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Aneuploidy and Intellectual Disability

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1. Introduction

Aneuploidy is the presence of an abnormal number of chromosomes in cells. The gain or loss of a chromosome in germ cells is the most common cause of chromosomal aneuploidy. Trisomy 21, trisomy 18, and trisomy 13 are characterized by congenital anomalies with intellectual disability (ID) or short lives. Recently, mosaic variegated aneuploidy (the presence of a different number of chromosomes in some cells) has been reported to be associated with ID and growth retardation, with or without microcephaly and tumors. In the cell cycle, the alignment of sister chromatids at metaphase plates is essential for the equational separation of chromatids. Misaligned chromosomes at metaphase plates, and/or aberration of the mitotic checkpoint, cause a disproportionate separation of chromatids, resulting in aneuploidy. To evaluate the association between aneuploidy and ID, we analyzed the chromosome numbers of over 200 metaphase plates of lymphoblastoid cells in patients with moderate or severe ID, with or without microcephaly. In this chapter, we summarize the previously reported cases and our own cases of patients with ID associated with aneuploidy or severely misaligned chromosomes at metaphase, and discuss the molecular mechanism underlying ID in cases in which aneuploidy is observed.

2. Aneuploidy

The most common forms of chromosomal (complete) aneuploidy are trisomy and monosomy. Trisomy refers to having an extra whole chromosome, and monosomy is the lack of 1 chromosome from a pair of chromosomes. Partial monosomy and partial trisomy, i.e., loss or gain of part of a chromosome, respectively, have preferentially been used instead of partial aneuploidy. Mosaic aneuploidy is the condition in which aneuploidy is detected in a fraction of cells in an individual.

2.1 Trisomy

Trisomy 21, also known as Down syndrome, is the most common chromosomal aneuploidy and a cause of ID. Down syndrome affects up to 1 in 1,000 live births (International Clearinghouse for Birth Defects Monitoring Systems, 1991). Down syndrome is caused by a

failure in the proper segregation of chromosome 21 during meiosis. This chromosome 21 nondisjunction is mostly due to maternal meiotic errors; the majority of these errors occur during meiosis I (~80%) (Antonarakis, 1991; Yoon et al., 1996). A recent study has suggested that pericentromeric exchange at meiosis II initiates or exacerbates the susceptibility to the risk of increased maternal age (Oliver et al., 2008). The Down syndrome critical region (DSCR) of human chromosome 21q22 was defined on the basis of analysis of familial cases of partial trisomy 21 (Korenberg et al., 1994; Ronan et al., 2007). One strategy for identifying the genes responsible for ID in Down syndrome is to analyze the genes located in the DSCR. Analyses of 2 unrelated patients with a *de novo* balanced translocation and a patient with a microdeletion within the DSCR demonstrated that *DYRK1A*, encoding the dual-specificity tyrosine phosphorylation-regulated kinase 1A, plays a critical role in brain development (Møller et al., 2008; Yamamoto et al., 2011). Therefore, the dosage of *DYRK1A* is quite important for brain development, and it could be one of the causative genes for ID in Down syndrome. Several studies demonstrated that a normal dosage of *DYRK1A* is critical for normal brain development and function. Transgenic mice overexpressing *Dyrk1A* show marked cognitive deficits and impairment in hippocampal-dependent memory tasks and the generation of both amyloid and tau pathologies, which are observed in early onset Alzheimer disease and Down syndrome (Altafaj et al., 2001; Ahn et al., 2006; Kimura et al., 2007; Park et al., 2007; Ryoo et al., 2008). A recent study showed that *Dyrk1A* directly interacts with and phosphorylates the regulator of calcineurin 1 (RCAN1) protein at Ser112 and Thr192. *RCAN1* is also located in the DSCR. The phosphorylation of RCAN1 enhances RCAN1 binding to calcineurin, resulting in reduced NFAT transcriptional activity. This activity is important for the outgrowth of embryonic axons (Graef et al., 2003; Jung et al., 2011). Thus, the increased expression of *Dyrk1A* caused by trisomy may cause impaired axon outgrowth during brain development, which may in turn cause ID in Down syndrome.

Other types of common aneuploidy include trisomy 18 (Edwards syndrome), which affects 1 in 6,000 births, and trisomy 13 (Patau syndrome), which affects 1 in 10,000 births. A recent study of the natural outcome of trisomy 13 and trisomy 18 after prenatal diagnosis indicates that the live birth rate is 13% for trisomy 18 and 33% for trisomy 13. Three of 4 live-born infants with trisomy 13 and all 3 trisomy 18 infants died early, within a maximum of 87 postpartum hours. Thus, trisomy 13 and trisomy 18 are associated with a high rate of spontaneous abortion, intrauterine death, and a short life-span (Lakovschek et al., 2011). ID is not clear in these patients because of their short lives.

2.2 Partial aneuploidy (partial monosomy and partial trisomy)

Quite a few reports exist on patients with ID harboring chromosomal microdeletions. This indicates that haploinsufficiency of a gene or genes located in the deletion region are associated with ID. Mutational analysis of the genes located in the deletion region leads the identification of the causal gene(s) of ID, with or without congenital anomalies. Duplications of some chromosomal segments are reported to be associated with ID (1q21.1, Brunetti-Pierri et al., 2008; 3q29, Goobie et al., 2008; Lisi et al., 2008; 16p13.11, Hannes et al., 2009; Xq28, Van Esch et al., 2005). This indicates that increased gene dosage(s) are associated with ID. It is noted that the clinical features of deletions or duplications at the same chromosomal segments are different. There is a tendency for duplications to show milder clinical features

than deletions, and autistic features more frequently appear in duplications (Table 1) (Marshall et al., 2008; Sebat et al., 2007).

Chromosomal location	Deletion		Duplication		References
	ID	Syndrome	ID	Clinical features	
5q35	+, ++	Sotos	+	Microcephaly	(1)
7q11.2	+	Williams-Beuren	+	Speech delay	(2)
15q11.2	+ / +++	Prader-Will / Angelman	++	Autism	(3)
16p13.3	+++	Rubinstein-Taybi	++	Speech delay	(4)
17p11.2	++	Smith-Magenis	++	ADHD, Autism	(3) (5)
22q11.2	±, +	DiGeorge	−, ±	ADHD, Autism	(6)

Table 1. Clinical features of duplication or deletion at the same chromosomal region. ID, intellectual disability; −, absent; ±, very mild; +, mild; ++, moderate; +++, severe; ADHD, Attention Deficit Hyperactivity Disorder. References: (1) Hunter et al., 2005; (2) Somerville et al., 2005; (3) Keller et al., 2003; (4) Marangi et al., 2008; (5) Potocki et al., 2000; (6) Mukaddes & Herguner, 2007.

2.3 Monosomy

Monosomy is most commonly lethal during prenatal development. X-chromosome monosomy (Turner syndrome) is a commonly observed monosomy that develops without obvious, or with very mild, ID.

2.4 Mosaic aneuploidy

The most common use of the term “mosaic aneuploidy” refers to the condition in which aneuploidy is detected in a fraction of cells, usually in lymphocytes (lymphoblastoid cells), in an individual. Mosaic aneuploidy is observed in 2%–4% of Down syndrome cases, in which 2 types of karyotypes (trisomy 21 and normal) are present (Mikkelsen et al., 1976). In general, individuals who are mosaic for chromosomal aneuploidy tend to have less severe clinical features than those with full trisomy. Therefore, only mosaic patients may survive in many of the chromosomal trisomies.

2.5 Mosaic variegated aneuploidy

Hsu et al. (1970) reported 3 children with sex chromosome mosaicism born to consanguineous parents. The authors suggested that a recessive gene causing mitotic instability is associated with the mosaicism. Tolmie et al. (1988) and Papi et al. (1989) reported male and female siblings with ID, growth retardation, microcephaly, and multiple chromosome mosaicism involving mainly chromosome 18 or chromosomes 7 and 8, respectively. These findings indicate that mutations of autosomal recessive genes are associated with aberrant mitosis causing the observed phenotype. The term “mosaic variegated aneuploidy” (MVA) has been suggested to apply to patients with ID, microcephaly, and the above-mentioned cytogenetic findings (Warburton et al., 1991).

Callier et al. (2005) summarized 28 previously reported cases of MVA and showed that 26 of 28 patients (93%) had microcephaly and 21 of 28 patients (75%) had ID, and in 2 of the 28 cases, clinical features were not described. MVA with premature chromatid separation (PCS) (also called PCS syndrome; Kajii et al., 2001) has been reported (Plaja et al., 2001). Patients with this condition exhibit ID, intrauterine growth retardation, microcephaly, and a characteristic facial appearance; the syndrome is often accompanied by malignancies (Wilms tumor, rhabdomyosarcoma, and acute leukemia). These patients have a variety of aneuploid cells (~40%), but PCS is more apparent (>50%) in these cells. It is noted that healthy parents of patients with MVA with PCS also have PCS (~10%–40%) in their lymphocytes (Kajii et al., 2001). Plaja et al. (2001) summarized 11 previously reported cases of MVA with PCS and showed that all 11 patients (100%) had microcephaly and 8 of 11 patients (73%) had ID, and in 2 of the 11 cases, the ID status was unknown. However, not all patients with MVA have microcephaly (Callier et al., 2005).

A causative gene of MVA, the *BUB1B* gene encoding BUBR1, has been identified in 5 families with MVA, including 2 with embryonal rhabdomyosarcoma (Hanks et al., 2004). These patients have truncating or missense mutations in both alleles of *BUB1B*. BUBR1 is a key protein in the mitotic checkpoint, and its deficiency causes aneuploidy and cancer development. *BUB1B* mutations were also identified in the patients from 7 Japanese families exhibiting MVA with PCS (Matsuura et al., 2006). Eight patients in the 7 families presented with intrauterine growth retardation, microcephaly, and a Dandy-Walker complex. Wilms tumor was also observed, except in 1 patient. Each patient had a loss-of-function mutation of *BUB1B* in one allele; the other allele exhibited a haplotype associated with decreased expression levels of BUBR1 protein. Therefore, a decrease of <50% in BUBR1 function at the mitotic checkpoint is associated with MVA with PCS. Recently, biallelic loss-of-function mutations in *CEP57* were identified in 4 patients with MVA (Snape et al., 2011). All the patients showed random gains and losses of chromosomes in ~25%–50% of the examined cells. It is noteworthy that 2 patients did not have ID and microcephaly, and none had malignancies. The Online Mendelian Inheritance in Man (OMIM) database defines mosaic variegated aneuploidy syndrome 1 (MVA1) (MIM: 257300) as a syndrome caused by homozygous or compound heterozygous mutations in *BUB1B* on chromosome 15q15, and MVA2 (MIM: 614114) as a syndrome caused by homozygous or compound heterozygous mutations in *CEP57* on chromosome 11q21. The proportion of aneuploid cells in MVA is usually >25% (Hanks et al., 2004).

Mitotic checkpoint: The mitotic checkpoint works to ensure accurate chromosome segregation to avoid aneuploidy by regulating the progression from metaphase to anaphase. The checkpoint arrests cells in mitosis, until all chromosomes have aligned at the metaphase plate. Chromosome alignment depends on the attachment of microtubules emanating from the spindle poles to the kinetochores on chromosomes. Once the checkpoint has been satisfied (switched off), the cell proceeds into anaphase and completes the cell cycle (Chan et al., 2005; Musacchio & Salmon, 2007).

3. Microcephaly

Microcephaly is the most common clinical feature (developing in ~1% of the population, Lizarraga et al., 2010) and is usually associated with ID. Microcephaly is defined in persons who have a head circumference (HC) (or occipitofrontal circumference [OFC]) more than 2

standard deviations (-2SD) below the average circumference for the individual's age, sex, race, and period of gestation.

The size of the mammalian neocortex is determined largely by the number of neurons generated at the ventricular zone (VZ) during embryonic neurogenesis. Thus, defects in embryonic neurogenesis decrease the number of neurons in the neocortex, leading to microcephaly and ID. The VZ comprises progenitor cells (mainly radial glial cells); these progenitor cells divide symmetrically to amplify their own cell population before the peak phase of neurogenesis (embryonic days 13–18 in mice). During the peak phase of neurogenesis, progenitor cells divide into a progenitor cell and a neuron, or an intermediate progenitor cell (IPC), by asymmetric division. IPCs continue additional division to generate neurons that migrate into the cortical plate and finally form the cerebral cortex. The term “asymmetric” is used to refer to the generation of either different types of progenitor cells or division (Chenn & McConnell, 1995). A recent study has indicated that asymmetric inheritance of daughter and mother centrosomes regulates the differential behaviors of renewing progenitors and their differentiating progeny (Wang et al., 2009). Therefore, this finding suggests that the centrosomes play essential roles in progenitor cleavage, differentiation, and migration (Higginbotham & Gleeson, 2007).

Centrosome: The centrosome is the microtubule-organizing center responsible for the nucleation and organization of cytoplasmic organelles, primary cilia, and mitotic spindle microtubules. It is located in the cell cytoplasm and contains 2 orthogonally arranged centrioles; each centriole has a barrel-shaped microtubule structure and is surrounded by pericentriolar material (PCM).

3.1 Autosomal recessive microcephaly

Autosomal recessive primary microcephaly (MCPH) is a neurodevelopmental disorder characterized by microcephaly at birth and nonprogressive ID. Its incidence is ~1 in 10,000 in consanguineous populations. The current clinical definition of MCPH is as follows: (1) congenital microcephaly with an HC at least 4SD below age and sex means; (2) ID, but no other neurological findings; and (3) mostly normal height, weight, facial appearance, chromosomal analysis, and brain structure as evaluated by brain MRI (CT) (Woods et al., 2005).

At least 8 MCPH loci exist, and the genes underlying 7 of these have been identified (MCPH1-*MCPH1*, MIM 251200; MCPH2-*WDR62*, MIM 613583; MCPH3-*CDK5RAP2*, MIM 608201; MCPH4-*CEP152*, MIM 613529; MCPH5-*ASPM*, MIM 605481; MCPH6-*CENPJ*, MIM 609279; and MCPH7-*STIL*, MIM 181590). The proteins encoding the causative genes of MCPH are specifically localized at the centrosome during a specific period of the cell cycle (Kumar et al., 2009). Therefore, the failure of proteins associated with the function and/or the structure (maturation) of the centrosome causes MCPH and aneuploidy. Hertwig's anemia (an) mutant (*Cdk5rap2^{an/an}*) mice, a mouse model of MCPH3, show reduced neuronal numbers and thinner superficial layers, but preserved cortical layer organization. These mice have a high level of aneuploidy in tissues, and neuronal progenitor cells exhibit mitotic defects with abnormal mitotic spindle pole number and mitotic spindle orientation. The abnormal number of centrosomes might produce abnormal mitosis and aneuploidy that would result in either cell death or cell cycle arrest in cortical progenitor cells (Lizarraga et

al., 2010). Taken together, neuronal progenitor cell death, accompanying abnormal mitotic defects and aneuploidy, could be the cause of ID in some types of MCPH. The decreased brain size in MCPH, without a major effect on the cortical layer structure, suggests that the causative genes of MCPH affect the symmetric division of progenitor cells, rather than asymmetric divisions associated with cortical layer formation and subsequent impaired cell functions or apoptosis.

Deficiencies of those proteins (genes) that are reported to be associated with mitotic defects and/or aneuploidy are listed in Table 2.

Mitotic defect: Mitotic defects include disrupted centrosomes, misaligned chromosomes, and spindle misorientation (spindle poles in different focal planes) at metaphase, which result in aneuploidy, lagging chromosomes, and anaphase bridges in dividing cells.

Gene	Cellular location at metaphase	Deficiency of the gene			References
		Misaligned chromosomes	Aneuploidy	Clinical features	
<i>BUB1B</i>	Kinetochores	++	++	GR, Microcephaly, ID, Cancer	(1) (2)
<i>CEP57</i>	Centrosome	++	++	GR, Microcephaly, ID	(3)
<i>CDK5RAP2 (Cdk5rap2)</i>	Centrosome	+	+	MCPH3, ID	(4) (5)
<i>CENP J</i>	Centrosome	+	ND	MCPH6, ID	(4) (6)
<i>STIL</i>	Pericentrosome	+	ND	MCPH7, ID	(7)
<i>UBE3A</i>	Centrosome	+	ND	Angelman syndrome, ID	(8)
<i>NDE1</i>	Centrosome	+	ND	Microlissencephaly, ID	(9)
<i>ASAP</i>	Centrosome	+	ND	ND	(10) (11)
	Mitotic spindle				
<i>CHD6</i>	Diffuse localization	+	+	ID	(12)
<i>PCNT</i>	Pericentrosome	ND	+	MOPD II	(13)

Table 2. Deficiencies of genes reported to be associated with misaligned chromosomes and/or aneuploidy. +, moderate; ++, severe; ND, not described; ID, intellectual disability; GR, growth retardation. References: (1) Hanks et al., 2004; (2) Matsuura et al., 2006; (3) Snape et al., 2011; (4) Bond et al., 2005; (5) Lizarraga et al., 2010; (6) Cho et al., 2006; (7) Pfaff et al., 2007; (8) Singhmar & Kumar, 2011; (9) Alkuraya et al., 2011; (10) Saffin et al., 2005; (11) Eot-Houllier et al., 2010; (12) Yamada et al., 2010; (13) Rauch et al., 2008.

4. Characterization of aneuploidy in patients with moderate and severe ID

Patients with microcephaly often present with ID, but its etiology is primarily unknown. As described above, recent studies have demonstrated that mitotic dysfunctions in the cell cycle are tightly associated with MCPHs. Although detailed data of aneuploidy in each MCPH are not available, aneuploidy could be found in some types of microcephaly with ID. We analyzed aneuploidy in 10 patients with moderate and severe ID, including 5 solitary cases with microcephaly (HC more than 3SD smaller than the mean) (Table 3). The number of cells exhibiting aneuploidy was determined by counting chromosome numbers in over 200 metaphases derived from lymphoblastoid cells from 5 normal control subjects and 10 patients with ID. Two patients (Lesch-Nyhan syndrome and Rett syndrome) with ID had the same ratio of aneuploidy as normal controls (5%–7%). In contrast, in 3 patients with microcephaly

(S1, S2, and S5), the ratio of aneuploidy increased 2–3 times (13%–21%) as compared with the ratio of aneuploidy in normal controls. This result indicates that there are 2 types of microcephaly with ID, i.e., that with and that without an increased ratio of aneuploidy in lymphoblastoid cells. The findings of the 3 patients with microcephaly and relatively high rates of aneuploidy suggest that these patients have mutations associated with mitotic defects, and the other 2 patients with microcephaly may have other etiologies underlying their ID that are not directly associated with mitotic defects of the cells and aneuploidy.

An increased rate of aneuploidy was also identified in a patient with chromodomain helicase DNA (CHD)-6 haploinsufficiency (S6) and in 2 patients with CHARGE syndrome (manifestations are coloboma of the eye [C], heart anomalies [H], choanal atresia [A], retardation of mental and somatic development [R], genital anomalies [G], and ear abnormalities and/or deafness [E]) caused by haploinsufficiency of CHD7 (S7 and S8), although they did not have microcephaly (Table 3) (Yamada et al., 2010). Both proteins are ATP-dependent chromatin-remodeling enzymes and play important roles in maintaining and regulating chromatin structure. Lymphoblastoid cells from the patients with CHD6 or CHD7 haploinsufficiency, and CHD6 or CHD7 knockdown HeLa cells, display aneuploidy and an increased frequency of misaligned chromosomes, respectively (Fig. 1, Table 3) (Yamada et al., 2010). CHD6 associates with many proteins to form a large protein complex (>2 MDa) (Lutz et al., 2006). This finding and the diffused distribution of CHD6 at metaphase (Yamada et al., 2010) suggest that the protein complex may act as a basis for the formation and/or stabilization of the mitotic spindle structure.

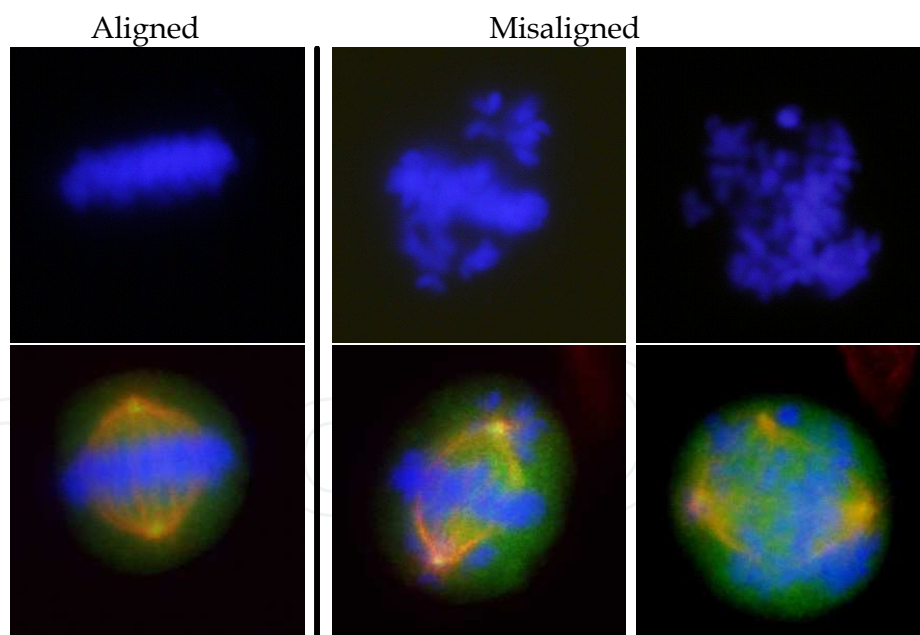


Fig. 1. Misaligned chromosomes observed in RNA interference (RNAi)-mediated knockdown of *CHD6* in metaphase HeLa cells. Aligned chromosomes (left panels, control) and 2 types of misaligned chromosomes – with bipolar centrosomes (middle panels) and with 3 centrosomes (right panels) – caused by knockdown of *CHD6* at metaphase are presented. Cells were fixed and stained with anti-alpha-tubulin (red) and anti-gamma-tubulin (green) antibodies. Chromosomes were stained with 4',6-diamidino-2-phenylindole (DAPI; blue) (upper panels). Lower panels show merged images.

The cytogenetic examination of the chromosomes of patients with ID (Table 3) thus gives us important information as to whether the patients exhibit aneuploidy. Several studies have demonstrated that a high level of aneuploidy (~50%) is a constant feature of human neurons under healthy conditions (Pack et al., 2005; Rehen et al., 2005; Yurov et al., 2005). Moreover, approximately 33% of neural progenitor cells display genetic variability, which is manifested as chromosomal aneuploidy (Kaushal et al., 2003; McConnell et al., 2004; Rehen et al., 2001; Yang et al., 2003). These findings indicate that the brain is a specific region for displaying much aneuploidy caused by genetic variability. We studied the aneuploidy of lymphoblastoid cells and identified increased aneuploidy in some patients with ID. However, it is not clear how increased aneuploidy in lymphoblastoid cells caused by the mutation affect the apoptosis or fate of neuronal progenitor cells. Patients with MVA and MVA with PCS have been shown to have a high incidence of ID (>73%) with increasing aneuploidy (>25%). Such increasing aneuploidy, caused by mutations, adds to the total aneuploidy in the neuronal progenitor cells and may cause the number of aneuploid cells to exceed critical thresholds for ID that is caused by the neuronal death or impaired functions of the progenitor cells. Therefore, it is critical to analyze the aneuploidy of neural progenitor cells in animal models of human diseases known to cause aneuploidy and ID. This study could clarify the relationship of ID and aneuploidy. To perform this kind of study, it is important to accumulate aneuploidy data from patients with ID, with or without microcephaly.

	ID	Microcephaly (HC, at age)	Others	Chromosome numbers				Total metaphase numbers	Aneuploidy (%)	PCS (%)
				<46	46	47	>47			
C1	–	–	Healthy control	21	277	1	1	300	7.7	ND
C2	–	–	Healthy control	14	283	2	1	300	5.7	ND
C3	–	–	Healthy control	20	278	1	1	300	7.3	ND
C4	–	–	Healthy control	14	281	4	1	300	6.3	1.0
C5	–	–	Healthy control	7	188	3	2	200	6.0	1.0
S1	++	-4SD (2y2m)	Epilepsy	21	173	6	0	200	13.5	ND
S2	++	-3.5SD (3y0m)	Epilepsy	20	170	9	1	200	15.0	ND
S3	++	-7SD (2y4m)	Polydactyly, Epilepsy	12	188	0	0	200	6.0	ND
S4	++	-6SD (1y8m)	Cerebellopontine hypoplasia	10	185	5	0	200	7.5	5.5
S5	++	-4.3SD (2y5m)	West syndrome	33	158	7	2	200	21.0	0.5
S6	++	–	CHD6 deficiency	56	329	11	4	400	17.8	–
S7	++	–	CHARGE syndrome, GR	50	333	11	6	400	16.8	–
S8	++	–	CHARGE syndrome, GR	47	338	14	1	400	15.5	1.0
S9	+	–	Lesch-Nyhan syndrome	9	186	4	1	200	7.0	2.0
S10	++	–	Rett syndrome	6	190	3	1	200	5.0	–

Table 3. Chromosome numbers in lymphoblastoid cells from healthy control subjects and patients with moderate and severe ID. ID, intellectual disability; y, year; m, month; ND, not determined; –, absent; +, moderate; ++, severe; HC, head circumference; GR, growth retardation.

5. Conclusion

The amplification of centrosome number and aneuploidy are frequently observed in cancer cells, which may reflect tumorigenesis (Fang & Zhang, 2011). Mitotic defects underlying misaligned chromosomes and/or aneuploidy have also been reported in some patients with ID. Patients with MVA and some types of microcephaly belong to this category. During embryonic neurogenesis, symmetrical and asymmetrical divisions of the progenitor cells are critically important. Impairment of neurogenesis caused by mitotic defects, such as abnormal functioning of centrosomes and/or spindle structures, could result in neuronal loss, with or without abnormal cortical layer formation. Therefore, the study of aneuploidy is important not only for diagnosing mitotic defects but also for analyzing the etiology of patients with ID.

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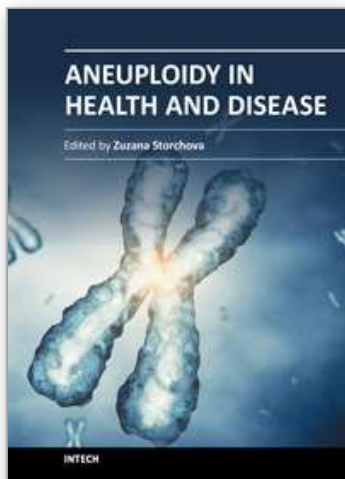
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Aneuploidy means any karyotype that is not euploid, anything that stands outside the norm. Two particular characteristics make the research of aneuploidy challenging. First, it is often hard to distinguish what is a cause and what is a consequence. Secondly, aneuploidy is often associated with a persistent defect in maintenance of genome stability. Thus, working with aneuploid, unstable cells means analyzing an ever changing creature and capturing the features that persist. In the book *Aneuploidy in Health and Disease* we summarize the recent advances in understanding the causes and consequences of aneuploidy and its link to human pathologies.

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