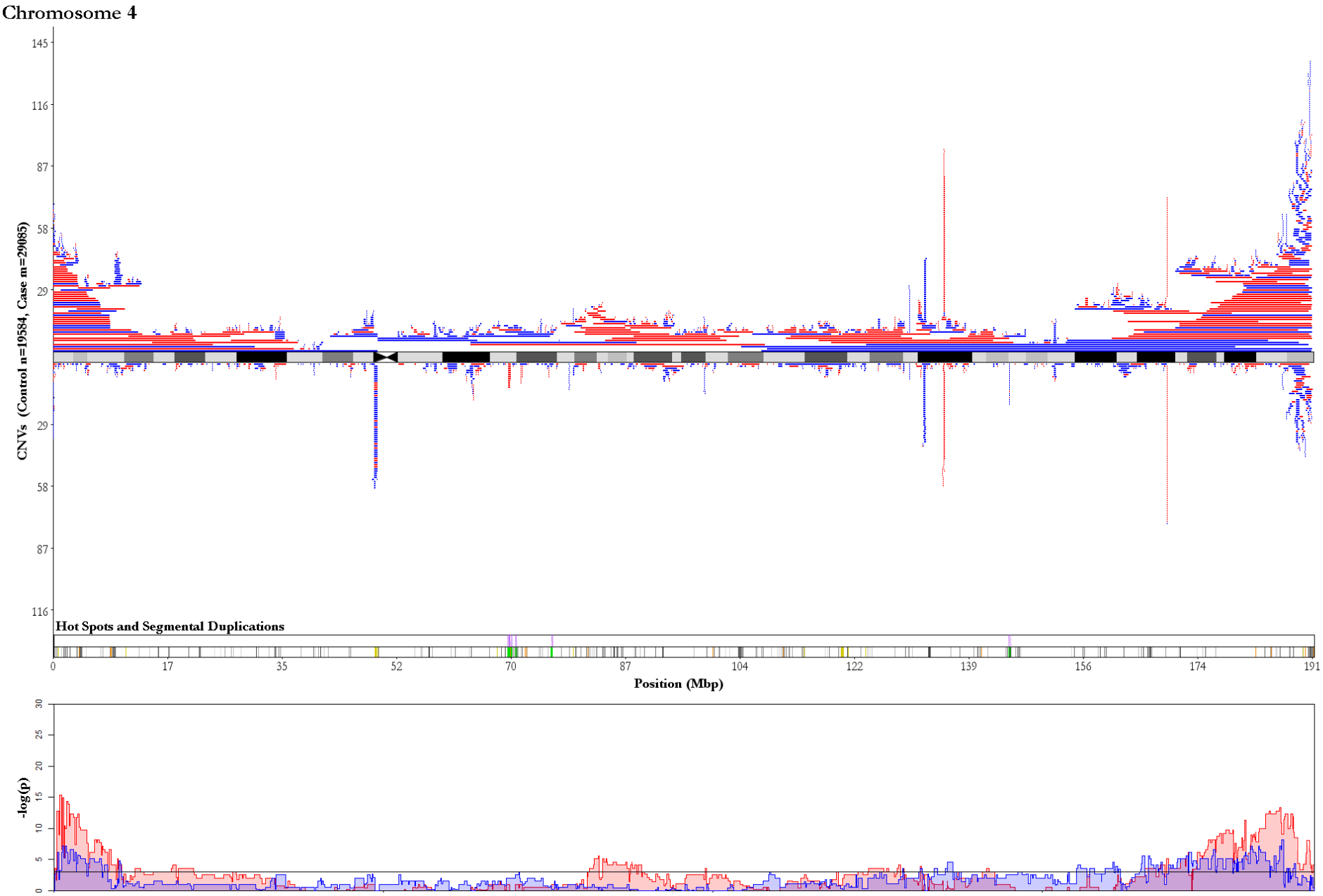
Supplementary Figure 3b



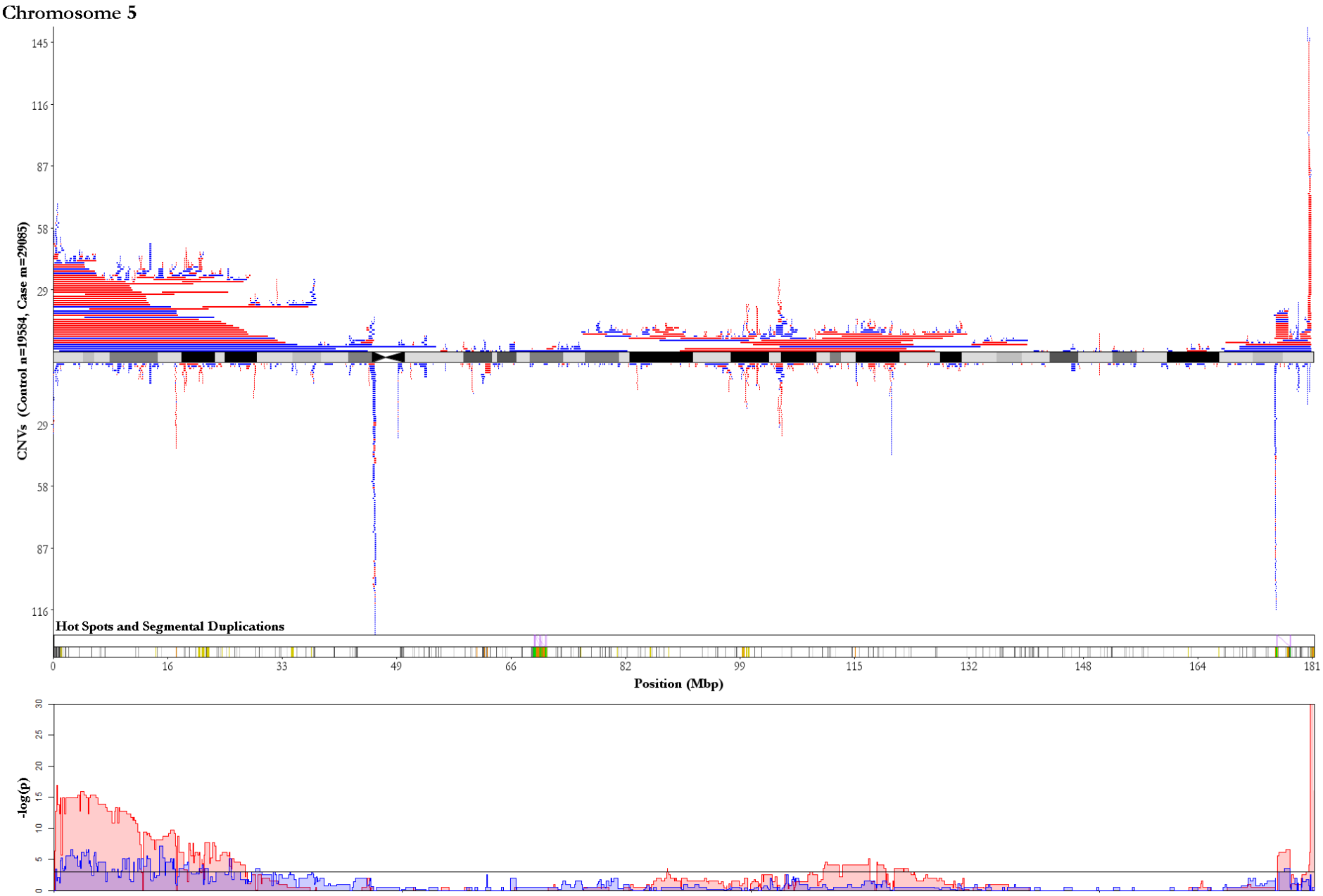
Supplementary Figure 3c



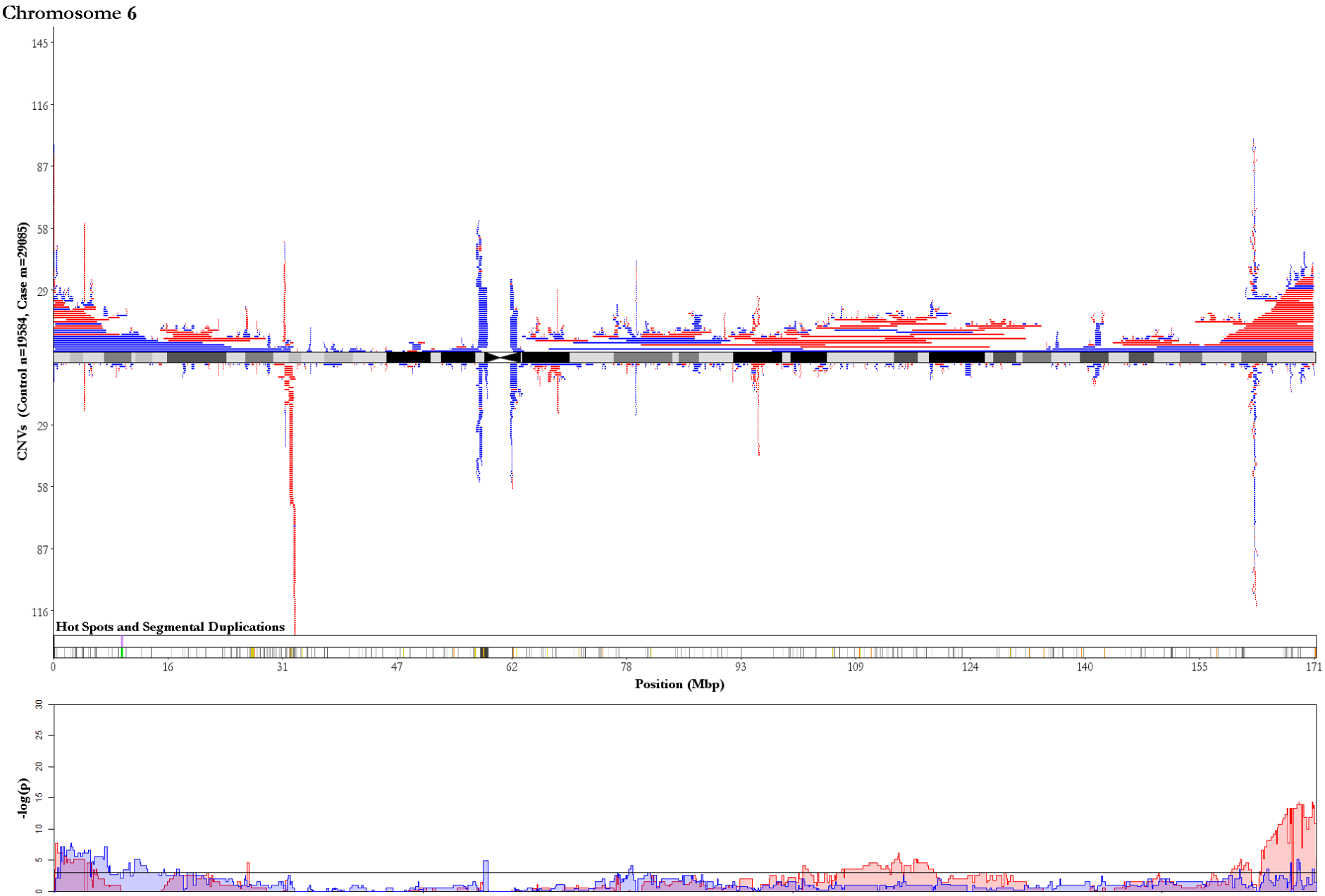
Supplementary Figure 3d



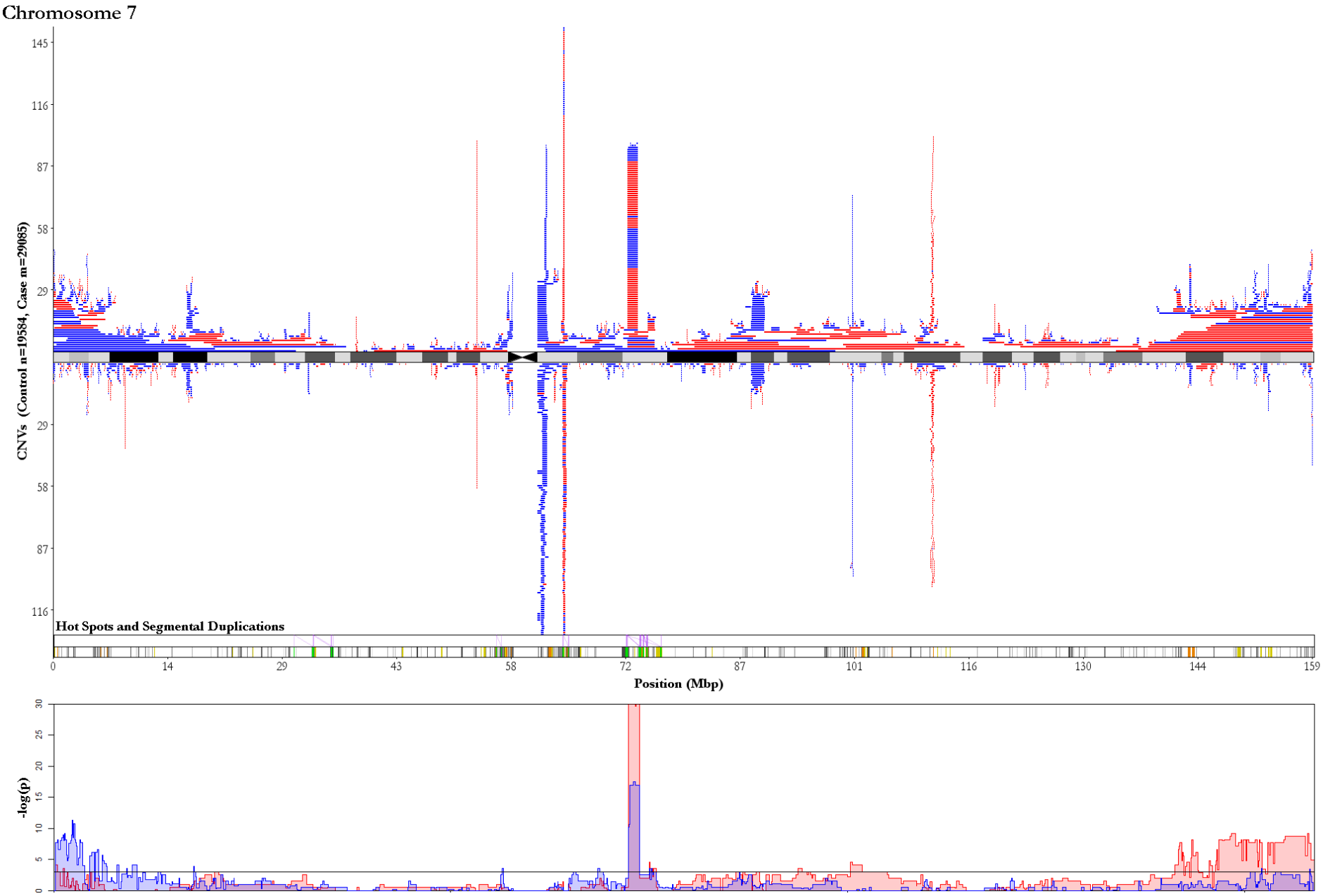
Supplementary Figure 3e



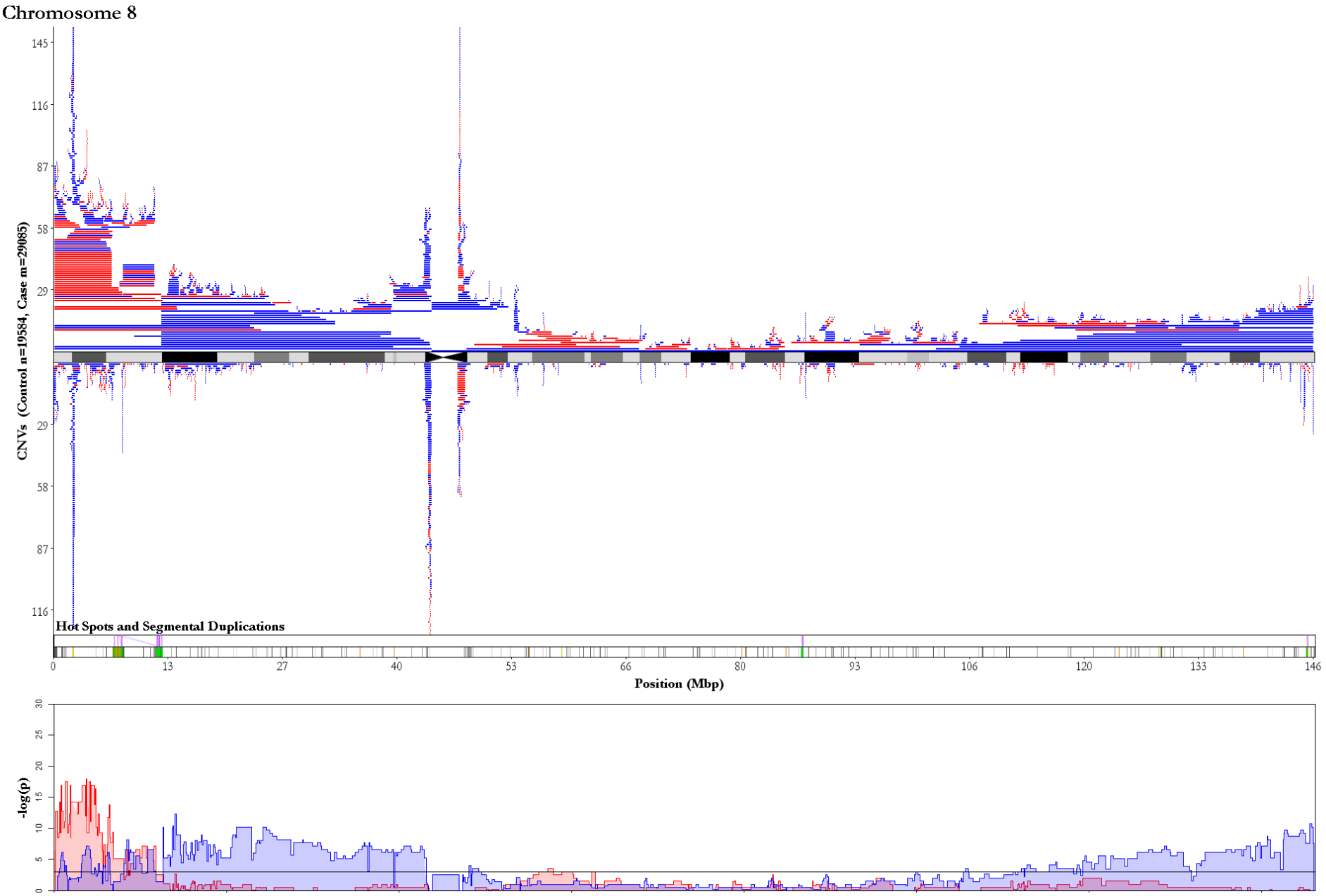
Supplementary Figure 3f



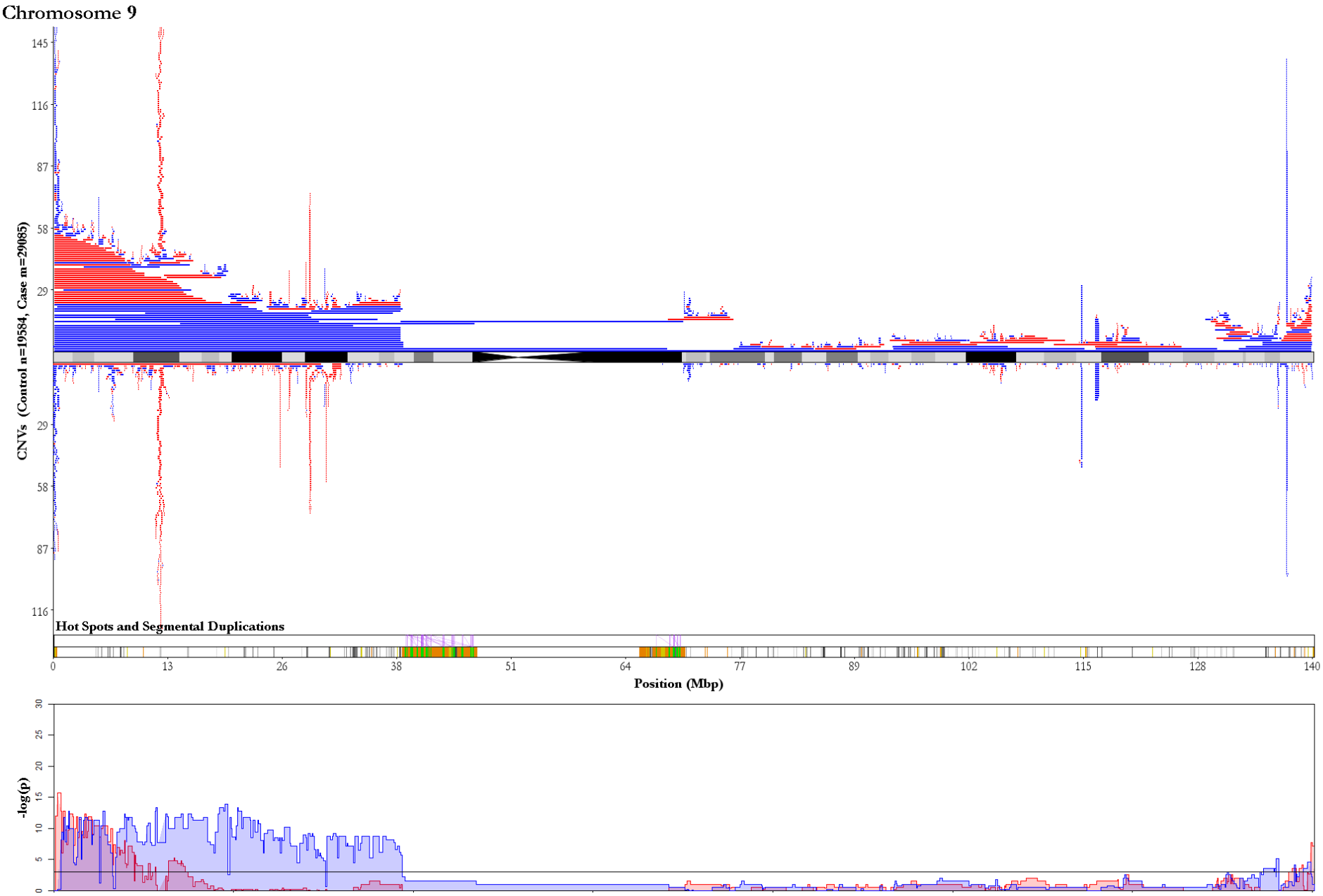
Supplementary Figure 3g



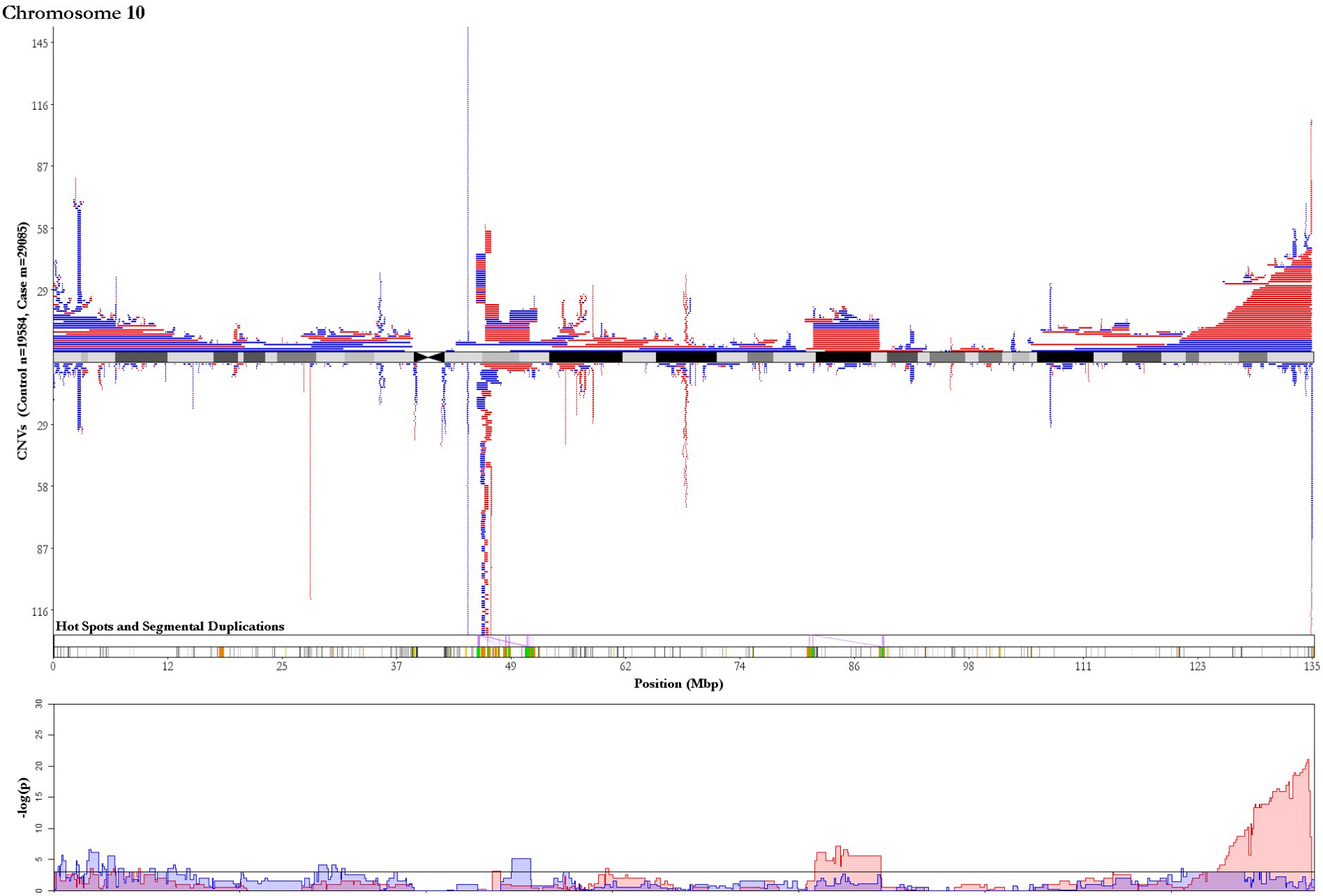
Supplementary Figure 3h



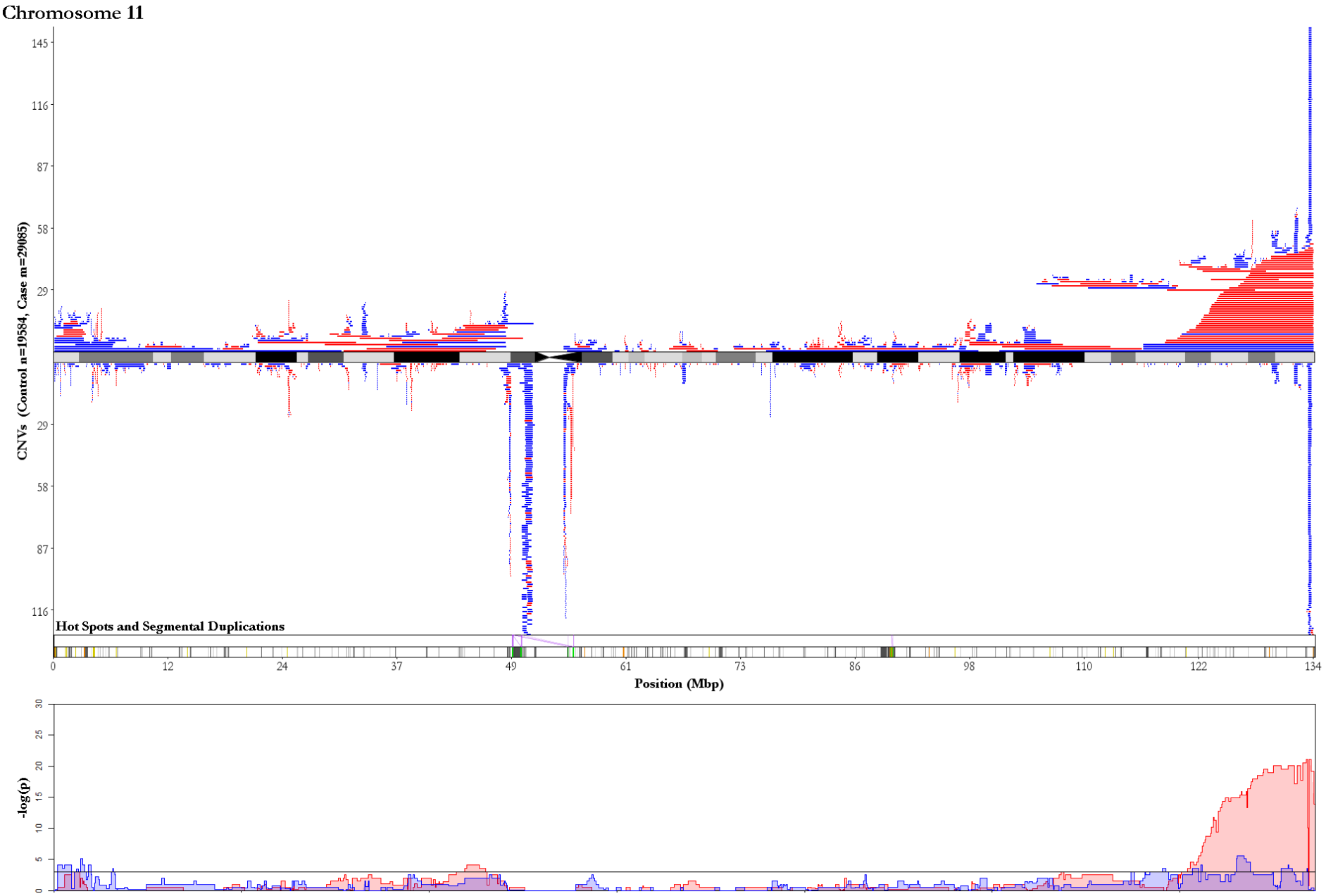
Supplementary Figure 3i



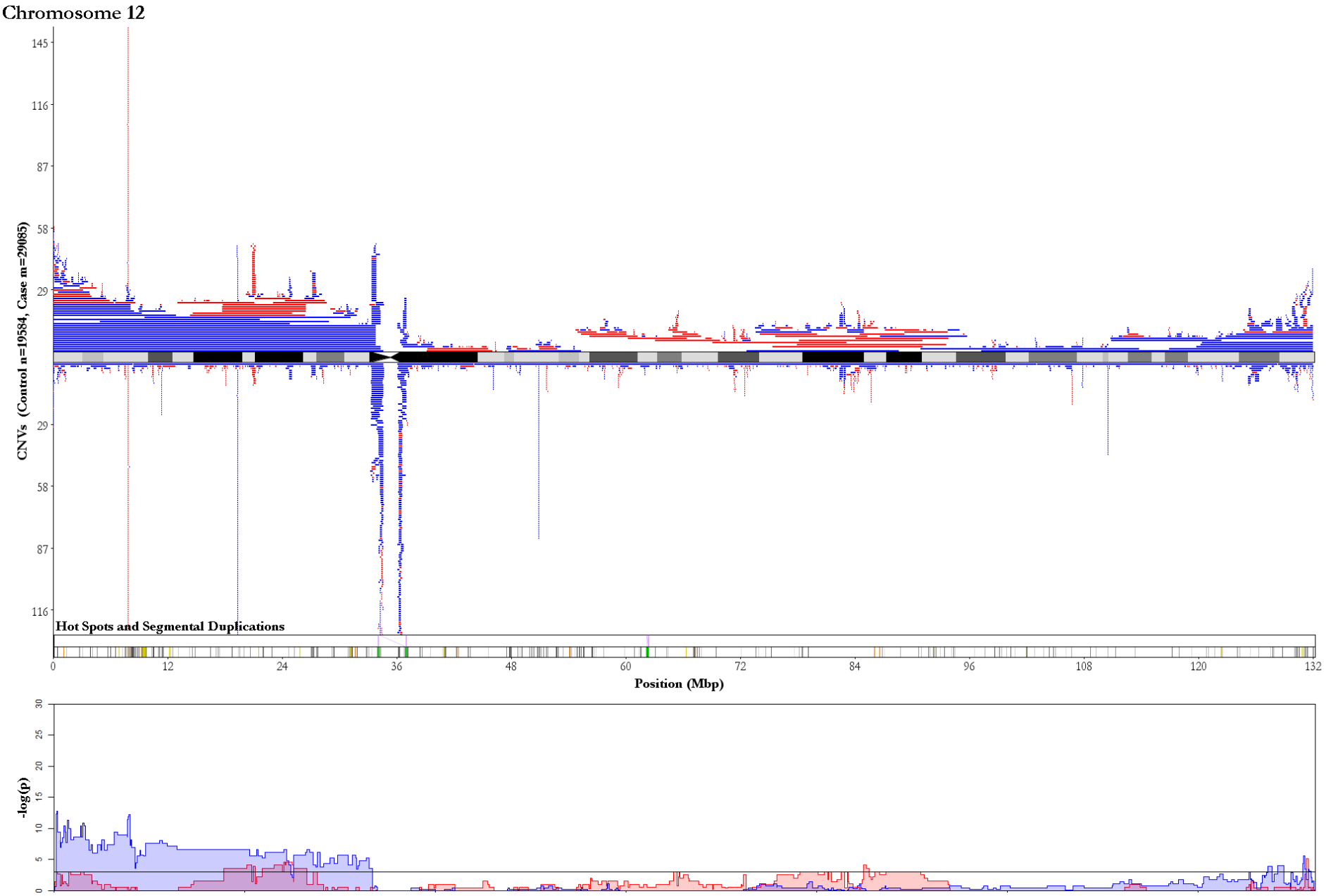
Supplementary Figure 3j



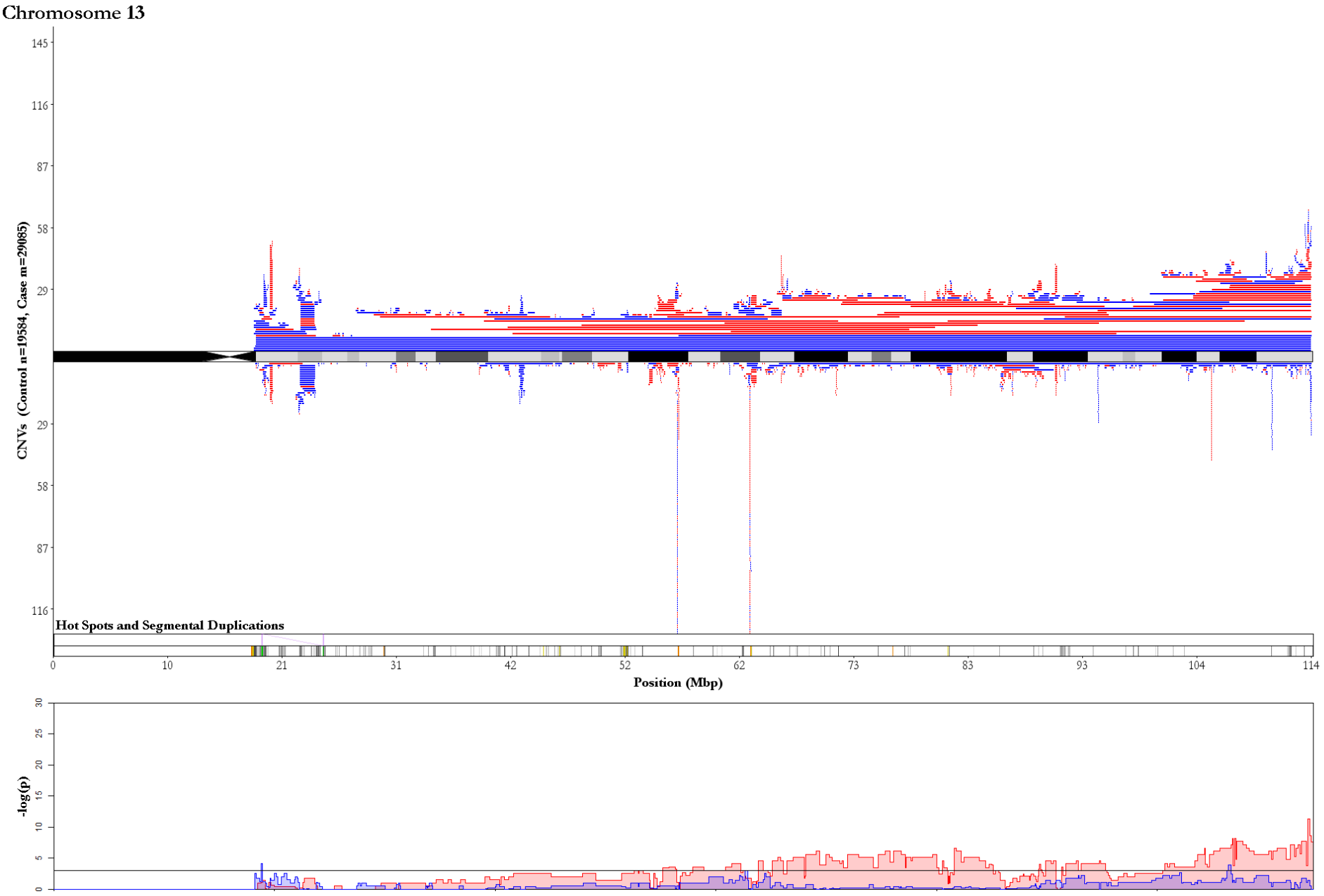
Supplementary Figure 3k



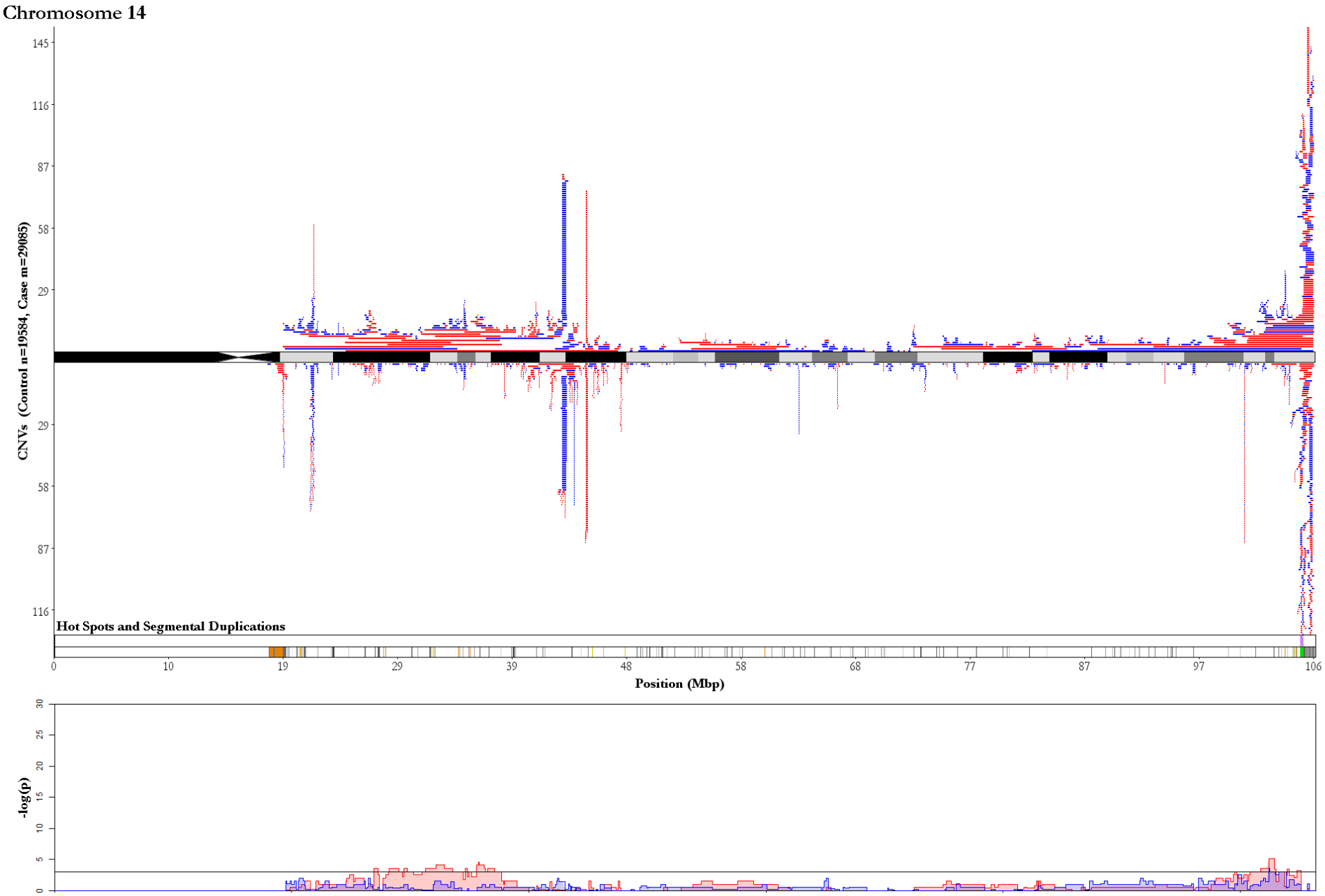
Supplementary Figure 3l



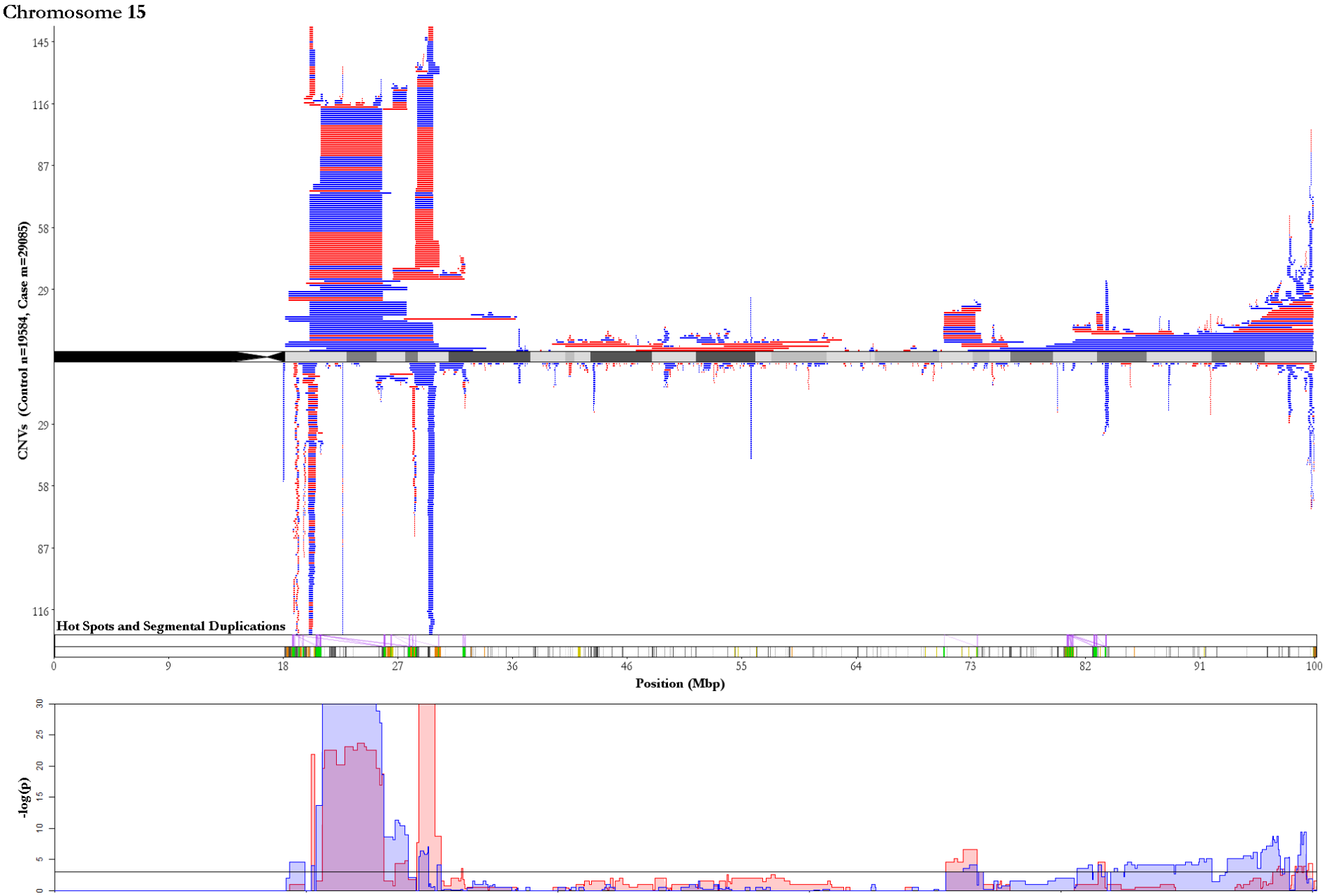
Supplementary Figure 3m



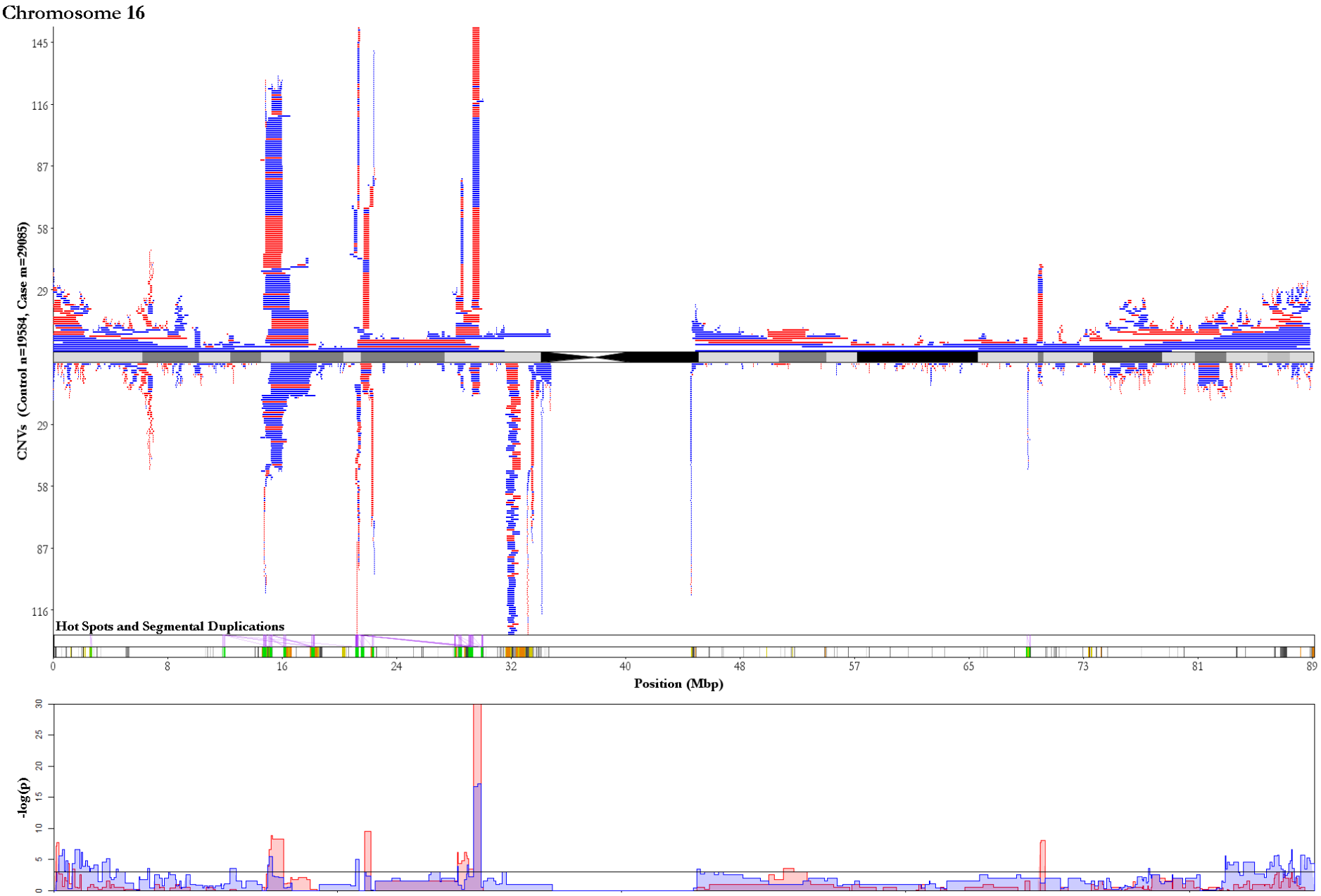
Supplementary Figure 3n



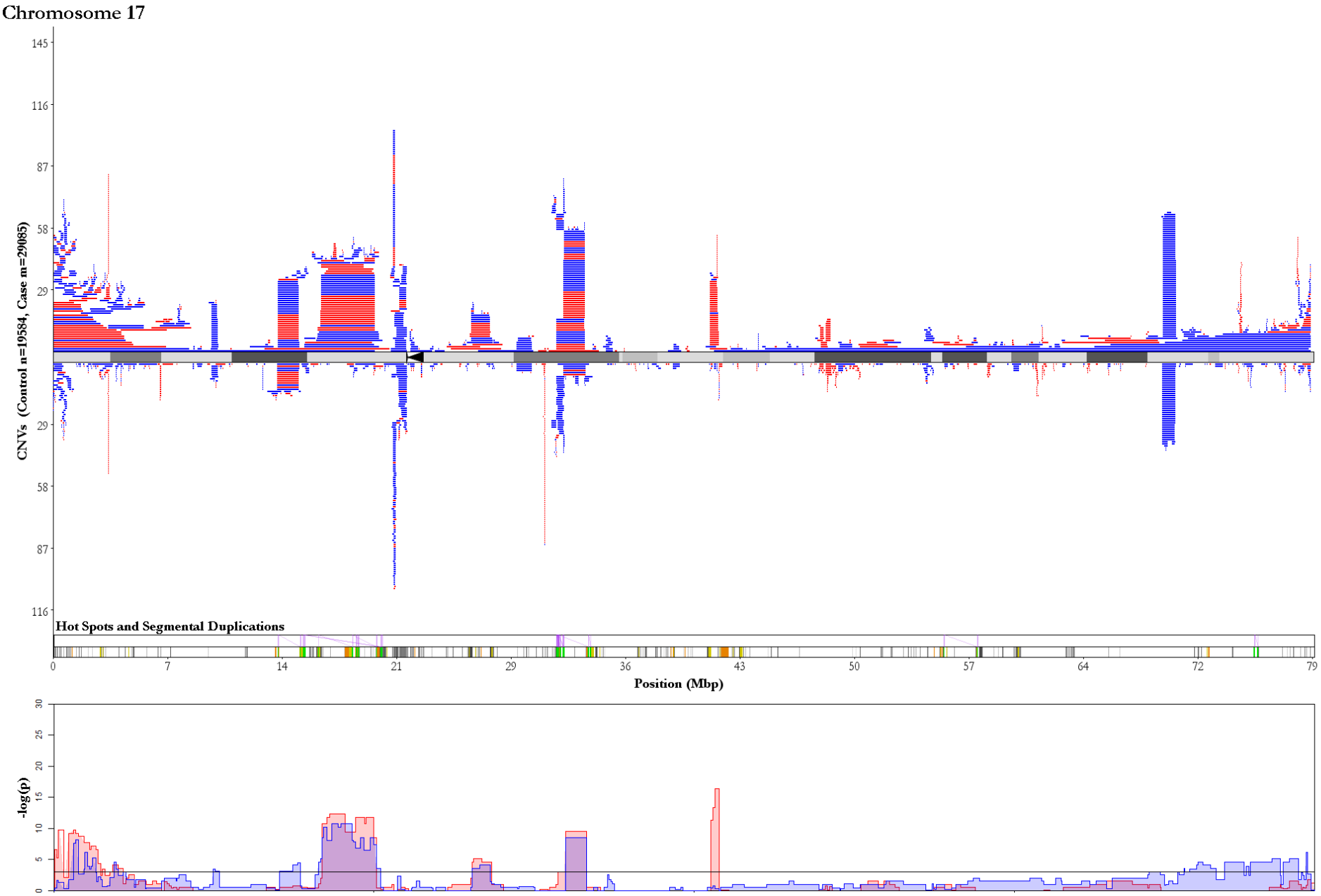
Supplementary Figure 3o



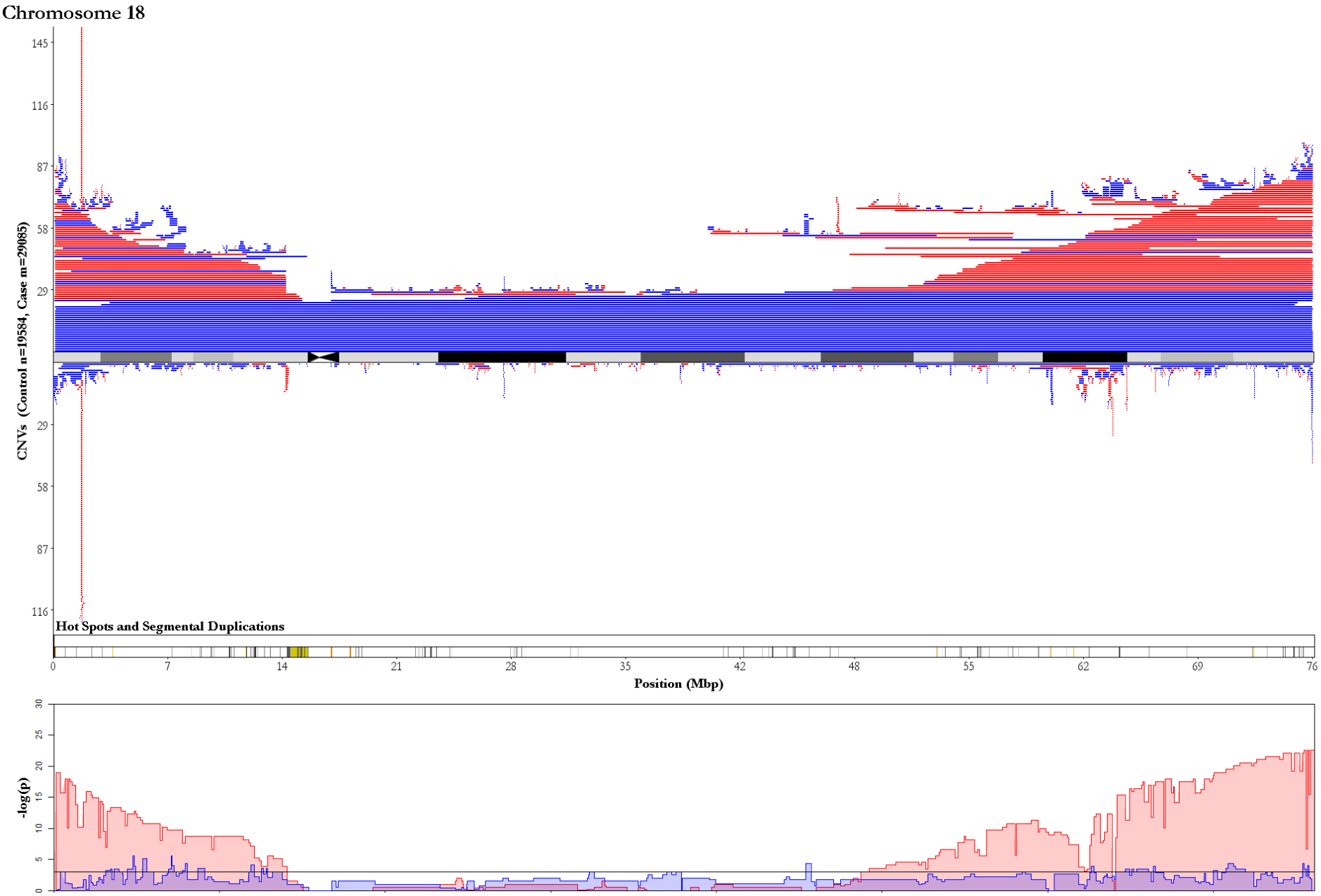
Supplementary Figure 3p



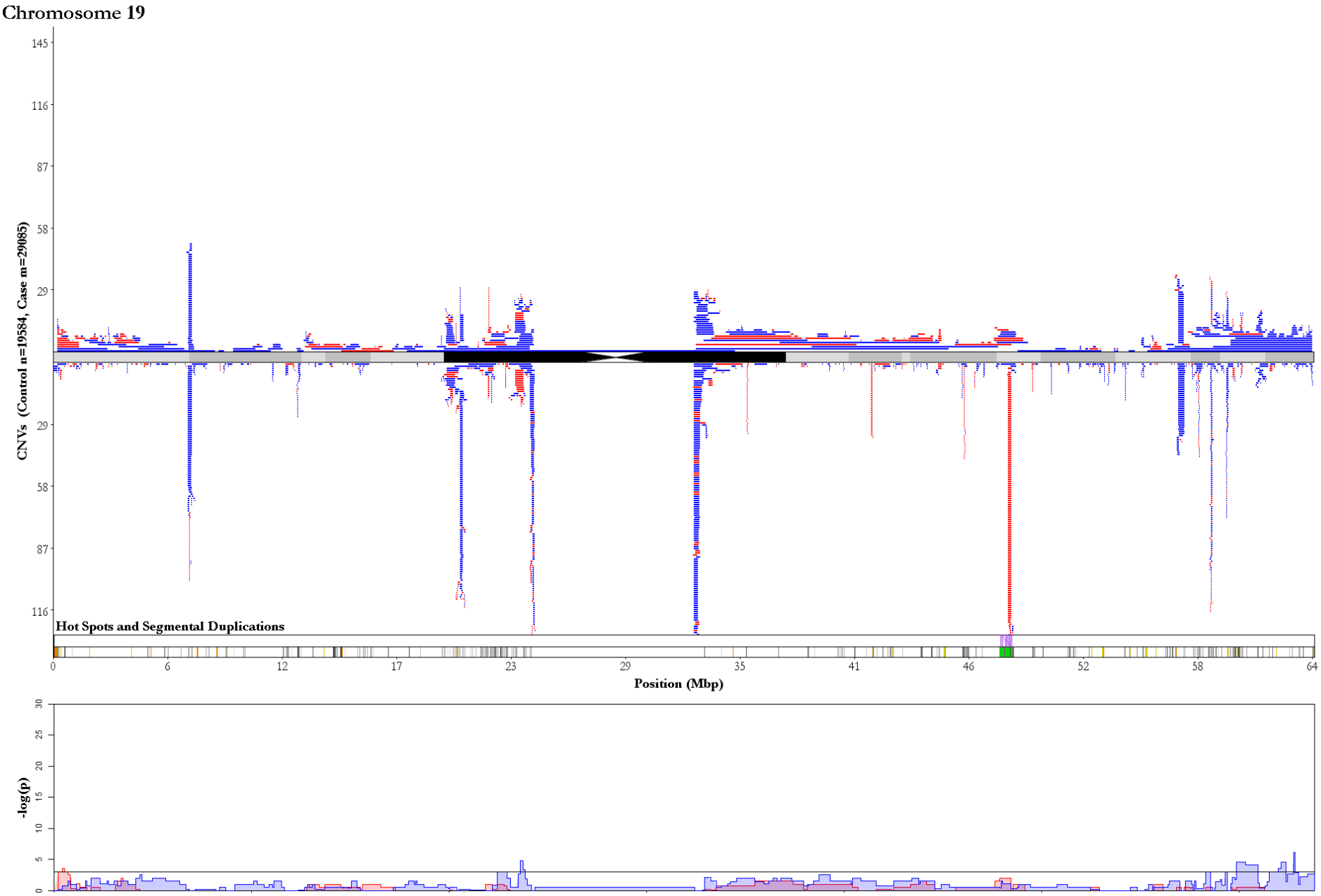
Supplementary Figure 3q



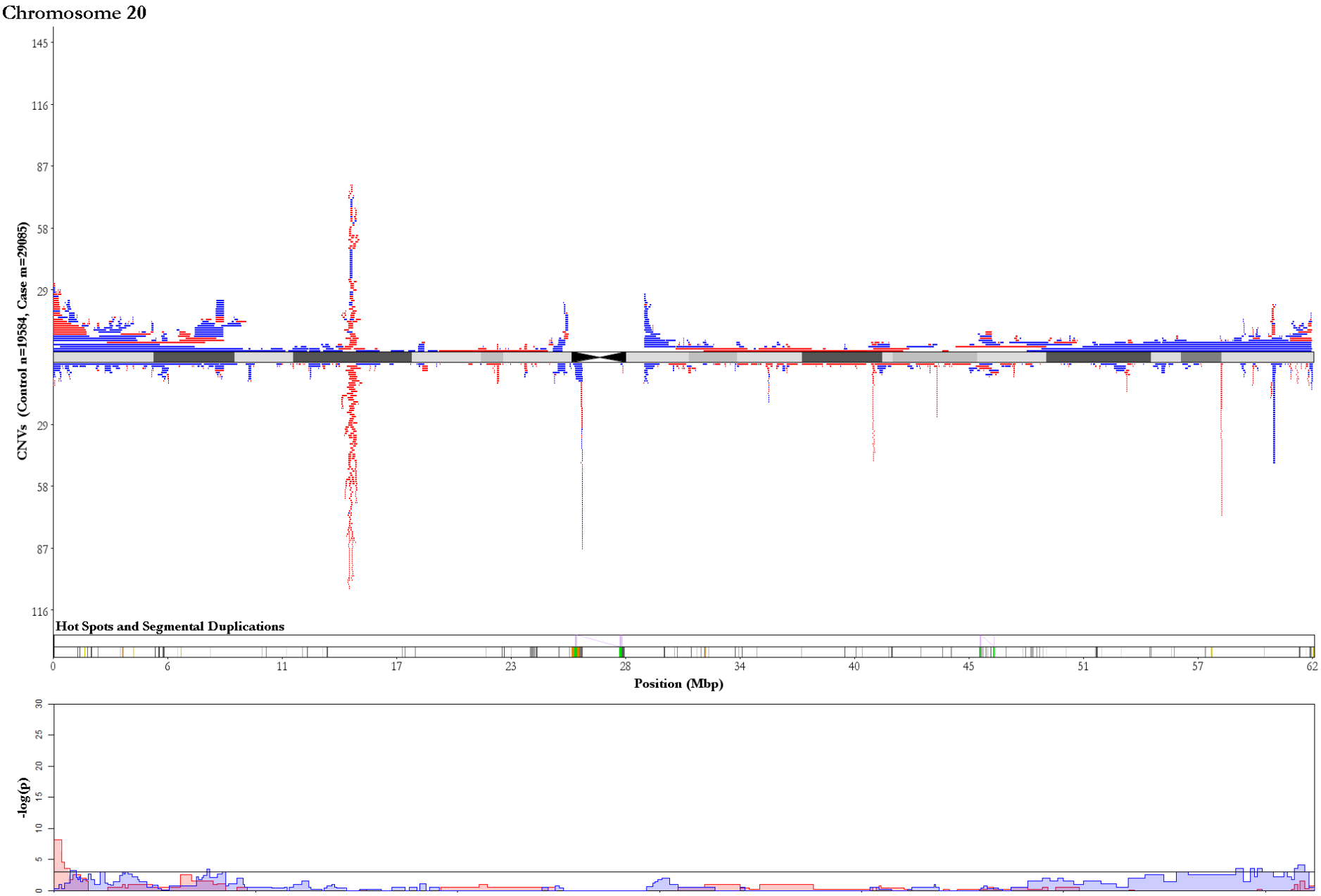
Supplementary Figure 3r



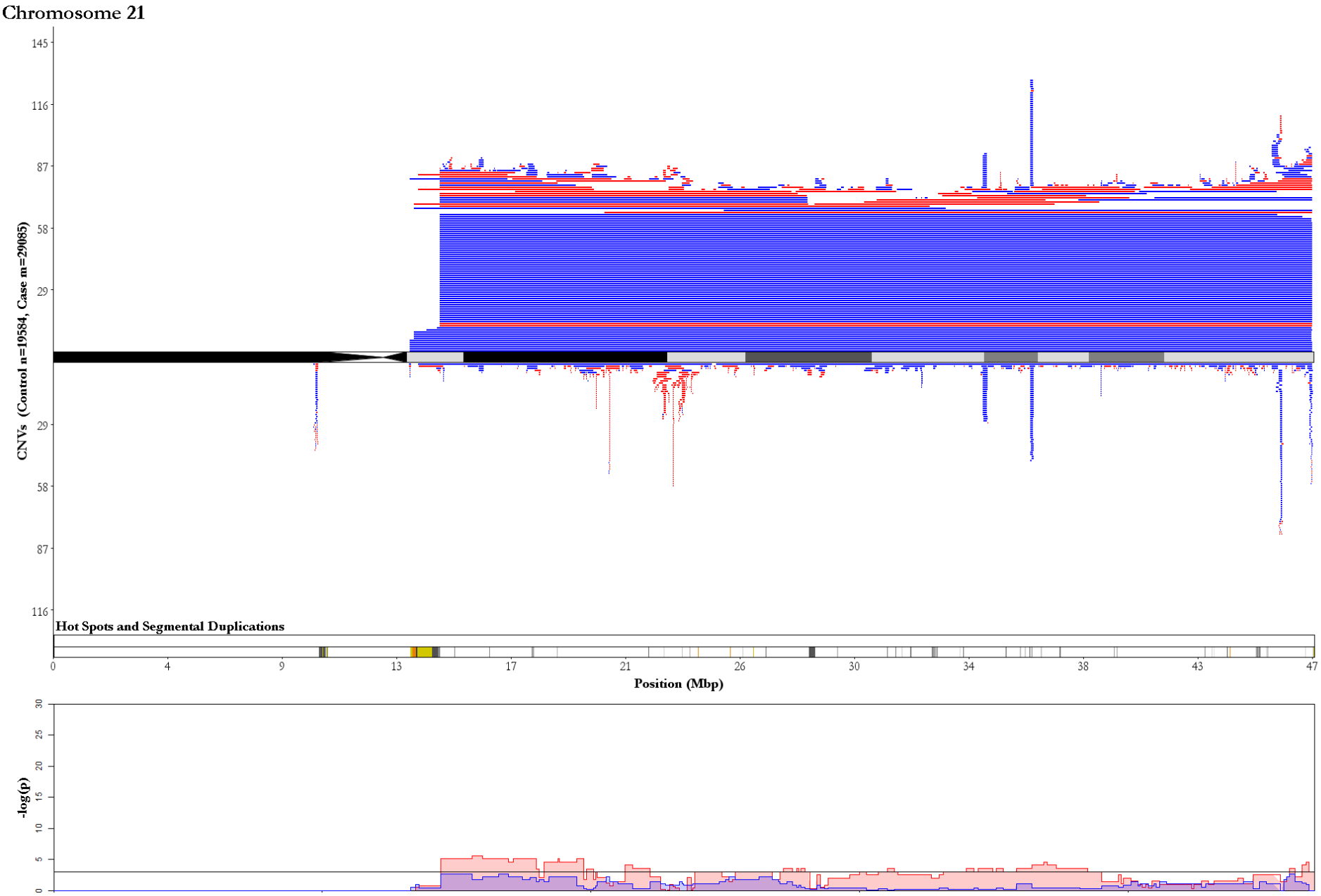
Supplementary Figure 3s



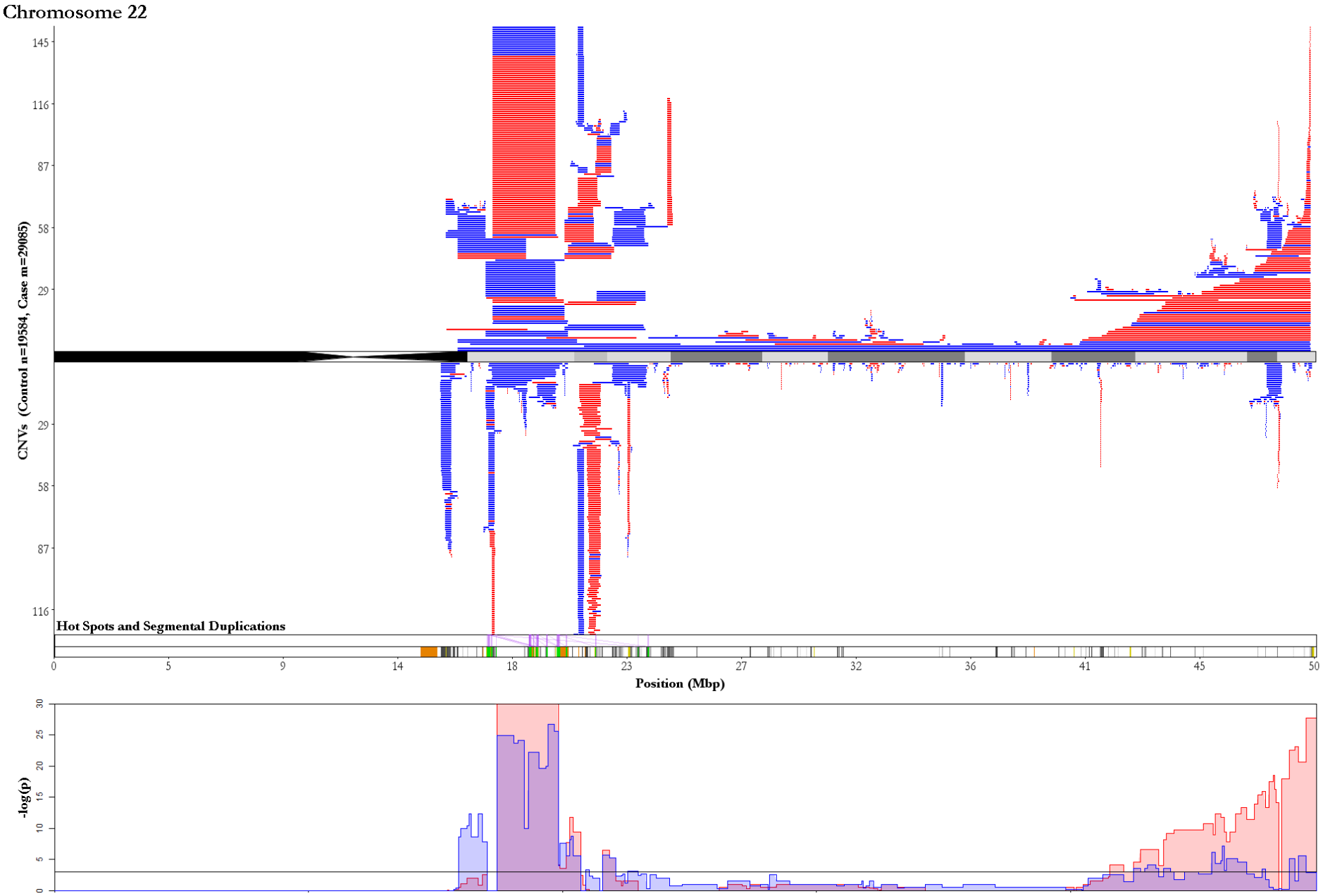
Supplementary Figure 3t



Supplementary Figure 3u



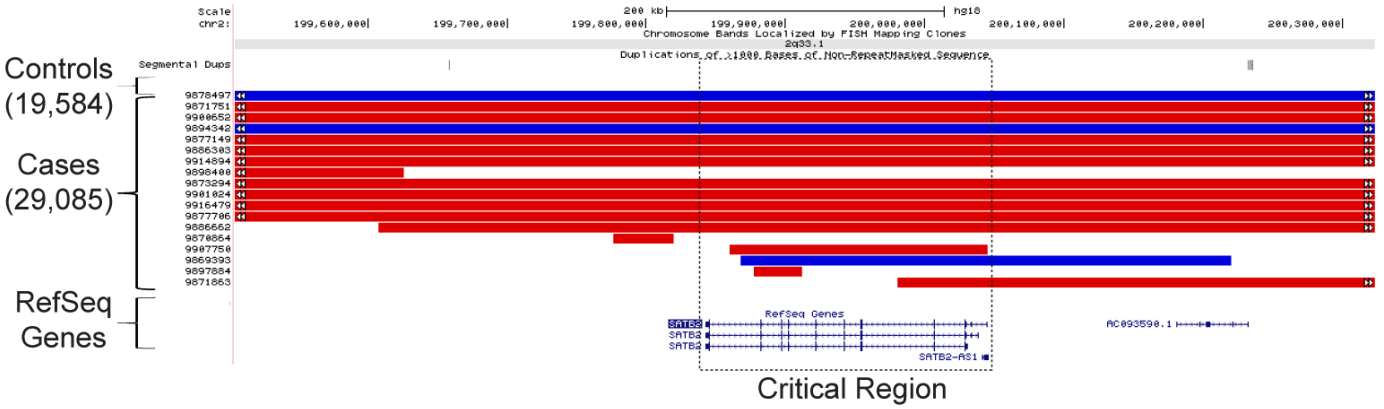
Supplementary Figure 3v



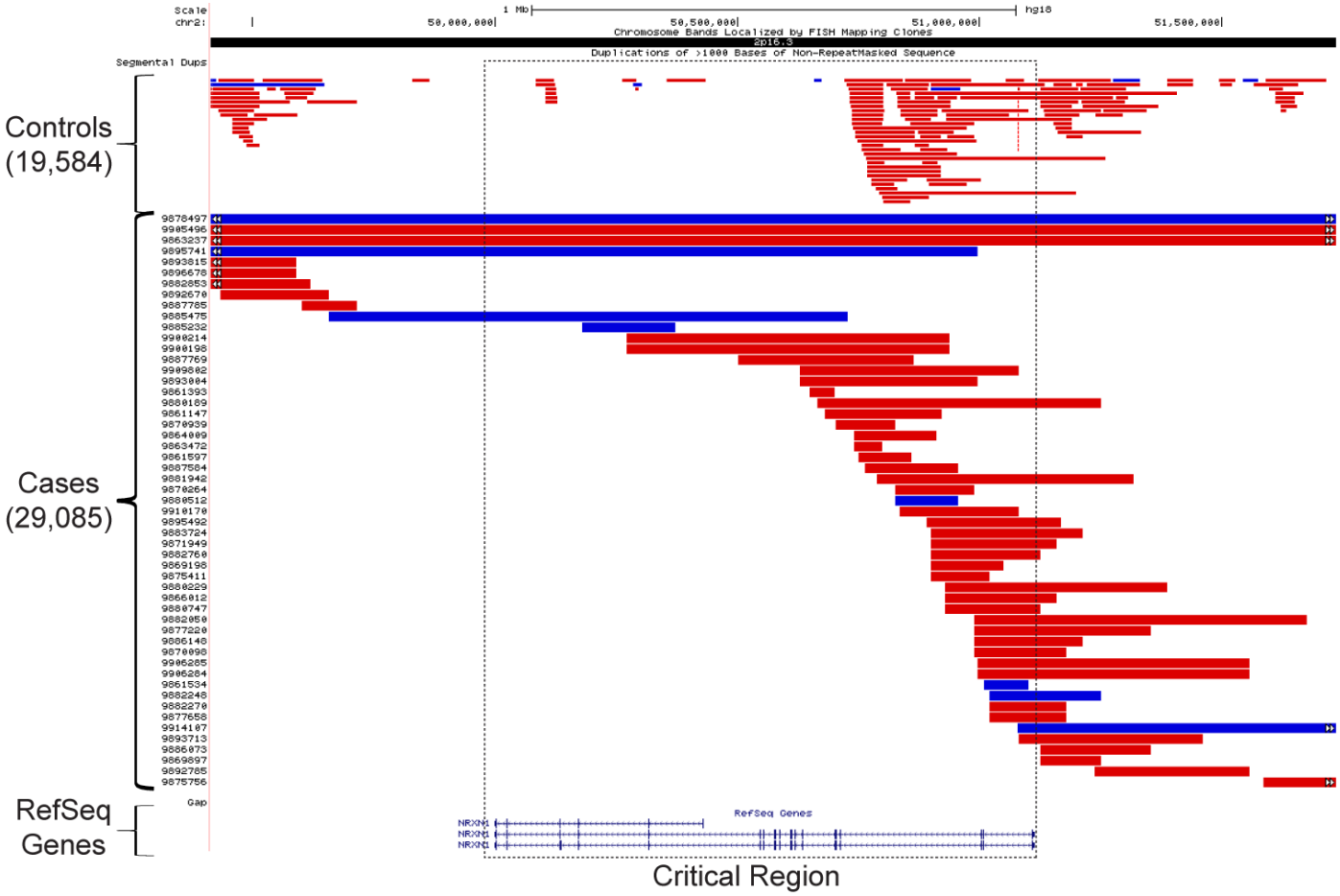
Supplementary Figure 4 – 14 Newly Significant Loci

Shown are UCSC Genome Browser (URL: http://genome.ucsc.edu/) screenshots for the 14 newly significant loci described in Table 2 (**a - m**). For each region the critical locus has been indicated by a dashed rectangle, either encompassing the critical gene or minimal region of overlap. CNVs that extend beyond the figure are indicated by white arrows at the edge of the display. All coordinates reference hg18.

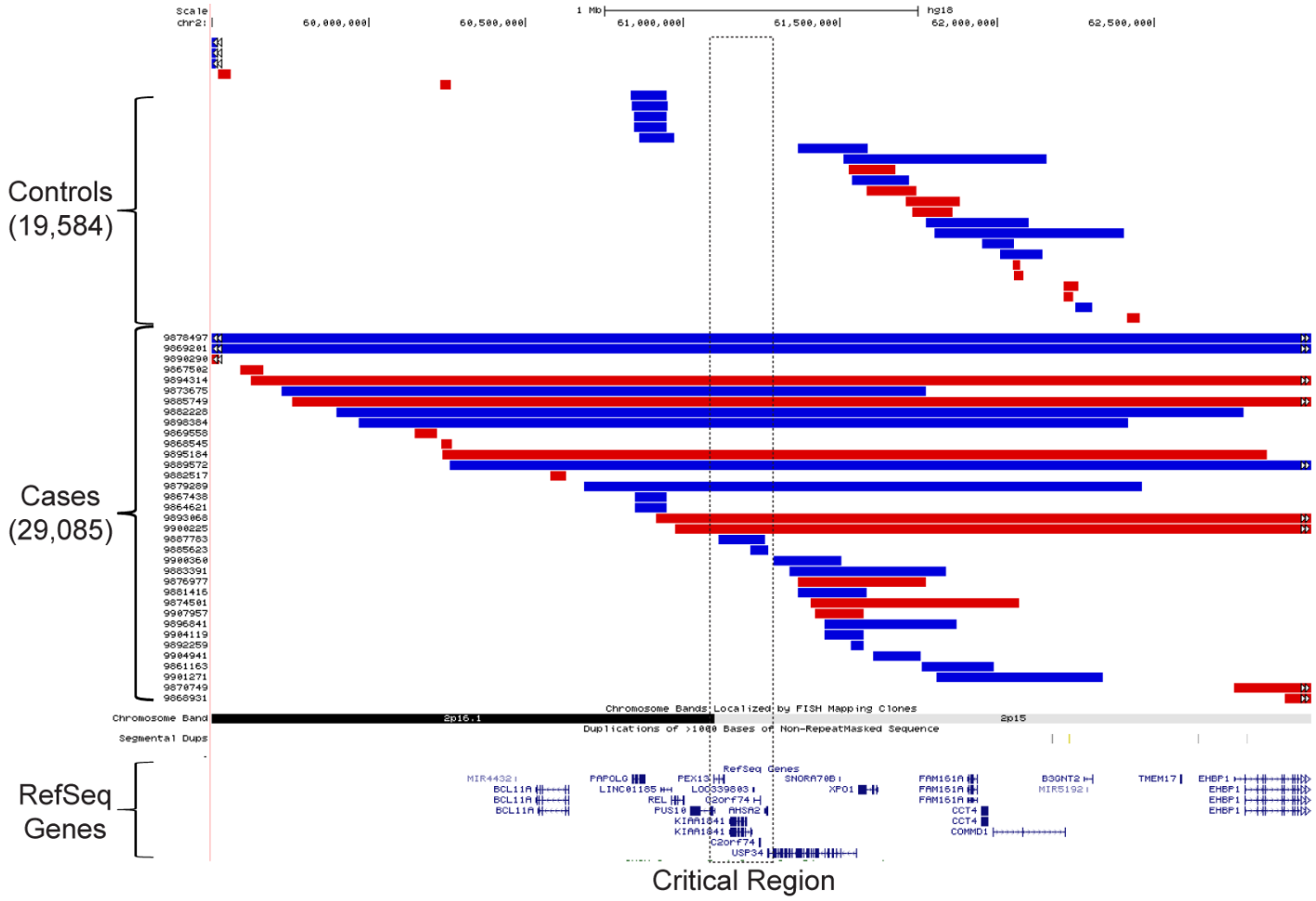
Supplementary Figure 4a



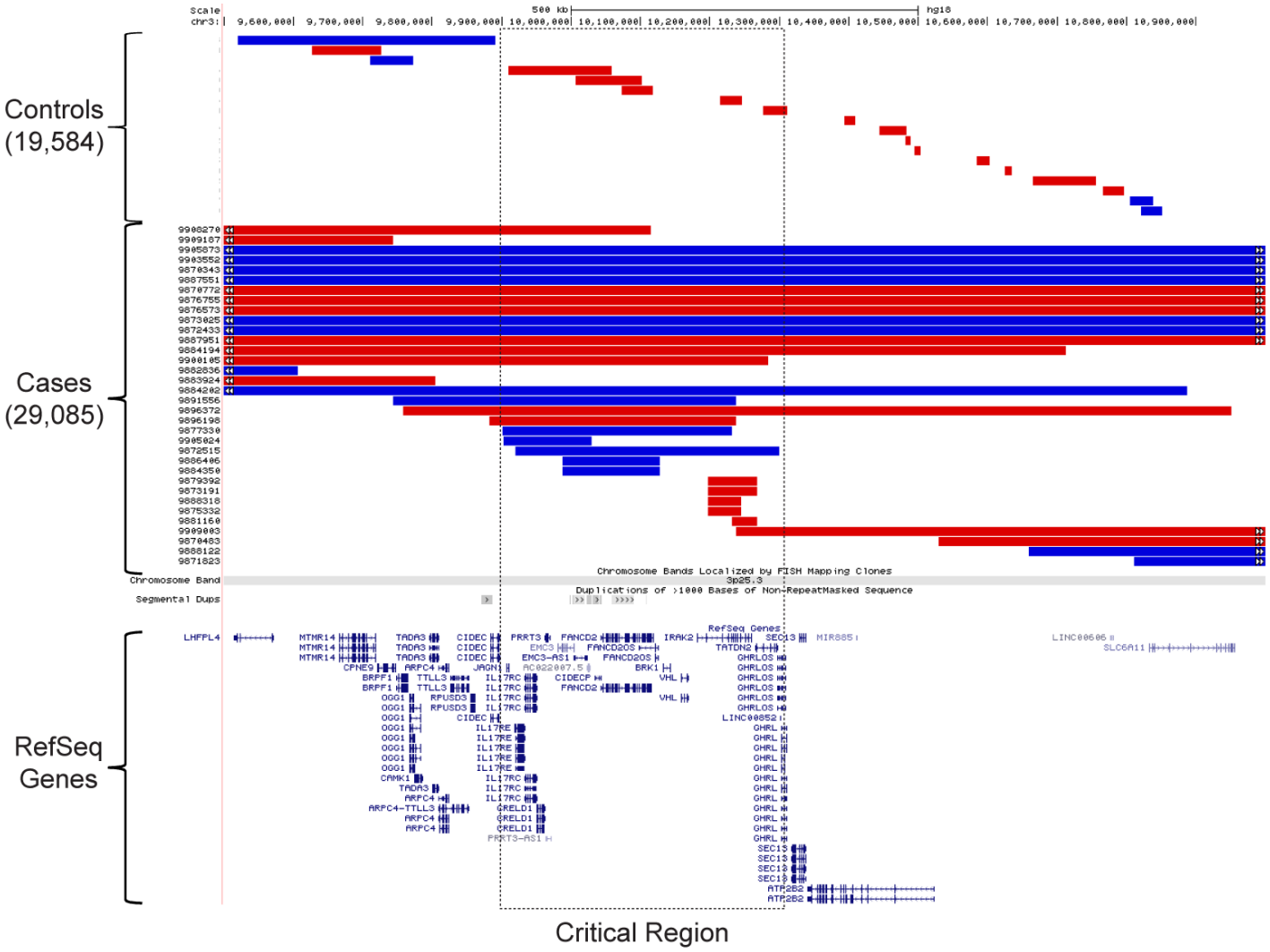
Supplementary Figure 4b



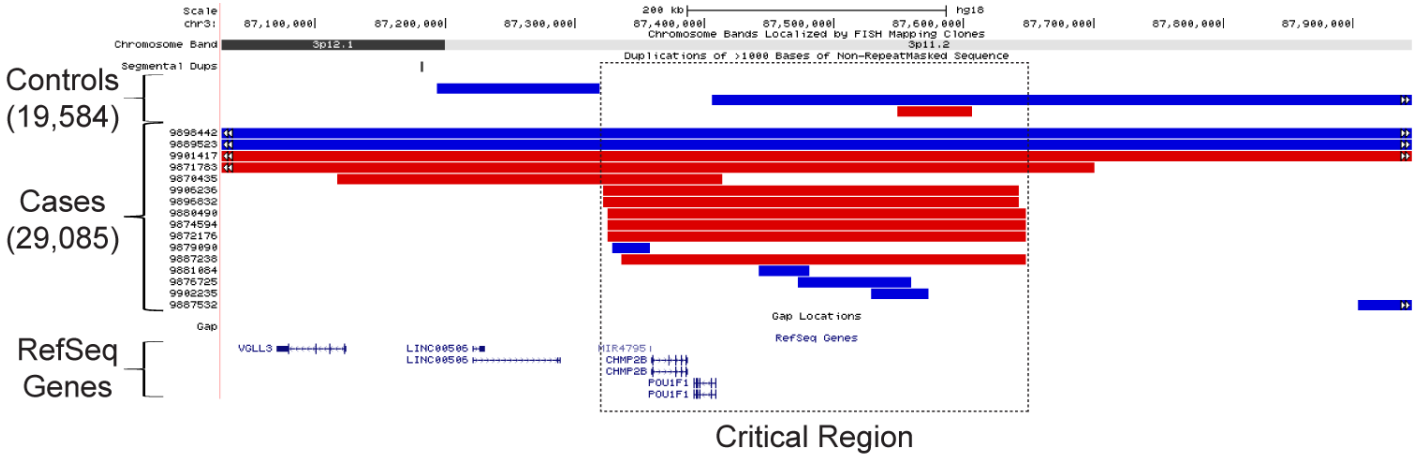
Supplementary Figure 4c



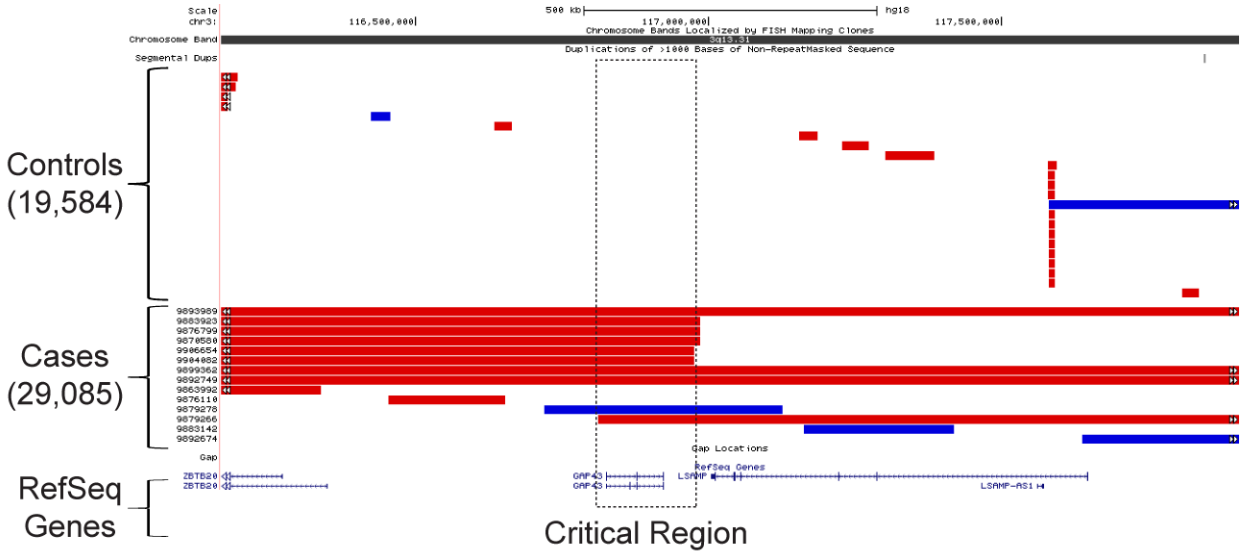
Supplementary Figure 4d



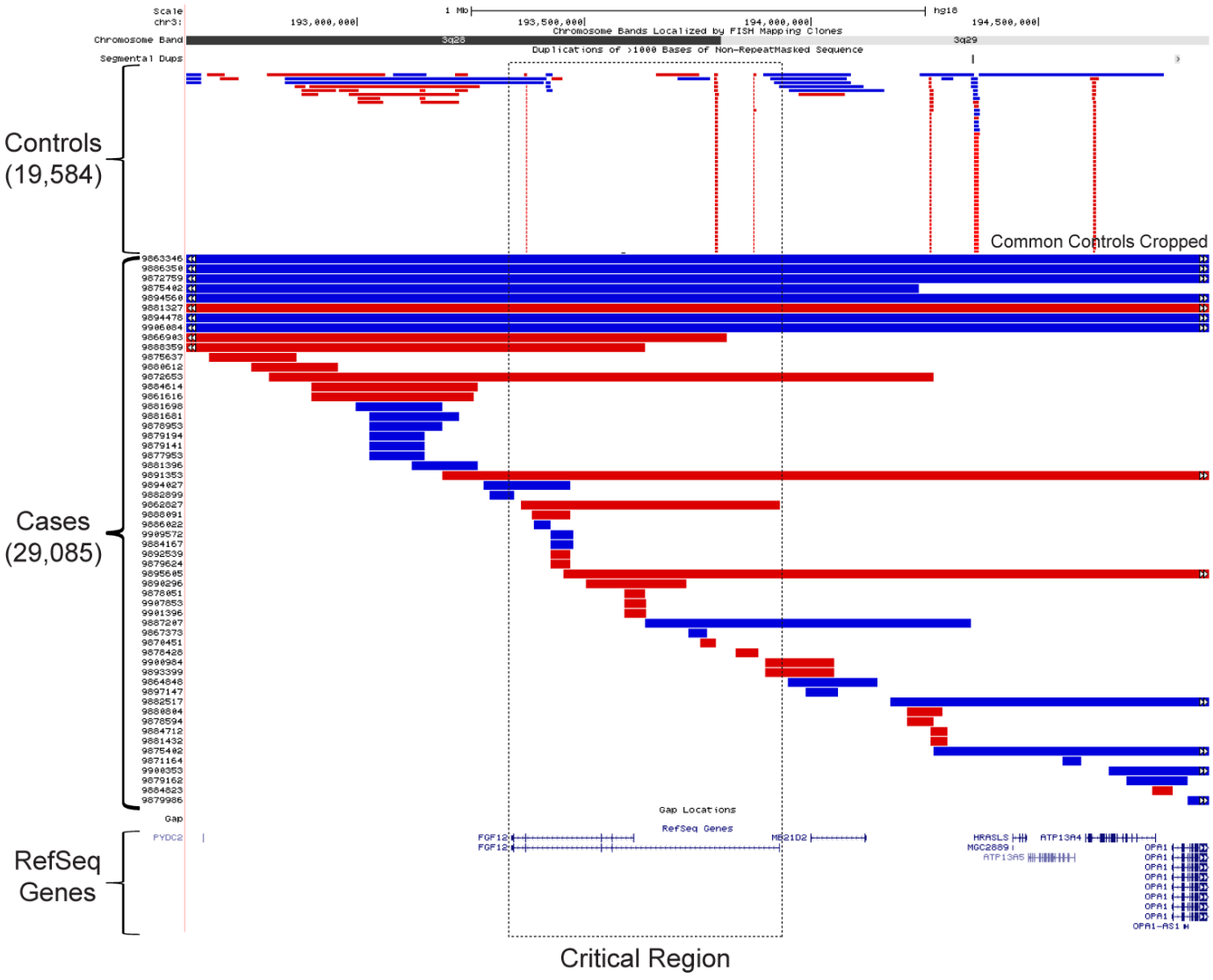
Supplementary Figure 4e



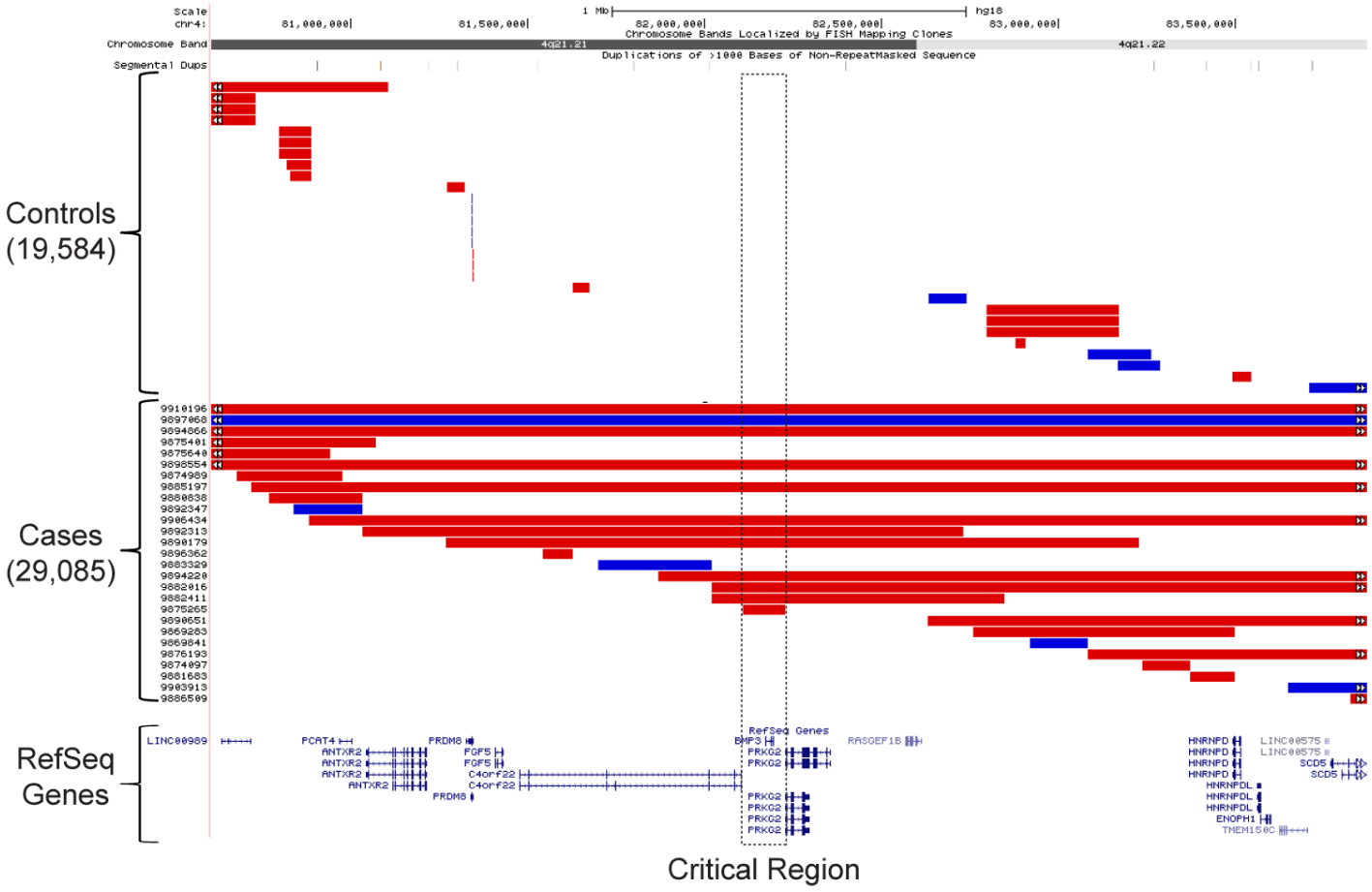
Supplementary Figure 4f



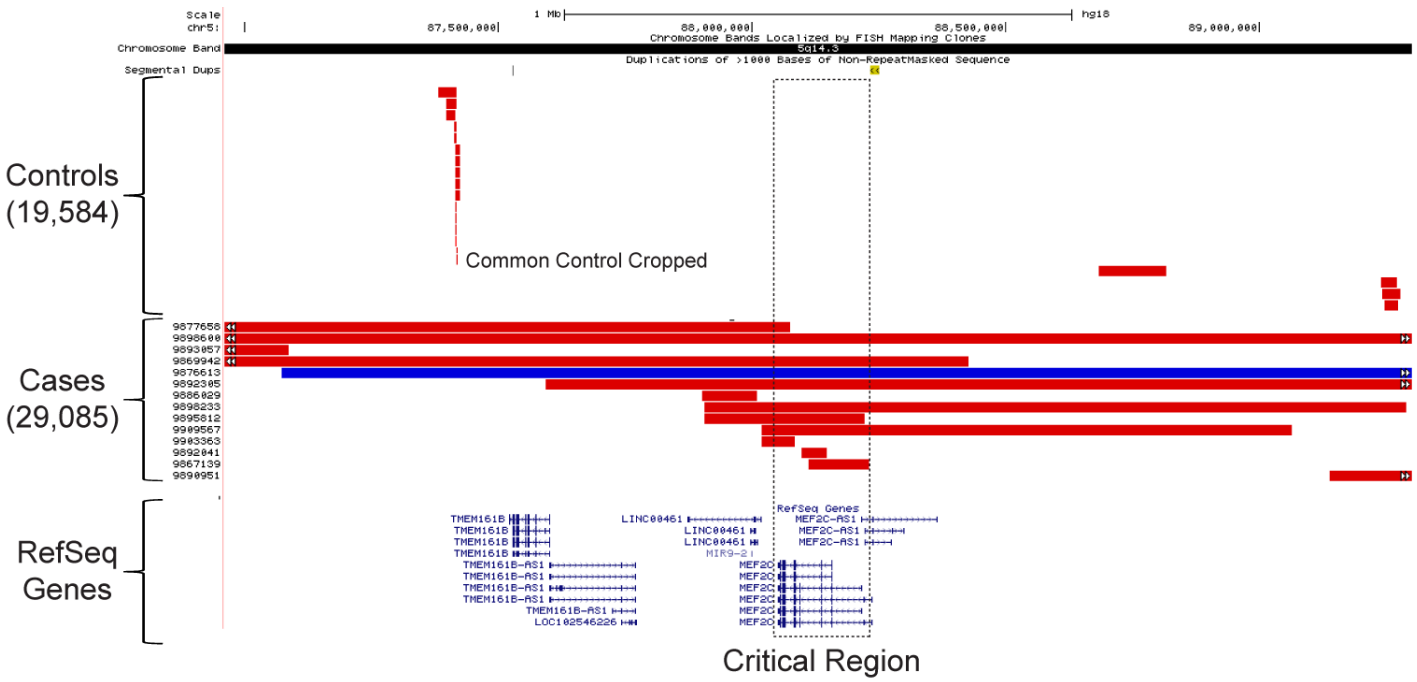
Supplementary Figure 4g



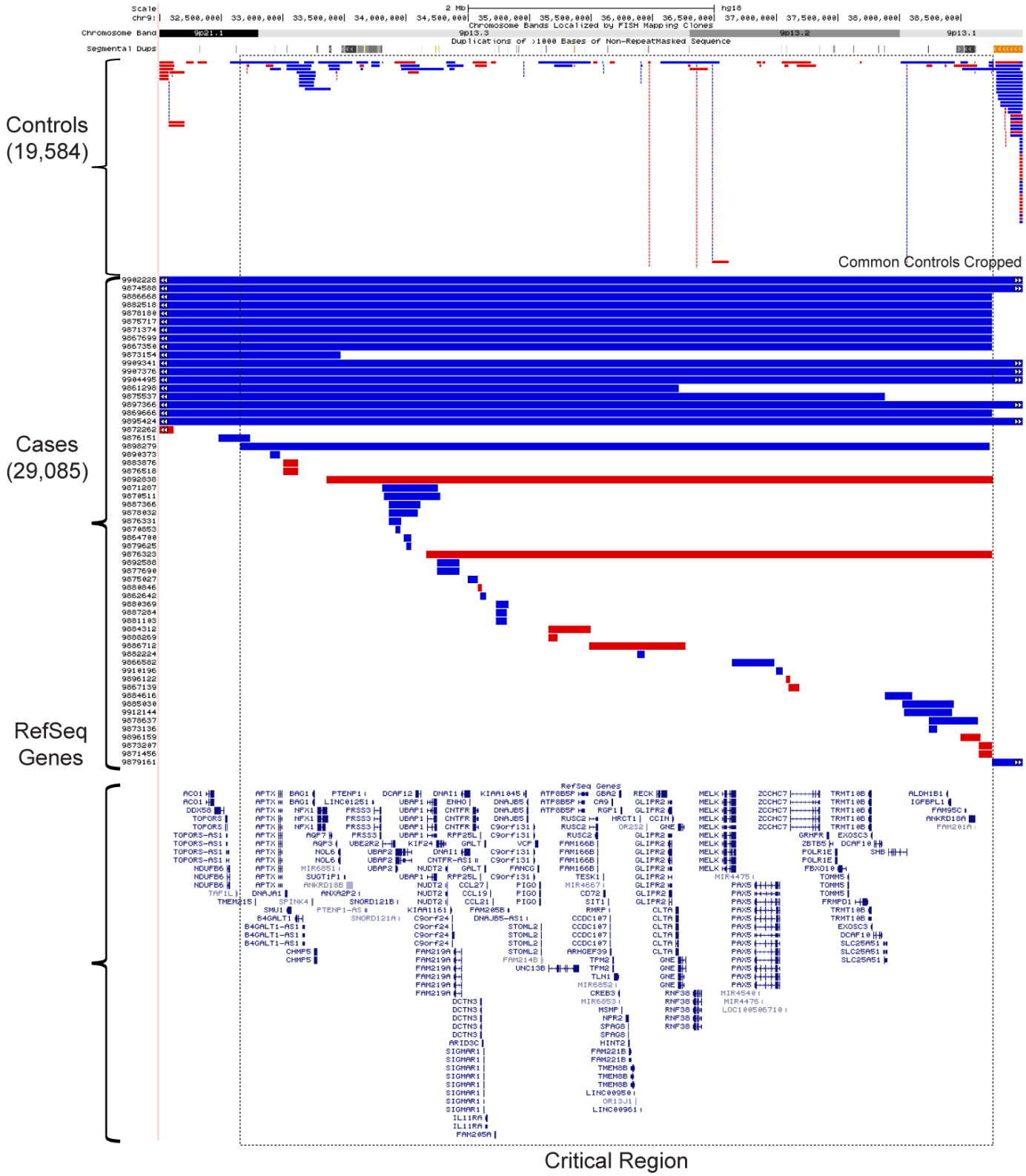
Supplementary Figure 4h



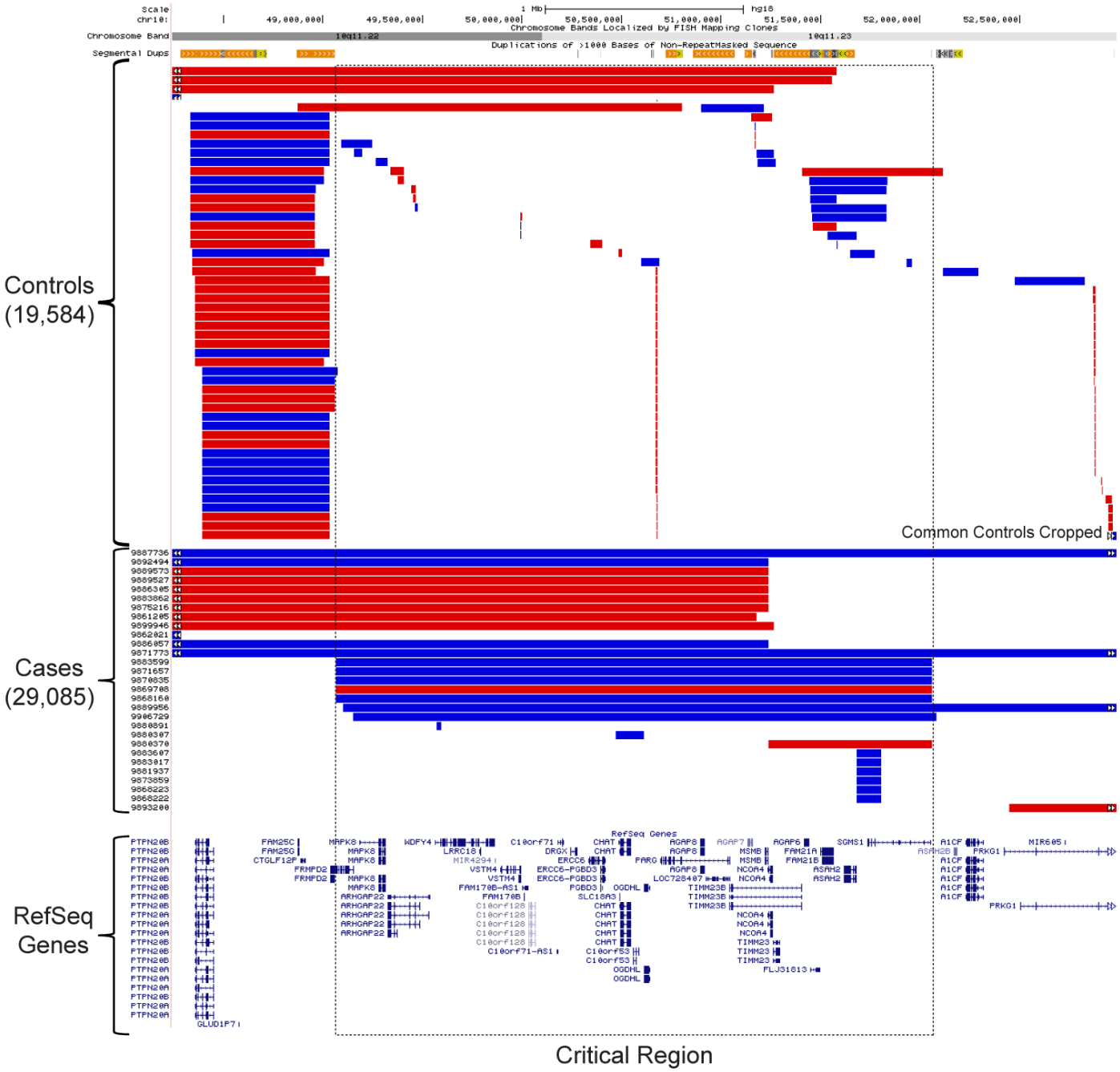
Supplementary Figure 4i



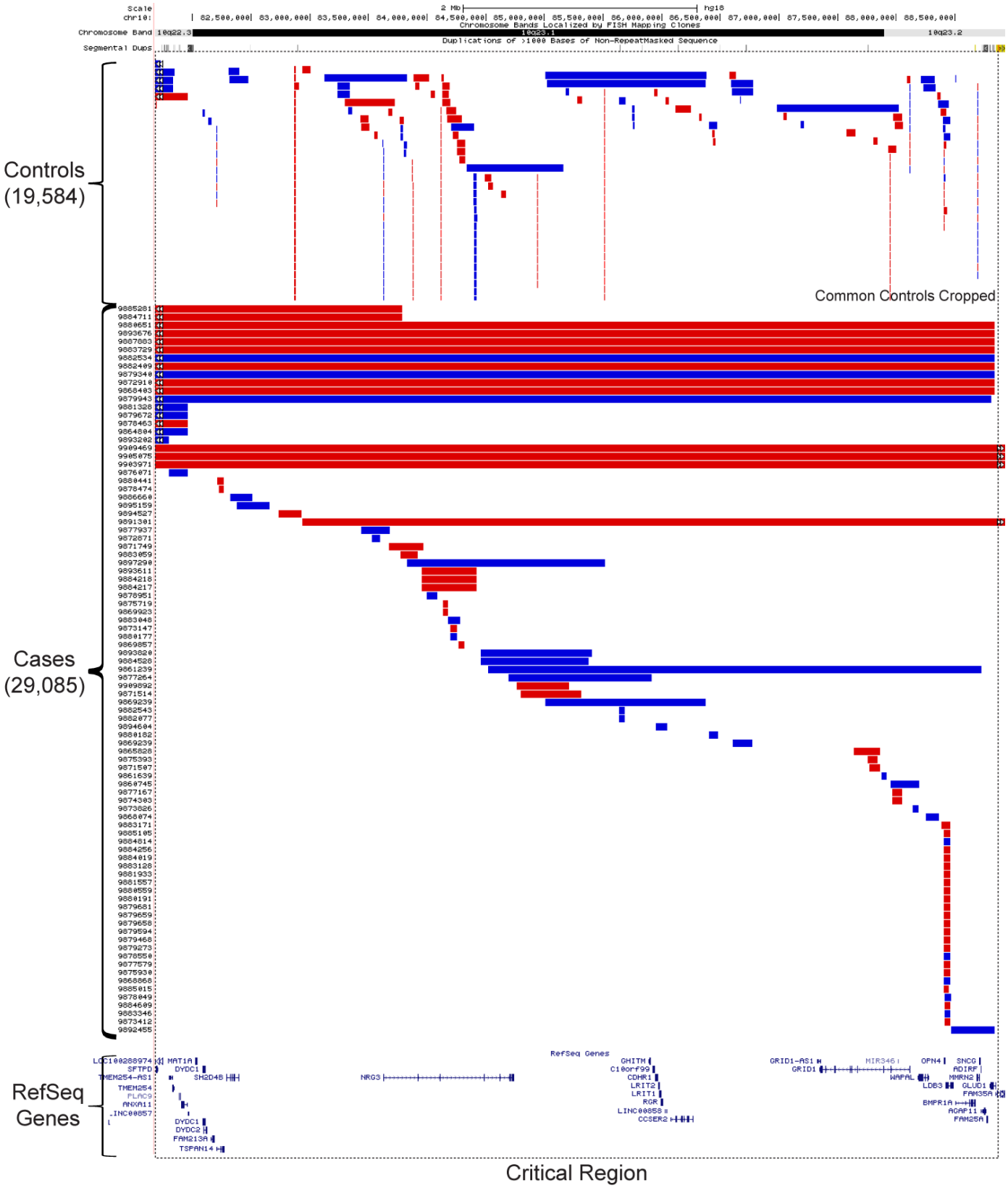
Supplementary Figure 4j



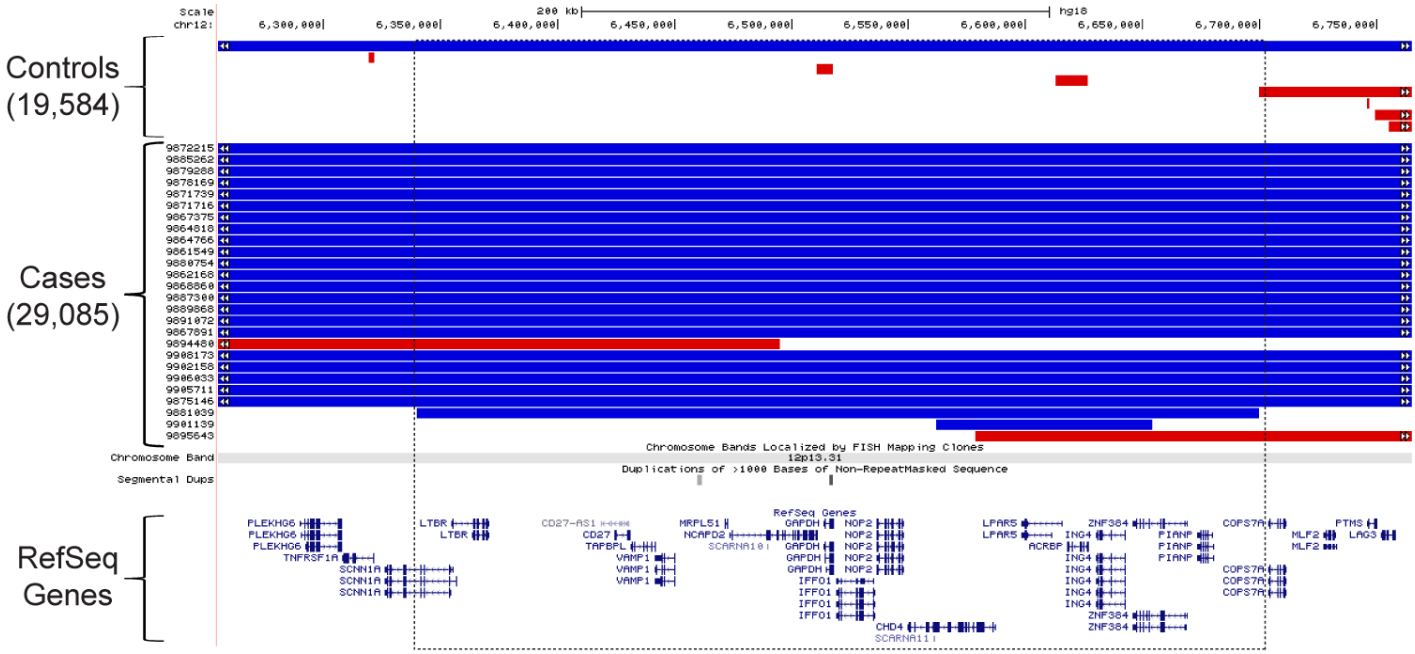
Supplementary Figure 4k



Supplementary Figure 4l

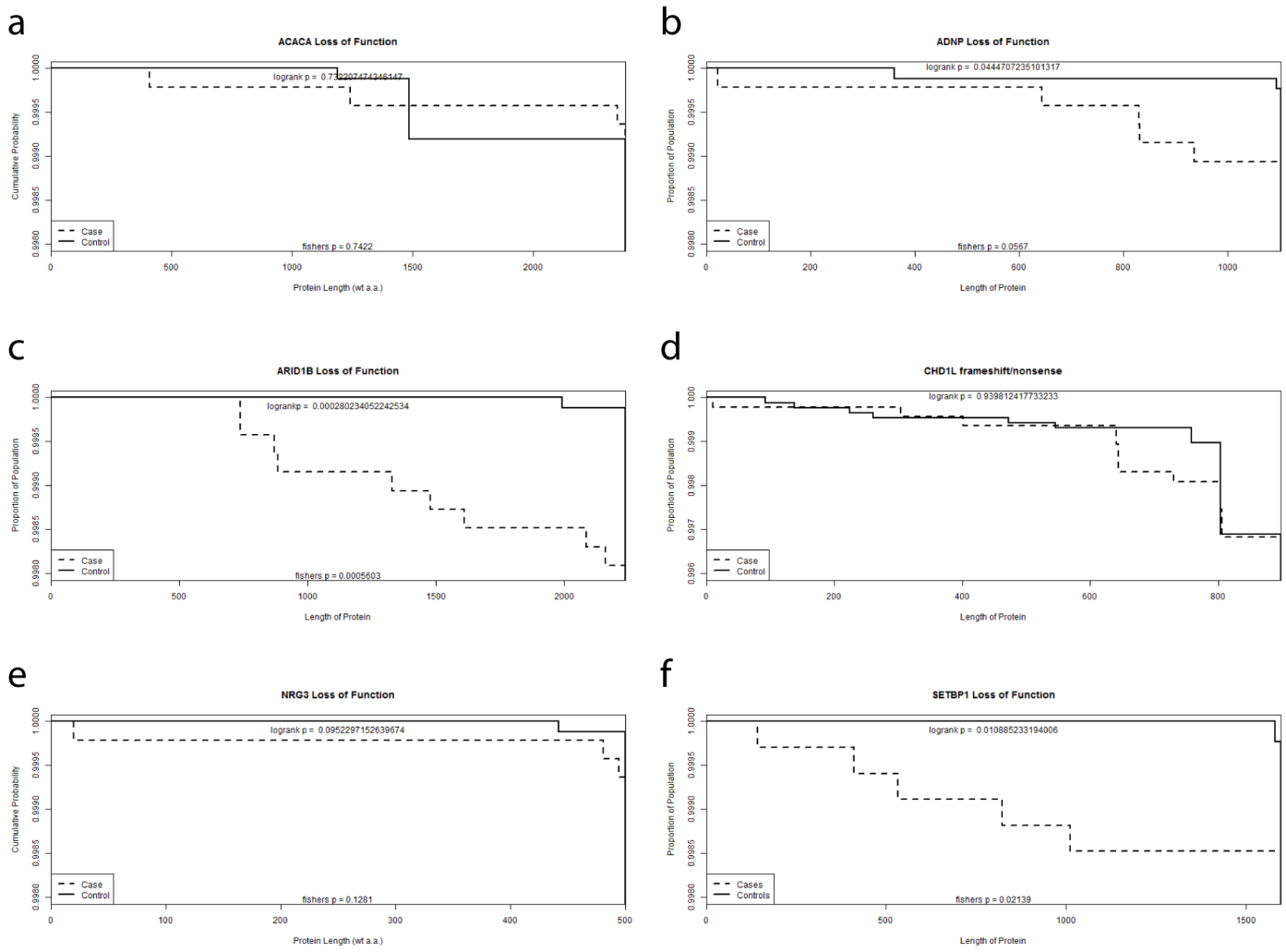


Supplementary Figure 4m



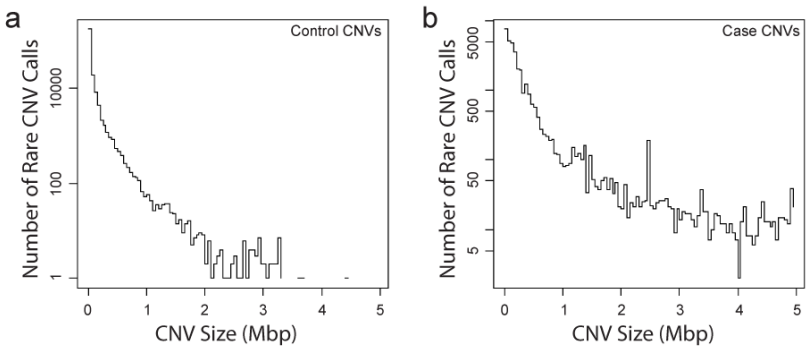
Supplementary Figure 5 – Predicted Effects of Truncating Mutations

Shown are predicted protein lengths for genes with truncating mutations in controls (**a - f**). Splice-site mutations were incorporated by deleting the most likely lost exon and determined the likely protein effect (in-frame loss or introduction of a frameshift/stop codon). All mutations were then expressed in terms of the predicted number of wild-type amino acids retained. Predicted protein lengths for ESP6500 and cases were compared using the log-rank test. For *CHD1L* (**d**) we did not incorporate splice-site variants due to the large number of control and case variants and the number of isoforms. For *SETBP1* (**f**) only cases with ID/DD are included in the presented calculation.



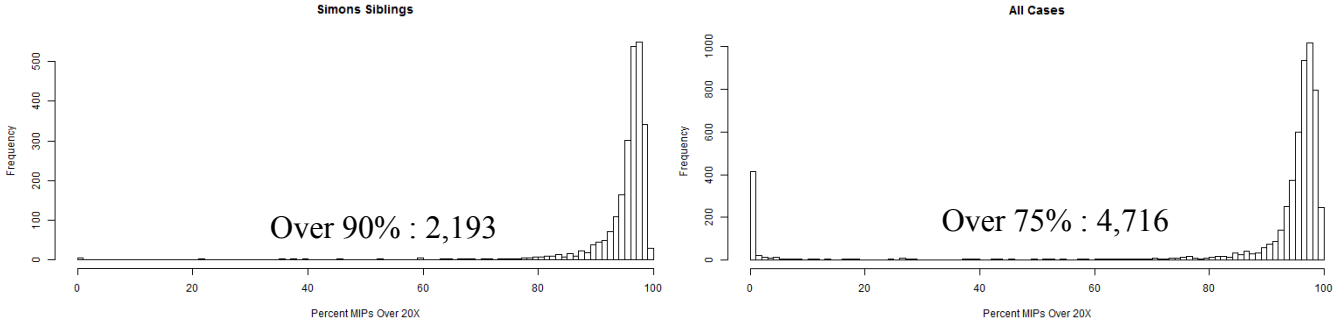
Supplementary Figure 6 – CNV Size Distribution in Cases and Controls

Shown is the distribution of CNV sizes detected in cases and controls.



Supplementary Figure 7 – QC of MIP Cohorts

Quality control analysis of the percentage of MIPs with at least 20 reads per sample.



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