Runs of homozygosity (ROH) reveal that segmental-UPD occurs as a result of recombination mediated repair of genomic imbalance

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INTRODUCTION

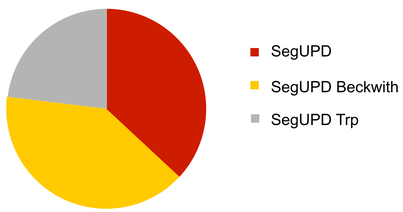
Whole chromosome UPD results from correction of trisomy and monosomy during embryogenesis. In contrast, segmental UPD (segUPD) is localized to specific chromosomal regions and the etiology and risks are not well understood. We show that segUPD occurs secondarily to recombination mediated selection driven repair of distinct genomic imbalances including deletions, derivative chromosomes and inverted duplication/deletions. Although the genetic lesion may be "repaired", segUPD is associated with residual clinical risks.

METHODS

The Affymetrix Cytoscan HD single nucleotide polymorphism (SNP) array was used to detect runs of homozygosity (ROH) associated with UPD. Cases were collected using criteria of positive UPD testing results, evidence of prior genetic abnormality located at the location of the ROH, mosaicism for the ROH, or ROH associated with a contiguous triplication.

RESULTS

65 cases of terminal segUPD were identified in prenatal, constitutional and product of conception testing



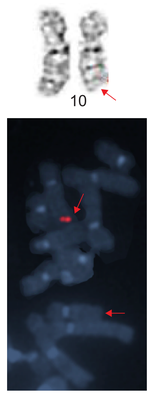
- 26 Beckwith-Wiedemann syndrome cases at 11p
- 15 cases with adjacent triplication
- 24 additional cases including 5 indicated in chart below and in figures 1 to 5

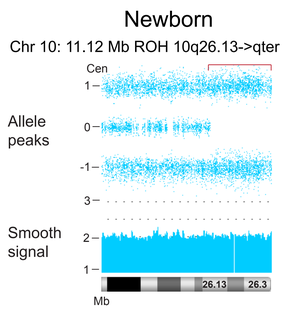
Case	SegUPD	ROH (Mb)	Source/Age	Indication
1	1pter->p36.13	16.32	AF	*NIPT: terminal del(1)(p36.23), dup(1)(p36.23p36.22)
2	1pter->p36.22	9.39	PB/9.3yr	Multiple congenital anomalies; der(1)(1;17) prior amniotic fluid analysis
5	10q26.13->qter	11.12	PB/Newborn	*CVS: del (10)(q26->qter)
21	15q13.3->q15.2 (15%) 15q15.2->q22.31 (45%) 15q22.31->qter (75%)	71.24	PB/12yr	Short stature, developmental delay
24	21q21.1->q22.2[a] (40%)	24.38	PB/29yr	Possible trisomy, developmental disorder of scholastic skills

*No clinical abnormalities observed
[a] seg-UPD likely extending to terminus of 21q
PB=peripheral blood AF=amniotic fluid

Figure 1

Case 5: CVS reveals a FISH confirmed terminal deletion of 10q26.13->qter that is replaced with 11.12 Mb segUPD mat in newborn





Paternal exclusions indicate segUPDmat

Biparental Inheritance

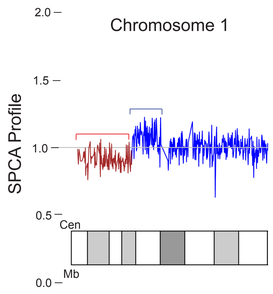
Chromosome	Position	Maternal	Paternal	Proband
10	24,997,433	BB	BB	BB
10	25,023,479	BB	BB	BB
10	25,028,792	AB	AB	AB
10	25,030,249	AB	AB	AB
10	25,031,272	AB	AB	AB
10	25,040,872	AB	AB	AB
10	25,059,017	BB	BB	BB
10	25,059,038	BB	BB	BB
10	25,059,463	AB	AB	AB
10	25,081,383	BB	BB	BB
10	25,081,865	BB	AB	AB
10	25,088,516	AB	AB	AB
10	25,091,035	AB	AA	AB
10	25,095,919	AA	AA	AA
10	25,097,929	BB	BB	BB
10	25,101,407	BB	AA	AB
10	25,110,480	AA	AA	AA
10	25,114,462	AB	BB	AB
10	25,117,741	BB	AA	AB
10	25,133,600	AA	AA	AA
10	25,140,737	AA	AA	AA
10	25,143,891	AB	BB	BB
10	25,144,061	AA	AA	AA
10	25,144,087	BB	BB	BB
10	25,149,446	AA	AA	AA
10	25,149,899	BB	BB	BB
10	25,151,784	BB	BB	BB
10	25,152,119	AA	BB	AB
10	25,161,261	AA	AA	AA
10	25,182,706	AB	BB	BB
10	25,184,541	BB	AB	BB
10	25,185,685	AA	AA	AA
10	25,185,696	BB	BB	BB
10	25,186,197	AA	AA	AA
10	25,186,482	AB	BB	BB
10	25,186,559	BB	BB	BB

Uniparental Inheritance

Chromosome	Position	Maternal	Paternal	Proband
10	125,631,631	AB	AA	BB
10	125,635,968	AA	AA	AA
10	125,636,063	AB	BB	AA
10	125,637,183	AA	AB	AA
10	125,643,090	AB	AA	BB
10	125,649,796	BB	AB	BB
10	125,661,410	BB	BB	BB
10	125,663,596	AA	AA	AA
10	125,666,239	BB	BB	BB
10	125,673,492	BB	BB	BB
10	125,673,547	AA	AB	AA
10	125,676,705	BB	AA	BB
10	125,677,075	BB	AA	BB
10	125,677,788	AA	BB	AA
10	125,681,274	BB	AB	BB
10	125,683,133	AB	BB	BB
10	125,683,842	AB	BB	BB
10	125,683,978	AB	AA	AA
10	125,684,960	AA	BB	AA
10	125,684,978	BB	BB	BB
10	125,686,115	AA	BB	AA
10	125,686,312	BB	AA	BB
10	125,686,488	BB	AA	BB
10	125,687,980	AA	AA	AA
10	125,701,803	BB	BB	BB
10	125,711,882	AB	AB	BB
10	125,728,064	AA	AA	AA
10	125,728,086	AA	AA	AA
10	125,739,009	AA	BB	AA
10	125,739,384	BB	AA	BB
10	125,739,665	BB	AA	BB
10	125,741,845	BB	AA	BB
10	125,742,864	AA	BB	AA
10	125,744,888	AA	BB	AA
10	125,746,281	BB	AA	BB
10	125,762,069	AB	BB	BB

Figure 2

Case 1: Routine NIPT screening detects complex genomic rearrangement (CGR): terminal deletion 1pter->p36.23 and contiguous duplication 1p36.23p36.22 (brackets)



Retention of CGR in placenta but replacement of CGR in amniotic fluid with terminal segUPD mat that extends proximally of CGR at 1p36.13 (arrow)

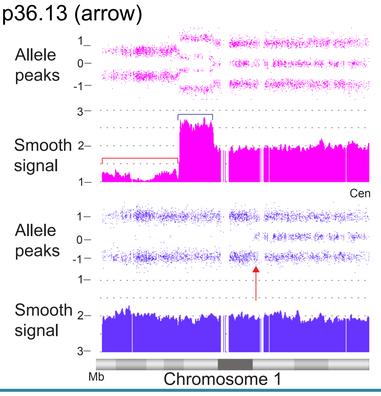
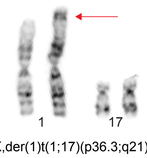


Figure 3

Case 2: Analysis of amniotic fluid cultures reveal a de novo der(1)t(1;17) in 21.4 week fetus with choroid plexus cysts



46,XX,der(1)t(1;17)(p36.3;q21)[48]/46,XX[2]

Replacement of der(1) with terminal 9.4 Mb segUPD from 1pter->p36.22 in PB from 9 yr old girl with global developmental delay, hearing impairment, autism spectrum disorder, precocious puberty, ependymal cyst

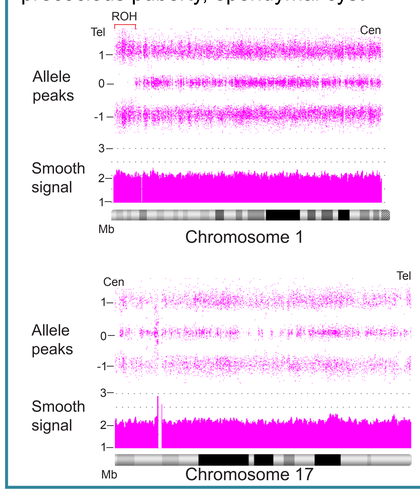
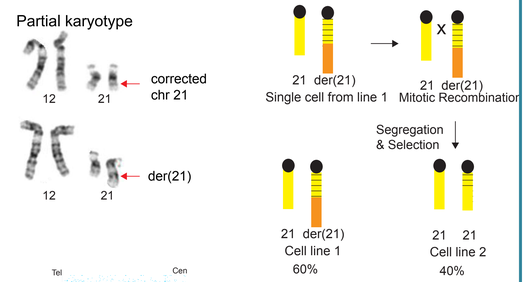
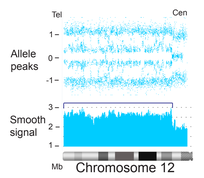


Figure 4

Case 24: PB from 29 yr old male reveals partial correction of der(21)t(12;21)(p11.22;q22.2) cell line with likely segUPD 21 diploid cell line





Microarray shows 30.51 Mb mosaic terminal duplication at 12pter->p11.22 (blue bracket) and 7.12 Mb mosaic terminal deletion at 21q22.2->qter (red bracket). LIkely mosaic terminal segUPD 21 indicated by 4 allele tracks extends from 21q21.1 recombination site (arrow).

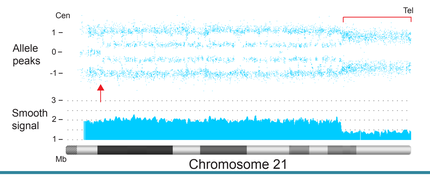


Figure 5

Case 21: PB from 12 yr old male shows evidence of multiple deletion repair lines

Cell lines initiated at different mitotic recombination sites (allele track, arrows). Interstitial deletion (smooth signal track, bracket) is still present in 25% of cells and allele track shows that 75% of cells are homozygous at region of deletion.

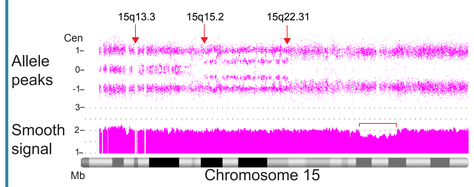
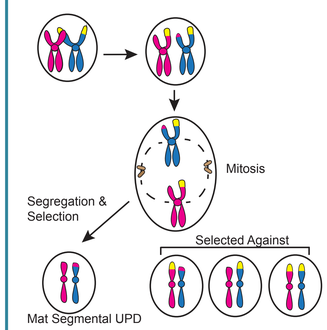


Figure 6

Model of mitotic inter-homologue sister chromatid mitotic recombination



CONCLUSION

- SegUPD occurs secondarily to recombination mediated selection driven repair of distinct genomic imbalances
- NIPT, CVS, and amniotic fluid analyses suggest the incidence of segUPD mediated correction is underestimated
- Although the genetic lesion may be corrected there may be clinical risks:
  - The early presence of the imbalance may interfere with development
  - New imbalance may be created
  - The imbalance may still be present in some tissues
  - Autosomal recessive mutation allele pairing may occur
  - Imprinting defects
  - In some cases, this may explain the etiology of clinical phenotypes undetected by routine microarray and WES studies