Appendix 1. Methods

SNP Microarray Laboratory Procedures

Maternal and products of conception samples were processed using the Illumina CytoSNP-12 genotyping microarray platform according to the manufacturer's instructions (Illumina, Inc., San Diego, CA). This particular array measures approximately 317,000 SNPs across the genome, (roughly one every 10 kb). DNA copy number, UPD and MCC was determined using the Parental Support™ (PS) informatics technique.[1,2]

Validating the ability to detect Microdeletions/Microduplications

We previously demonstrated the ability of the PS technique to accurately detect cytogenetically visible imbalances[2] in products of conception specimens. In order to validate the ability of our PS methodology to detect genomic imbalances below the threshold of routine cytogenetic analysis (i.e., gains and losses < 10Mb), 35 products of conception specimens processed in the Natera laboratory were de-identified and sent to the Columbia University Medical Center clinical microarray laboratory for processing on their standard clinical array platform. The Columbia laboratory was blinded to the copy number imbalances detected by the Natera laboratory. The validation set contained 6 control (46,XX and 46,XY) specimens. The remaining specimens contained genomic imbalances as small as 0.88 Mb and as large as complete trisomy of chromosome 15. Sixteen products of conception specimens had imbalances below 10 Mb, seven specimens had imbalances from 10-17 Mb and the remaining imbalances were all >20 Mb. All imbalances detected on the Illumina CytoSNP-12 array using PS technology were observed by the Columbia laboratory using the Affymetrix Cytoscan HD array (containing 2.6 million copy number markers of which 750,000 are genotype–able SNPs and 1.9 million are non–polymorphic probes).

Levy B, Sigurjonsson S, Pettersen B, Maisenbacher MK, Hall MP, et al. Genomic imbalance in products of conception: single nucleotide polymorphism chromosomal microarray analysis. Obstet Gynecol 2014;124.

The authors provided this information as a supplement to their article.

Appendix 2. Maternal and Gestational Ages for Products of Conception Results That Were of Maternal Origin

POC Result	n	Average Maternal Age (n, SD)	Average Gestational Age for First-Trimester Losses (n, SD [wks])
Normal (>10Mb)	752	34.5 years (650, 4.7)	7.6 weeks (260, 2.1)*
Single Aneuploidy	795	37.6 years (776, 4.5)	7.5 weeks (275, 1.5)†
Multiple Aneuploidy	63	41.1 years (57, 3.9)‡	7.5 weeks (18, 1.5)
Triploidy	72	35.4 years (65, 4.8)	7.9 weeks (31, 1.1)
Tetraploidy	4§	37.8 years (3, 2.6)	8.4 weeks (3, 1.0)
Partial Aneuploidy (>10 MB)	47	34.3 years (45, 3.7)	7.7 weeks (19, 1.1)
46,XX Maternal cells	529	36.1 years (495, 4.9)	7.3 weeks (201, 1.4)

*Twelve second-trimester losses that were chromosomally normal (>10Mb) were excluded from this average.
†Three second-trimester losses with a single aneuploidy were excluded from this average.
‡Two cases with a trisomy and a monosomy were excluded from this average.
§Parental origin was unknown for these 4 cases. (n) indicates the data for samples where information was provided.

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Appendix 3: Egg Donors

The proportion of cytogenetically abnormal cases due to single/multiple aneuploidy, triploidy and structural imbalances is consistent with previous reports.[2] However, the slightly lower abnormality rate when compared to more recent products of conception studies[2] may be due to the use of egg donors, which could reduce the age-related aneuploidy incidence. Because egg donors are usually in their 20s or early 30s, and egg donor recipients are typically 34-41 years of age, age effects may reduce overall aneuploidy rates. Additionally, the laboratory provides aneuploidy screening of preimplantation embryos (PGS) to many of the same institutions that referred products of conception specimens. The use of PGS may therefore have reduced the overall incidence of chromosomally abnormal results in this patient cohort.

Specifically, of the 1,831 women providing information regarding use of assisted reproductive technologies (ART), 90 (4.9%) utilized an egg donor. Seventy-five of 755 (9.9%) fetal samples with a normal products of conception result were facilitated through in vitro fertilization using an egg donor. By contrast, 17 of 860 (2.0%) fetal samples with a single aneuploidy result used an egg donor ($p<10^{-9}$).

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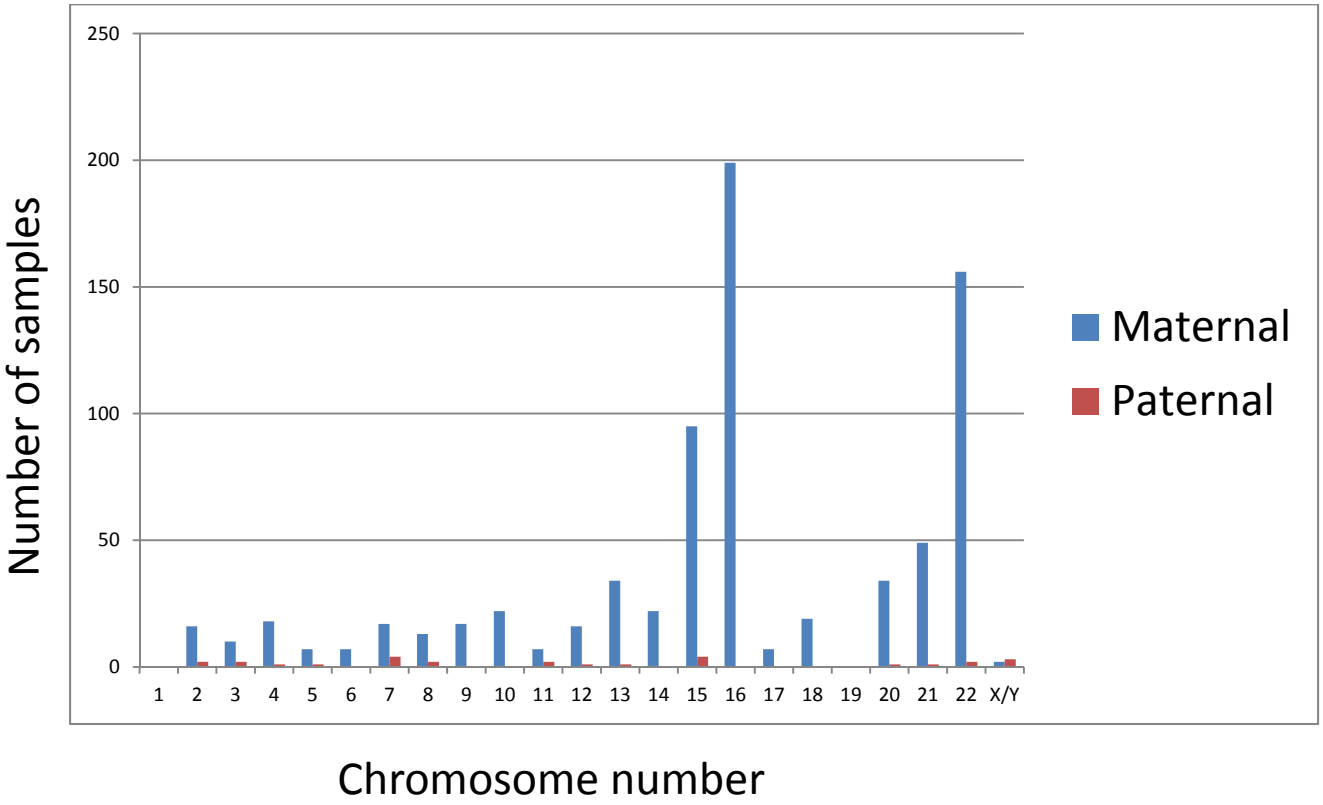
Appendix 4: Incidence of Maternal and Paternal Trisomies by Chromosome Number



Levy B, Sigurjonsson S, Pettersen B, Maisenbacher MK, Hall MP, et al. Genomic imbalance in products of conception: single nucleotide polymorphism chromosomal microarray analysis. Obstet Gynecol 2014;124.

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Appendix 5: Predicted Structural Abnormality of Partial Aneuploidies (>10Mb)

Predicted Mechanism	Predicted Structural Abnormality	Imbalance 1 Type	Imbalance 1 Size (Mb)	Imbalance 2 Type	Imbalance 2 Size (Mb)	Parent of Origin
Translocation (unbalanced)	der(13)t(13;17)(q21.2;q24.3)	Loss 13q	56.0	Gain 17q	**13.6**[*]	Maternal
Translocation (unbalanced)	der(11)t(4;11)(q11;q24.1)	Gain 4q	141.7	Loss 11q	**11.1**[*]	Maternal
Translocation (unbalanced)	der(18)t(9;18)(p21.3;q21.1)	Gain 9p	21.9	Loss 18q	31.2	Maternal
Translocation (unbalanced)	der(18)t(8;18)(q24.23;q21.32)	Gain 8q	**7.2**[†]	Loss 18q	21.55	Maternal
Translocation (unbalanced)	der(13)t(13;20)(q14.11;p11.1)	Gain 20p	26.2	Loss 13q	73.3	Maternal
Translocation (unbalanced)	der(18)t(9;18)(q31.2;q21.31)	Gain 9q	27.5	Loss 18q	22.9	Maternal
Translocation	der(14)t(9;14)(q33.3;q32.2)	Gain 9q	**12.9**[*‡]	Loss 14q	**7.3**[†‡]	Paternal

analysis. Obstet Gynecol 2014;124.

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(unbalanced)						
Translocation (unbalanced)	der(7)t(2;7)(p22.2;q31.33)	Gain 2p	36.7	Loss 7q	33	Paternal
Translocation (unbalanced)	der(22)t(7;22)(p14.1;q13.3)	Loss 7q	47.3	Gain 22q	33	Paternal
Translocation (unbalanced)	der(8)t(8;12)(p21.2;q23.3)	Gain 12q	25.1	Loss 8p	24.6	Paternal
Translocation (unbalanced)	der(22)t(8;22)(q13.2;q13.21)	Gain 8q	76.0	Loss 22q	**7**[†]	Paternal
Translocation (unbalanced)	der(9)t(4;9)(q31.3;p24.1)	Gain 4q	50.0	Loss 9p	**6.6**[†]	Unknown
Translocation (unbalanced)	der(17)t(11;17)(p15.4;p11.2)	Gain 11p	**9.4**[†]	Loss 17p	17.3	Unknown
Translocation	der(17)t(11;17)(p15.4;p11.2)	Gain 11p	**6.6**[†]	Loss 17p	17.2	Unknown

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(unbalanced)						
Terminal deletion	del(5)(p14.1)	Loss 5p	27.8			Maternal
Terminal deletion	del(10)(q25.3)	Loss 10q	17.5			Maternal
Terminal deletion	del(8)(p22)	Loss 8p	16.0			Maternal
Terminal deletion	del(17)(p11.2)	Loss 17p	19.2			Maternal
Terminal deletion	del(4)(q34.3)	Loss 4q	**12.2**[*] [‡]			Paternal
Terminal deletion	del(Y)(q11.1)	Loss Yq	45.8			Paternal
inv dup del	der(8)(qter→p23.1::p23.1→p11.23::p2	Gain 8p	27.6	Loss 8p	**5**[†]	Maternal

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	3.1→p23.2:)					
inv dup del	der(15)(pter→q25.3::q25.3→q25.3::q25.3:)	Gain 15q	**1.1**[†]	Loss 15q	15.9	Maternal
inv dup del	der(18)(pter→q21.2:q21.2→q11.2::q21.2:)	Gain 18q	27.9	Loss 18q	27.7	Paternal
inv dup del	der(5)(qter→p15.2::p15.2→p12::p15.2:)	Gain 15q	28.2	Loss 5q	**14.9**[*]	Paternal
inv dup del	der(4)(qter→p15.32::p15.32→p14::p15.32:)	Gain 4p	23.1	Loss 4p	15.85	Unknown
Marker	der(22)(pter→q11.21:)	Gain 22p-22q	16.7			Maternal
Marker	der(17)(pter→q11.1:)	Gain 17p-17q	22.6			Paternal
Marker	der(21)(pter→q22.13::q22.3→qter)	Gain 21p-	24.8			Paternal

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		21q				
Marker	der(2)(:p11.1→qter)	Gain 2p-2q	151.7			Unknown
Isodicentric	idic(8)(qter→p12:p12→qter)	Gain 8p-8q	109.0	Loss 8p	37.27	Paternal
Isodicentric	idic(8)(qter→p23.2:p23.2→qter)	Gain 8p-8q	144.9	Loss 8p	**6.96**[†]	Unknown
Isodicentric	idic(21)(pter→q22.13::q22.13→pter)	Gain 21p-21q	31.7	Loss 21q	**9.8**[†]	Unknown
Marker + terminal duplication	dup(11)(q23.3qter),der(13)(pter→q12.2:)	Gain11q	**13.8**[*]	Gain 13p-13q	26.9	Both Maternal
Marker + terminal duplication	dup(10)(q24.1qter),der(12)(pter→q13.13:)	Gain10q	36.0	Gain 12p-12q	50.94	Both Maternal
Interstitial deletion	del(2)(q11.2q12.3)	Loss 2q	**10.2**[*‡]			Paternal

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Inversion (recombinant)	der(8)(qter→q13.3::p11.23→qter)	Loss 8p	39.6	Gain 8q	76	Maternal
Terminal duplication	dup(4)(p15.31pter)	Gain 4p	20.7			Paternal
Whole arm tetrasomy	qdp(12)(p11.1pter)	Gain 12p	34.4			Unknown

*Gains and loses between 10-15Mb in size, i.e. at the threshold of detection by routine cytogenetic analysis.
†Gains and losses below 10Mb in size, ie microdeletions/microduplications.
‡These cases may have been missed by routine cytogenetic testing.

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Appendix 6. Predicted Structural Abnormality, Partial Aneuploidies (>10Mb) With an Accompanying Aneuploidy

Predicted Mechanism	Predicted Structural Abnormality	Imbalance 1 Type	Imbalance 1 Size (Mb)	Imbalance 2 Type	Imbalance 2 Size (Mb)	Imbalance 3 Type	Imbalance 3 Size (Mb)	Accompanying Aneuploidy	Parent of Origin
Terminal Deletion	del(X)(q21.2)	Loss Xq	75.0					Trisomy 22	Paternal (Deletion); Maternal (Trisomy)
Marker	r(X)(p21.2q26.3)	Gain Xp-Xq	106.3					Pentasomy 2	Maternal (Marker); Maternal (Pentasomy)
inv dup del + Terminal Duplication	der(X)(qter→p22.13::p22.13→p11.22::p22.13:),dup(6)(q25.1qter)	Gain 6q	17.2	Loss Xp	21.8	Gain Xp	27.82	Trisomy 15	Both Paternal (inv dup del + Terminal Duplication); Maternal (Trisomy)
inv dup del	der(4)(qter→p15.33::p15.33→p15.31::p15.33:)	Gain 4p	10.2	Loss 4p	23.17			Monosomy X	Unknown (inv dup del); Paternal (Monosomy)
Whole Arm Tetrasomy	qdp(12)(p11.1pter)	Gain 12p	34.4					Trisomy 20	Unknown (12p Tetrasomy); Maternal (Trisomy)

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Appendix 7: Tetraploidy

Tetraploidy caused by the failure of cytoplasmic cleavage at the first division in the zygote will not be detected using a SNP-based array, as the genotypes cannot be distinguished (i.e. AA, AB and BB cannot be distinguished from AAAA, AABB, and BBBB, respectively, if the change is genome-wide). Tetraploidy caused by alternate mechanisms will be detected (e.g., fertilization of a diploid ovum by two sperm). These mechanisms are thought to occur very infrequently. This finding nonetheless provides important information regarding the mechanisms generating tetraploid fetuses by indicating that up to 17% of tetraploids may arise by alternative mechanisms (Tetraploidy is typically found in approximately 1% of products of conception.[2] Here, that translates to about 24 samples. We detected four tetraploidy cases, representing 16.67% of the expected number.).

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Appendix 8: Clinically Significant Copy Number Changes

Chromosome	Cytogenetic Region	Type	Parent of Origin	Inheritance	Size (<MB)	Start *	End *	Additional Aneuploidy
1	q21.1-q21.2	Deletion	Pat	-	4.05	144,397,794	148,445,751	-
7	q11.23	Deletion	Mat	-	3.00	72,000,000	75,000,000	-
14	q32.2-q32.33	Deletion	Pat	-	7.30	99,039,627	106,368,585	-
15	q11.2	Deletion	Mat	Mat	2.79	18,450,000	21,240,000	-
16	p11.2	Deletion	Mat	-	1.60	29,830,000	31,430,000	-
18	p11.32-p11.23	Deletion	Pat	-	8.00	0	7,956,303	-
22	22q11.21	Deletion	Mat	Mat	3.50	16,980,000	20,130,000	-
22	q13.2q13.33	Deletion	Pat	-	7.00	42,520,000	49,510,000	-
22	q13.2q13.33	Deletion	Pat	-	9.50	40,020,000	49,510,000	-
8	q24.23q24.3	Duplication	Mat	-	7.20	139,000,000	146,200,000	-

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11	p15.5-p15.4	Duplication	-	de novo	6.60	0	6,638,049	-
11	p15.5-p15.4	Duplication	Pat	de novo	9.20	193,788	9,388,462	-
					Average Size: 5.81 Mb			
4	p16.3	Deletion	Pat	-	1.16	929,900	2,087,000	Trisomy 9
15	q11.2	Deletion	Mat	-	2.87	18,470,000	21,310,000	Trisomy 21
16	p13.11	Deletion	Mat	Mat	2.15	14,650,000	16,800,000	Trisomy 21
22	q11.2	Duplication	Pat	-	3.01	20,000,000	23,010,000	Trisomy 15
					Average Size: 2.68 Mb			

*****All genomic coordinates map to human genome build 18.

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Appendix 9: Variants of Unknown Clinical Significance

Chromosome	Cytogenetic Region	Type	Parent of Origin	Inheritance	Size (<MB)	Start *	End *	Additional Aneuploidy
1	p36.22p36.21	Deletion	Mat	-	3.65	11,000,000	14,650,000	-
4	p16.3	Deletion	Pat	-	1.30	50,160	1,355,000	-
9	p24.3-p24.1	Deletion	Mat	-	6.60	0	6,622,590	-
16	q23.1	Deletion	Mat	-	0.49	75,810,000	76,300,000	-
3	p26.2p26.1	Duplication	Mat	Mat	1.43	5,073,000	6,500,000	-
5	q21.1-q21.2	Duplication	Mat	Mat	1.40	102,100,000	103,500,000	-
8	p23.3-p23.2	Duplication	Mat	-	5.00	0	4,988,021	-
11	p15.1-p14.3	Duplication	Mat	-	1.40	20,170,000	21,570,000	-
15	q13.3	Duplication	Mat	Mat	0.80	29,700,000	30,500,000	-
15	q13.3	Duplication	Mat	Mat	0.89	29,610,000	30,500,000	-
15	q13.3	Duplication	Mat	-	1.10	29,700,000	30,800,000	-

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16	q24.3	Duplication	Mat	-	0.66	88,000,000	88,660,000	-
16	p13.11	Duplication	Mat	-	1.50	15,040,000	16,540,000	-
16	p12.1	Duplication	Pat	-	1.50	22,500,000	24,000,000	-
16	p13.12-p13.11	Duplication	Mat	Mat	1.52	14,850,000	16,370,000	-
16	p13.12-p13.11	Duplication	Mat	Mat	1.82	14,380,000	16,200,000	-
18	q21.1q21.2	Duplication	Mat	-	2.50	43,410,000	47,120,000	-
19	q12- q13.11	Duplication	Und	-	7.40	31,626,566	39,001,848	-
20	p11.21	Duplication	Mat	Mat	0.40	24,530,000	24,930,000	-
21	q22.3	Duplication	Mat	Mat	0.56	43,480,000	44,040,000	-
21	q22.1	Duplication	Pat	-	2.50	44,285,000	46,920,000	-
					Average Size:			

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					2.12 Mb			
4	q24-q25	Deletion	Pat	-	2.80	105,400,000	108,200,000	Trisomy 15
10	q24.32-q24.33	Deletion	Pat	-	1.50	104,000,000	105,500,000	Trisomy 16
6	q27	Duplication	Mat	Mat	1.22	167,283,938	168,500,000	Trisomy 22
6	q27	Duplication	Mat	Mat	1.85	167,345,042	169,200,000	Trisomy 22
8	q13.2q13.3	Duplication	Mat	Mat	2.16	69,840,000	72,000,000	Trisomy 20
8	q21.11q21.13	Duplication	Mat	-	4.10	77,490,000	81,575,000	Trisomy 16&21
15	q13.3	Duplication	Pat		1.02	29,700,000	30,720,000	Trisomy 8
15	q13.3	Duplication	Mat	Pat	1.07	29,670,000	30,740,000	Trisomy 21
15	q13.3	Duplication	Mat	Mat	1.10	29,640,000	30,740,000	Trisomy 13&20
15	q13.3	Duplication	Pat	-	1.73	28,500,000	30,230,000	Trisomy 16

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15	q26.3	Duplication	Mat	-	3.00	97,000,000	100,200,000	Trisomy 20
17	q25.1	Duplication	Pat	-	1.43	69,199,193	70,628,637	Trisomy 15
20	q13.13	Duplication	Pat	-	1.00	45,800,000	46,800,000	Trisomy 16
20	p13	Duplication	Mat	-	1.73	3,570,000	5,304,000	Trisomy 16
20	q11.23q12	Duplication	Mat	-	5.25	35,600,000	40,850,000	Trisomy 16&21
22	q11.21	Duplication	Pat	-	1.12	18,890,000	20,010,000	Trisomy 11
					Average Size: 2.01 Mb			

Und: parent-of-origin was undetermined. *All genomic coordinates map to human genome build 18.

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Appendix 10: Anomalies Detected in This Study That Would Also be Detected by Traditional Cytogenetics Analysis

Finding	Cases	Percent of All Cases (N=1,861)	Percent of Abnormal Cases (n=1,106)	Identifiable by Traditional Cytogenetics
Maternal cell contamination	528	22.0%*	N/A	No
Normal	755	40.6%	68.3%	Yes
Single aneuploidy	860	46.2%	77.8%	Yes
Multiple aneuploidy	85	4.6%	7.7%	Yes
Triploidy	114	6.1%	10.3%	Yes
Tetraploidy	4	0.21%	0.36%	Yes
Whole-genome UPD	3	0.16%	0.27%	No
Single UPD	4	0.21%	0.36%	No
Partial aneuploidies	38	2.0%	3.4%	60.5-73.7%†

UPD, uniparental disomy; N/A, not applicable.

*Percentage calculated from total number of successfully analyzed samples (N=2,397)2 cases with single-aneuploidy and microdeletion or microduplication.

†Ten cases had cytogenetically visible imbalances but had a second imbalance that was below cytogenetic detection (<10Mb). These cases would have incorrectly designated the structural abnormality present in the fetus. Four cases had cytogenetically visible imbalances but had a second imbalance that was at the threshold of detection by cytogenetics (10-15 Mb) and may have been missed depending on the banding resolution. If missed, these cases would have incorrectly designated the structural abnormality present in the fetus. Two cases contained single imbalances that were each at the threshold of detection by cytogenetics (10-15 Mb) and may have been missed completely depending on the banding resolution. One case contained 2 imbalances, the first being at the threshold of detection by cytogenetics (10-15 Mb) and may have been missed depending on the banding resolution. Since the second imbalance in this case was below cytogenetic detection limits (<10Mb), the overall assignment of the structural abnormality in the fetus would still have been incorrectly designated. See Appendix 5 for a full listing and details of these partial aneuplodies.

Appendix 11: Clinical Implications of Submicroscopic Imbalances

Miscarriage causality may be unclear in cases with submicroscopic deletions. This is compounded by the fact that pathogenic copy number changes may result in abnormalities that are not evident early in pregnancy. For example, 22q11.2 deletions are associated with DiGeorge/Velocardiofacial syndrome, the clinical severity of which can vary considerably between unrelated patients and between patients from the same family.[4] There are multiple reports of prenatally-ascertained cases of 22q11.2 microdeletions with severe cardiovascular anomalies inherited from an undiagnosed parent with little to no clinical features of the syndrome.[5] Additionally, the 22q13.3 deletion syndrome presents with developmental delay, hypotonia, delayed or absent speech, autistic-like behavior, and dysmorphic facial features; more severe cases affecting essentially every organ system have been reported.[6] There are also reports of intrauterine growth restriction and congenital heart defects,[6] which may factor into miscarriage etiology. The finding of isolated deletions in the 22q11.2 (1 case) and 22q13.3 (2 cases) regions suggest that genomic imbalances in these regions may be associated with an increased miscarriage risk, especially when the phenotype falls on the most severe side of the syndrome's clinical spectrum.

The most frequently occurring copy number variant was a gain of the 15q13.3 region, including the *CHRNA7* gene (~1:267 specimens), which has been associated with autism, behavioral problems and other neuropsychiatric disorders,[7] but is also observed in phenotypically normal individuals.[8] This duplication occurred as frequently in cytogenetically normal specimens as it did in the specimens with gross cytogenetic aberrations, making it more likely to be a coincidental finding.

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