Mol Neurobiol (2012) 46:125–135
DOI 10.1007/s12035-012-8262-0

Cell Cycle Activation and Aneuploid Neurons in Alzheimer's Disease

Thomas Arendt

Received: 15 February 2012 / Accepted: 20 March 2012 / Published online: 13 April 2012

Abstract Alzheimer's disease (AD) is a chronic neurodegenerative disorder, characterized by synaptic degeneration associated with fibrillar aggregates of the amyloid-ß peptide and the microtubule-associated protein tau. The progression of neurofibrillary degeneration throughout the brain during AD follows a predictive pattern which provides the basis for the neuropathological staging of the disease. This pattern of selective neuronal vulnerability against neurofibrillary degeneration matches the regional degree of neuronal plasticity and inversely recapitulates ontogenetic and phylogenetic brain development which links neurodegenerative cell death to neuroplasticity and brain development. Here, we summarize recent evidence for a loss of neuronal differentiation control as a critical pathogenetic event in AD, associated with a reactivation of the cell cycle and a partial or full replication of DNA giving rise to neurons with a content of DNA above the diploid level. Neurons with an aneuploid set of chromosomes are also present at a low frequency in the normal brain where they appear to be well tolerated. In AD, however, where the number of aneuploid neurons is highly increased, a rather selective cell death of neurons with this chromosomal aberrancy occurs. This finding add aneuploidy to the list of critical molecular events that are shared between neurodegeneration and oncogenesis. It defines a molecular signature for neuronal vulnerability and directs our attention to a failure of neuronal differentiation control as a critical pathogenetic event and potential therapeutic target in AD.

T. Arendt (✉)
Paul Flechsig Institute of Brain Research, Universität Leipzig,
Jahnallee 59,
04109 Leipzig, Germany
e-mail: aret@medizin.uni-leipzig.de

Keywords Apoptosis · Brain development · Cell death · Chromosome segregation · DNA replication · Neuronal vulnerability

Neurodegeneration in Alzheimer's Disease Has a Developmental Dimension

Neurodegeneration in Alzheimer's disease (AD) is not a random process and its progression throughout the brain follows a predictive pattern that provides the basis for the neuropathological staging of the disease [1]. Due to systematic differences in selective neuronal vulnerability, certain cortical areas and types of neurons are more early and more constantly involved than others. In the cerebral cortex, neurofibrillary degeneration preferentially affects lamina III and V pyramidal neurons, leaving interneurons largely unaffected. Further, the limbic cortex and cortical association areas are most early and most severely affected while primary sensory and motor areas are spared until most advanced stages of the disease. This pattern in the distribution and progression of neurodegeneration provides a key to understand the AD pathomechanism, and several suggestions have been made to explain the underlying mechanisms [2, 3]. Of note, selective neuronal vulnerability against neurofibrillary degeneration matches the regional degree of neuronal plasticity and inversely recapitulates ontogenetic and phylogenetic brain development [2, 4, 5] (Fig. 1).

Based on this phenotypic link between vulnerability and plasticity, we have hypothesized that adult neurons with a high plastic potential rest in a labile state of differentiation which is prone to a loss of differentiation control and a subsequent de-differentiation which renders these neurons highly vulnerable for neurodegeneration [2, 6]. This concept is supported by observations on the neuronal expression of

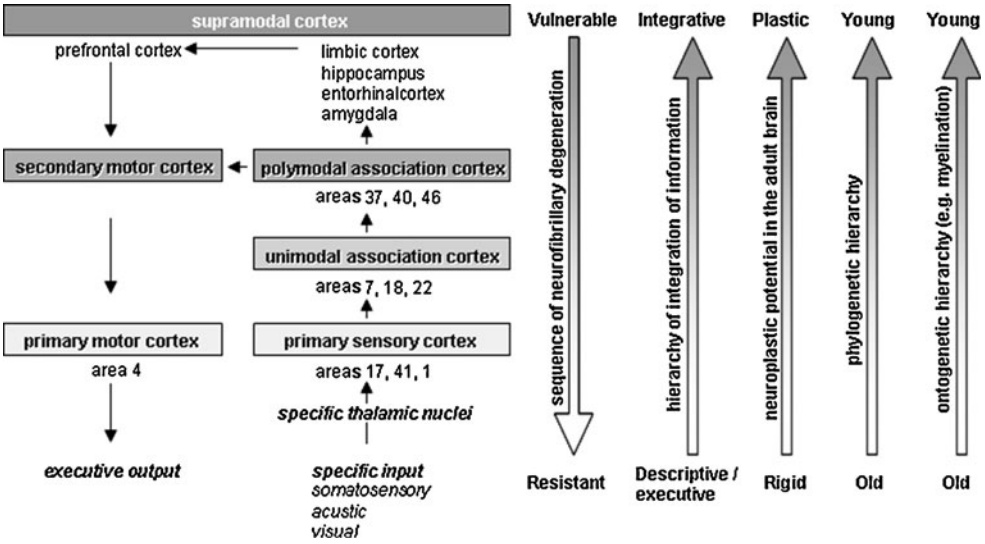

Fig. 1 Hierarchy of cortical vulnerability to neurofibrillary degeneration in Alzheimer's disease. The progression of neurofibrillary degeneration throughout cortical areas follows a defined sequence that represent systematic differences in vulnerability, which matches inversely the hierarchic pattern of complexity of cortical information processing, structural plasticity, and phylogenetic and ontogenetic age. (Modified after Arendt et al. [4, 9] and [182])

developmentally regulated genes in AD which corresponds to a condition of de-differentiation and links neurodegeneration to cell cycle-related events [7, 8]. The re-expression of a multitude of cell cycle regulators known to control the activation and progression of the cell cycle in dividing cells has been observed in degenerating neurons in AD [9–17], suggesting a reactivation of the cell cycle in the process of neurodegeneration [18–20] (Fig. 2).

Still, a number of recent studies indicate that, contrary to classical beliefs, molecules known to be involved in activation and progression of the cell cycle are not entirely repressed in differentiated neurons. As multifunctional proteins, they might subserve alternative "non-canonical functions" such as regulation of plasticity, depending on the cellular context [21–24]. After having withdrawn from the cell cycle, differentiated neurons are, thus, able to use molecular mechanisms primarily developed to control proliferation alternatively to control synaptic plasticity [18]. The existence of these alternative effector pathways within a neuron might put it at risk to erroneously convert signals derived from plastic synaptic changes into positional cues that will activate the cell cycle. This cell cycle activation potentially links synaptic plasticity to cell death.

Alzheimer's Disease Pathology Is a Structural Reflection of Brain Ontogeny

Neurofibrillary degeneration in the cerebral cortex in AD typically occurs in clusters. Degeneration predominantly involves pyramidal neurons within supra- and infragranular layers with the clustering in these layers often being in register with each other [25] indicating a columnar organization of degeneration [26]. This NFT clustering is highly correlated with symptoms [27]. Also, plaques appear to

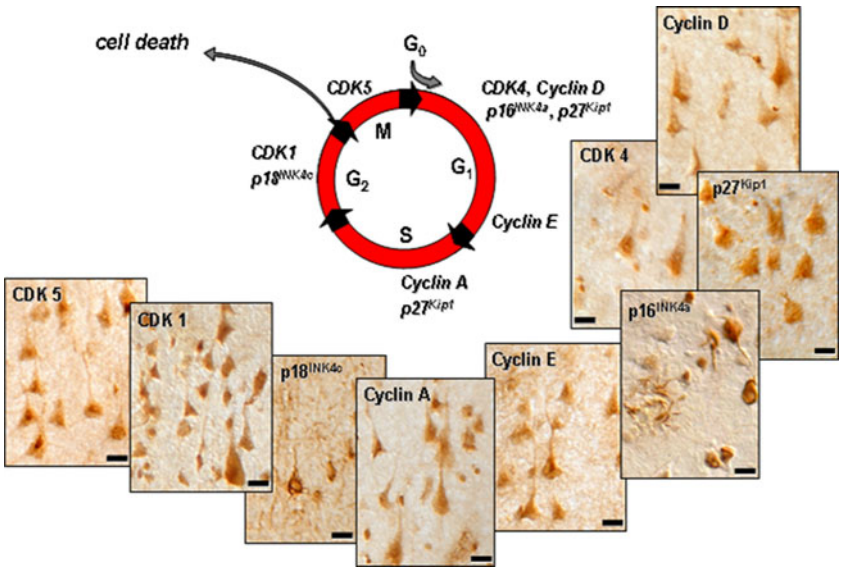

Fig. 2 Major regulators of the activation of the cell cycle and its orderly progression are re-expressed in pyramidal neurons in Alzheimer's disease prior to neurofibrillary degeneration. (Modified after [182, 184])

show a degree of vertical clustering between apical dendritic clusters [28].

The columnar cortical structure is disorganized in cortical areas affected by pathology in AD [29]. Cortical atrophy in AD, moreover, basically reflects a decrease in cortical length while cortical thickness remains largely unaffected which indicates a shrinkage or loss of columns [30, 31]. Also during normal aging, minicolumn width shrinks in those cortical regions that are potentially vulnerable to degeneration in AD [32].

This issue of columnar organization and clustering has been pursued with respect to other pathological structures. Disruption of the columnar organization of glial processes has been reported for AD [33]. Lewy bodies and Pick bodies [34, 35] also exhibit clustered distribution which reflect a modular structure. Thus, available evidence on the distribution of cortical pathology indicates a determination of the pattern of pathology through the modular organization of the cortex [36] which basically is a structural reflection of its ontogeny.

Phylogenetic Extension of Mitotic Activity During Neurogenesis Provides the Basis for a Higher Rate of Mitotic Errors

AD is a disorder that selectively affects the human brain, lacking any equivalent in other species including nonhuman primates. It is thus tempting to suggest that AD is specific to man because of molecular genetic events which promoted a rapid evolution of the hominid brain [37]. The phylogenetic expansion of the hominid neocortex most likely arose through a rapid multiplication of the fundamental columnar building blocks.

During embryonic development of the cerebral cortex, cells migrate towards the surface and form minicolumns of cells. They appear to be grouped into larger macrocolumns, which form the basis of the mapping of functions across the brain's surface. Pyramidal neurons, potentially vulnerable to neurofibrillary degeneration in AD, derive from radially migrating neurons that originate in the ventricular zone of the pallium (cortex). In the primate brain, they find their way to the distant cortex by using radially oriented glial fibers as guides. Recent studies of the embryonic brain have shown that about approximately one third of the dividing cells that arise from mitotic neural progenitor cells in the ventricular zone have genetic variability, manifested as chromosome aneuploidy [38–40]. On the contrary, cortical interneurons, unaffected by degeneration in AD, are born outside the cortex in the ganglionic eminence and reach their final position through tangential migration [41, 42].

Following the last mitotic division, immature neurons of the ventricular and sub-ventricular zones attach to an adjacent set of glial guidance fibers. Thus, clonally related neurons generated serially in time at the same locus in the germinal epithelium migrate sequentially along the same or adjacent set of glial guidance fibers and settle in the inside to outside pattern aligned in a single vertical column [43–45]. Neurons of this radial column form an ontogenetic unit, the fundamental building block in the developing neocortex [46]. Thus, the basic columnar organization of the cortex reflects its mode of generation [47–49].

The evolutionary expansion of neocortical size in mammals which is particularly prominent in anthropoid primates (i.e., monkeys, apes, and humans) reflects an increased number of cortical cells. According to the radial unit hypothesis, this phylogenetic expansion in cortical surface area results from an increase in the number of founder cells prior to neurogenesis. This increase in the number of cells is generated by two mechanism: (a) an increase in the size of the embryonic SVZ and (b) a prolonged period of cell cycle activity of progenitor cells during neurogenesis [50]. In macaque monkey, the period during which cell division occurs is ten times longer than in rodent and the cell cycle duration is two to five times longer than in mouse [51] Substantially more total rounds of cell divisions elapse during the prolonged neurogenetic period of the monkey cortex, providing the basis for increased cell proliferation. Moreover, unlike the progressive slowing that occurs during cortical development in rodents, cell division accelerates during neurogenesis of the enlarged cortical layers in monkeys. These findings suggest that evolutionary modifications of the duration and number of progenitor cell divisions contribute to both the expansion and laminar elaboration of the primate neocortex [52]. The enlarged cortex of great apes reflects a longer period of neuronal formation during prenatal development, so that each dividing progenitor cell undergoes more cell cycles before stopping cell division [52]. Cortical progenitors undergo 11 rounds of cell division in mice [53], at least 28 in the macaque [52], and probably fare more in human [54]. This phylogenetic prolongation of mitotic activity provides the basis for a potentially higher rate of accumulating mitotic errors during neurogenesis that might give rise to abnormal copies numbers of a genomic region.

Thus, loss or gain of copies of a genomic region occurs naturally during the course of evolution and might provide a mechanism of phylogenetic importance to regulate gene expression in the adult vertebrate brain. Recent studies of brain tissue from equivalent regions of different primate species suggest an upregulation of gene expression in the human cortex compared to chimpanzee cortex [55–58]. These upregulated genes tend to be enriched in genomic regions that have been recently duplicated in human evolution and can give rise to new genes [59, 60]

The Human Brain Is a Chromosomal Mosaic

With a very few exception [61, 62], all somatic mammalian cells have basically been assumed to contain identical genomes corresponding to a diploid set of chromosomes. Accordingly, cellular heterogeneity might largely be regulated by epigenetic mechanisms. More recent studies in the human brain, however, indicate that structural variations in the human genome due to loss or gain of whole chromosomes or fragments thereof might be an additional mechanism to generate neuronal diversity [39, 40, 63–70].

A more than diploid level of neuronal DNA was first reported about 50 years ago on rat Purkinje cells (Brodsky and Kusc [71]) and neurons of the cerebellar dentate nucleus in human brain [72]. These initial observations prompted a number of subsequent studies, reporting on similar findings for a large variety of neurons of different mammalian species, including cerebellar Purkinje cells of human [73, 74], cat [75], mice [76], rat [77–87], and chick [88], hippocampal and cortical pyramidal cells of cat [75, 89], rat [90–92], and guinea pig [93], nerve cells of the cervical superior ganglion in rabbit (Kut and Iarygin [94]), cat spinal motoneurons [75], and bat olfactory bulb [95].

After an ongoing controversy as to whether the DNA content of a very large part of neurons [77, 78] or even all neurons [80, 96, 97] exceeds the diploid level or not [98–103], a consensus was reached that the majority of neurons are diploid. Discrepant results were mainly attributed to various technical limitations and cytophotometric artifacts of heterochromatin in interphase nuclei of postmotitic neurons [104–106] but also to large individual variations [107]. Still, a small but constant fraction of a few percent of neurons continuously escaped the diploid DNA amount, irrespectively of the analytical method or other confounding factors of tissue sampling and preparation. This argues in favor of the presence of a "low-frequency" DNA content variation of neurons deviating from the diploid content giving rise to mosaic aneuploidy in the brain [107–109].

More recent studies applying state-of-the-art approaches for evaluating chromosome numbers in brain cells using multicolor fluorescence in situ hybridisation or chromogenic in situ hybridisation (CISH) with site-specific and centromeric DNA probes [39, 65–67] or interphase high-resolution chromosome-specific multicolor banding for the visualization of whole chromosomes [40, 63, 64, 68] constantly revealed a low frequency of aneuploid neurons in the human brain. This "low-frequency aneuploidy" which roughly amounts to about 10 % of all neurons [64, 66, 67] appears to be well tolerated in the normal brain, where it might contribute to genetically mosaic neuronal circuits [65, 110].

"High-Frequency Neuronal Aneuploidy" Might Trigger Apoptotic Clearance

While the rate of aneuploidy in proliferating neuroblasts has been reported as high as 33 % [39, 40], it decreases to about 10 % in the postmitotic cells in the adult brain [66, 111, 112]. This marked decrease in the rate of aneuploidy during ontogenetic brain development might indicate a higher rate of elimination due to higher susceptibility to cell death [39]. Alternatively, however, it could not be ruled out that aneuploid cells are less well able to proliferate and instead exit the cell cycle and terminally differentiate.

The apoptotic clearance of neuronal cells observed during cortical development [113] might be influenced by inherited mutations in genes implicated in the maintenance of chromosome stability. Alterations in mechanisms of apoptotic clearance may result in a lack of abnormal neuronal

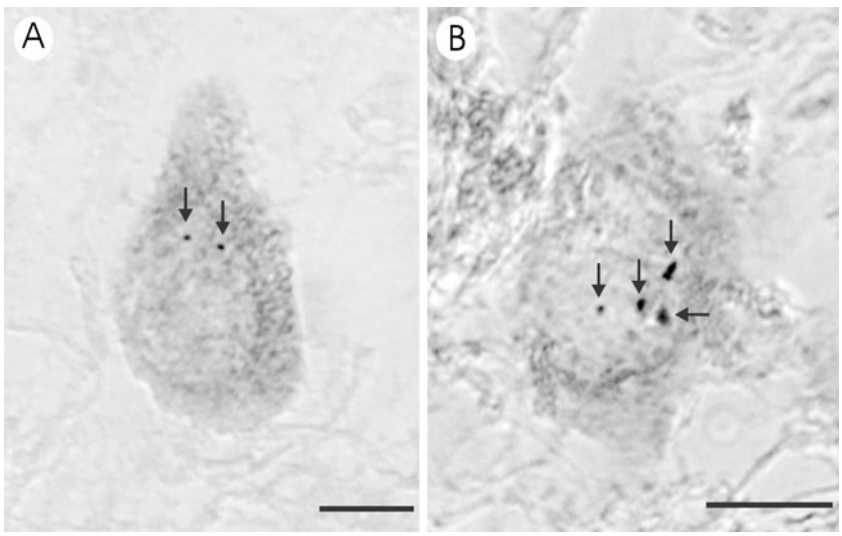

Fig. 3 Chromogenic in situ hybridisation with a chromosome 17 probe in the entorhinal cortex in Alzheimer's disease, demonstrating the simultaneous presence of pyramidal neurons with a diploid set of chromosomes (**a**) and with a chromosome number above the diploid level (tetraploid; **b**). (Modified after [66])

clearance during early brain development, leading, therefore, to neurodevelopmental abnormalities. Because extensive apoptotic clearance should disturb the maintenance of the established neuronal cell content in the adult brain, delayed apoptotic clearance may be considered a cause of late-onset neurodegenerative diseases. Different types of chromosomal imbalances may relate to an uneven apoptotic signaling potential. Therefore, each type of chromosome complement abnormality might possess a different propensity for apoptotic clearance [112, 114, 115].

Chromosomal Mosaicism of the Brain During Aging and in Mental Disorders

The functional significance of a brain composed of an intermixed population of aneuploid and euploid neurons is currently unknown. One possibility is that aneuploidy serves a mechanism for generating cellular diversity within the CNS. Indeed, aneuploid cells display distinct gene expression profiles compared with euploid cells from the same lineage as shown in a mouse model of loss of heterozygosity [38]. This indicates that functional gene expression can be permanently altered in living cells by chromosomal aneuploidy.

As shown recently, moreover, human autosomes typically show a high rate of random monoallelic gene silencing, expressing only either the maternal or the paternal allele [116]. This can clearly lead to differences in expressed protein sequences and to differences in levels of gene expression, a mechanism that further enhances molecular diversity of individual cells. Repression of neuronal gene expression, furthermore, has recently been identified as a phylogenetically evolved feature of brain aging in primates [117]. Through alterations in gene dosage by chromosomal gain or loss, aneuploid cells may also increase susceptibility to disease, as has been suggested for germline mutations resulting in large-scale copy number polymorphisms [118] and locus triplications [119].

Moreover, aneuploidy due to meiotic errors is the most common cause of fetal death, stillbirth, and disorders associated with chromosome abnormalities in humans [120]. Apart from trisomy of chromosomes 13, 18, and 21, as well as additional supernumerary marker chromosomes, all remaining autosomal aneuploidy conditions are supposed to occur in live births as mosaic forms only. Mental impairment is a characteristic feature of all recognizable autosomal aneuploidy syndromes. It is frequently accompanied by morphological changes in the brain of affected children, supporting the contention that the presence of neuronal cells with a gained or lost autosome may be related not only to impaired functioning but to conspicuous morphological abnormalities [121].

The two best studied biological processes associated with numerical chromosome imbalances are tumorigenesis and aging. Brain tumors demonstrate aneuploid karyotypes in at least about 50 % of cases [122, 123]. The variation of chromosome complement observed at the cytogenetic level as a feature of human aging has been well documented [124–126]. More recently, this phenomenon was found to be likely explained by mitotic misregulation [127]. Although tissue-specific chromosome complement variation in human aging

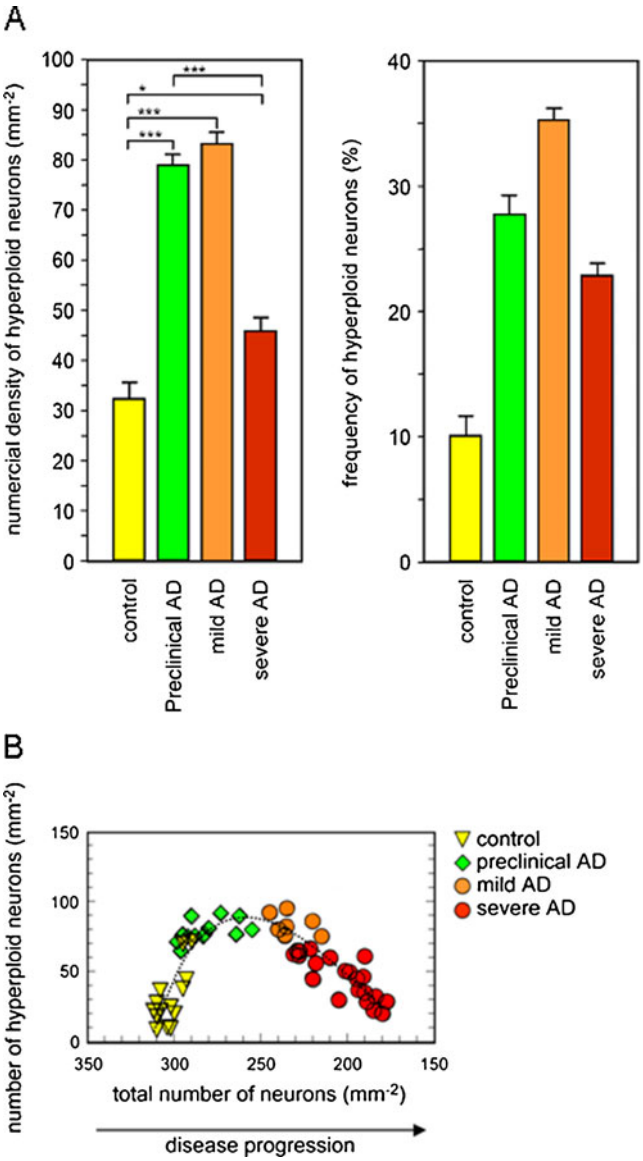

Fig. 4 Quantification of neurons with a DNA content above the diploid level (hyperploid) in the entorhinal cortex by slide-based cytometry in healthy controls, preclinical, mild, and severe Alzheimer's disease (**a**). The progression of the disease is paralleled by an inverse U-shaped curve in the number of hyperploid neurons with an initial increase in number during the transition from healthy controls towards preclinical and mild AD, followed a decrease during further disease progression (**b**). (*$p<0.05$; ***$p<0.001$; Student's t test). (Modified after [160])

is poorly understood, current data provide indirect evidence for an acquired aneuploidy in numerous tissues. In addition, the CNS possesses parts in which long-term production of neurons occur and, therefore, low-level chromosomal mosaicism in the human brain may also contribute to aging processes either through mitotic errors or the onset of expression of age-related genes in aneuploid mature neurons.

Human diseases with reported aneuploidy include Alzheimer's disease [39, 128–137], Down's syndrome [138–141], ataxia telangiectasia [63, 111], schizophrenia [115, 142–147], mosaic variegated aneuploidy [148–152], and various tumors such as gliomas [122, 153], glioblastomas [154, 155], and medulloblastomas [156]. To analyse the precise frequency and distribution of aneuploid neurons in AD, we developed a cytomic approach for single-cell DNA quantification in brain slices, combining slide-based cytometry after DNA staining with propidium iodide, CISH with chromosome-specific probes, and laser microdissection followed by quantitative PCR of *alu* repeats [66, 157–159]. With this technique, which allows to quantify the DNA content in single identified neurons within a preserved cytoarchitectonic context, we could obtain clear evidence for an increase in the number of neurons containing a more than diploid amount of DNA reaching about twice the frequency seen in controls (Figs. 3 and 4).

Aneuploidy in Alzheimer's Disease Is a Molecular Signature of Neurons Prone to Cell Death

Contrary to the "low-frequency neuronal aneuploidy" which appears to be well tolerated, numerical chromosome aberrancies might be detrimental if its abundance exceeds a certain threshold, leading to apoptotic clearance (see above). We could, thus, show recently that neurons with a chromosomal number above the normal diploid level are rather selectively affected by cell death at very early stages of Alzheimer's disease [160] (Fig. 4).

Neurodegeneration mediated by chromosome instability appears not to be unique to AD and has recently also been reported for cerebellar degeneration in patients with ataxia-telangiectasia [63]. These findings support previous suggestions that certain types of numerical chromosome abnormalities in the brain might contribute to neurodegenerative diseases [64, 66, 161– 166]. Despite this clear evidence for the deleterious sequelae of numerical chromosome abnormalities in AD, there still is controversy about its modes of generation [167].

Potentially, these neurons might derive from a partial reinitiation of DNA replication that actively takes place in the adult brain shortly before cell death. Reasons for an incomplete replication of DNA could be an accumulation of DNA damage and a decreased expression and activity of replication enzymes [168–171]. Developmental deficiencies in chromosome segregation [172] giving rise to aneuploid neuronal progenitors that have failed to undergo apoptotic clearance have also been suggested as a critical pathogenetic mechanism in AD [173, 174]. This "chromosome malsegregation hypothesis" is supported by a large body of evidence arising from cytogenetic studies carried out to assess structural and numerical chromosome aberrations in cultured peripheral cells of AD patients, as well as an increased risk to develop AD and show chromosomal malsegregation in lymphocytes in young mothers of patients with trisomy 21 [130, 137, 175–180]. In particular, mutations in the presenilin genes that cause AD also cause chromosome instability [161, 165, 181]. Further, neuronal aneuploidy might contribute to inflammation and amyloidogenic processing of APP which are critical features of AD [173].

Taken together, the data presented here provide direct evidence for an increased frequency in AD of neurons containing a DNA content above the normal diploid level and the deleterious consequences of this chromosomal aberrancy. These findings add aneuploidy to the list of critical molecular events that are shared between neurodegeneration and oncogenesis [182]. Irrespectively of whether aneuploidy results from a lack of apoptotic clearance during brain development or an aberrant attempt of cell cycle reentry [66, 114, 183], it defines a molecular signature for neuronal vulnerability and directs our attention to a failure of neuronal differentiation control as a critical pathogenetic event and potential therapeutic target in AD.

References

1. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239–259
2. Arendt T (2001) Alzheimer's disease as a disorder of mechanisms underlying structural brain self-organization. Neuroscience 102:723–765
3. Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A, Fraser G, Stalder AK, Beibel M, Staufenbiel M, Jucker M, Goedert M, Tolnay M (2009) Transmission and spreading of tauopathy in transgenic mouse brain. Nat Cell Biol 11 (7):909–913
4. Arendt T, Brückner MK, Gertz HJ, Marcova L (1998) Cortical distribution of neurofibrillary tangles in Alzheimer's disease matches the pattern of neurons that retain their capacity of plastic remodelling in the adult brain. Neuroscience 83(4):991–1002
5. Braak H, Braak E (1996) Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. Acta Neuropathol 92(2):197–201
6. Arendt T, Holzer M, Stobe A, Gartner U, Luth HJ, Bruckner MK, Ueberham U (2000) Activated mitogenic signaling induces a process of dedifferentiation in Alzheimer's disease that eventually results in cell death. Ann N Y Acad Sci 920:249–255
7. Arendt T (1993) Neuronal dedifferentiation and degeneration in Alzheimer's disease. Biol Chem Hoppe-Seyler 374:911–912
8. Heintz N (1993) Cell-death and the cell-cycle—a relationship between transformation and neurodegeneration. Trends Biochem Sci 18:157–159

9. Arendt T, Holzer M, Gartner U (1998) Neuronal expression of cycline dependent kinase inhibitors of the INK4 family in Alzheimer's disease. J Neural Transm 105:949–960
10. Arendt T, Rodel L, Gartner U, Holzer M (1996) Expression of the cyclin-dependent kinase inhibitor p16 in Alzheimer's disease. Neuroreport 7:3047–3049
11. Busser J, Geldmacher DS, Herrup K (1998) Ectopic cell cycle proteins predict the sites of neuronal cell death in Alzheimer's disease brain. J Neurosci 18:2801–2807
12. Ding XL, Husseman J, Tomashevski A, Nochlin D, Jin LW, Vincent I (2000) The cell cycle Cdc25A tyrosine phosphatase is activated in degenerating postmitotic neurons in Alzheimer's disease. Am J Pathol 157:1983–1990
13. McShea A, Harris PL, Webster KR, Wahl AF, Smith MA (1997) Abnormal expression of the cell cycle regulators P16 and CDK4 in Alzheimer's disease. Am J Pathol 150:1933–1939
14. Nagy Z, Esiri MM, Cato AM, Smith AD (1997) Cell cycle markers in the hippocampus in Alzheimer's disease. Acta Neuropathol (Berl) 94:6–15
15. Nagy Z, Esiri MM, Smith AD (1997) Expression of cell division markers in the hippocampus in Alzheimer's disease and other neurodegenerative conditions. Acta Neuropathol (Berl) 93:294–300
16. Smith TW, Lippa CF (1995) Ki-67 immunoreactivity in Alzheimer's disease and other neurodegenerative disorders. J Neuropathol Exp Neurol 54:297–303
17. Vincent I, Jicha G, Rosado M, Dickson DW (1997) Aberrant expression of mitotic cdc2/cyclin B1 kinase in degenerating neurons of Alzheimer's disease brain. J Neurosci 17:3588–3598
18. Arendt T (2003) Synaptic plasticity and cell cycle activation in neurons are alternative effector pathways: the Dr. Jekyll and Mr. Hyde concept of Alzheimer's disease or the yin and yang of neuroplasticity. Progr Neurobiol 71:83–248
19. Herrup K, Arendt T (2002) Re-expression of cell cycle proteins induces neuronal cell death during Alzheimer's disease. J Alzheimers Dis 4:243–247
20. Herrup K, Yang Y (2007) Cell cycle regulation in the postmitotic neuron: oxymoron or new biology? Nat Rev Neurosci 8:368–378
21. Arendt T, Brückner MK (2007) Linking cell-cycle dysfunction in Alzheimer's disease to a failure of synaptic plasticity. Biochim Biophys Acta 1772(4):413–421
22. Schmetsdorf S, Gartner U, Arendt T (2005) Expression of cell cycle-related proteins in developing and adult mouse hippocampus. Int J Dev Neurosci 23:101–112
23. Schmetsdorf S, Gärtner U, Arendt T (2007) Constitutive expression of functionally active cyclin-dependent kinases and their binding partners suggests noncanonical functions of cell cycle regulators in differentiated neurons. Cereb Cortex 17:1821–1829
24. Frank CL, Li-H T (2009) Alternative functions of core cell cycle regulators in neuronal migration, neuronal maturation, and synaptic plasticity. Neuron 62(3):312–326
25. Pearson RC, Esiri MM, Hiorns RW, Wilcock GK, Powell TP (1985) Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease. PNAS 82:4531–4534
26. Esiri MM, Chance SA (2006) Vulnerability to Alzheimer's pathology in neocortex: the roles of plasticity and columnar organization. J Alzheimers Dis 9(3 Suppl):79–89
27. Nagy Z, Esiri MM, Jobst KA, Morris JH, King EM, McDonald B, Litchfield S, Barnetson L (1996) Clustering of pathological features in Alzheimer's disease: clinical and neuroanatomical aspects. Dementia 7:121–127
28. Kosik KS, Rogers J, Kowall NW (1987) Senile plaques are located between apical dendritic clusters. J Neuropathol Exp Neurol 46:1–11
29. Buldyrev SV, Cruz L, Gomez-Isla T, Gomez-Tortosa E, Havlin S, Le R, Stanley HE, Urbanc B, Hyman BT (2000) Description of microcolumnar ensembles in association cortex and their disruption in Alzheimer and Lewy body dementias. PNAS 97:5039–5043
30. Duyckaerts C, Hauw JJ, Piette F, Rainsard C, Poulain V, Berthaux P, Escourolle R (1985) Cortical atrophy in senile dementia of the Alzheimer type is mainly due to a decrease in cortical length. Acta Neuropathol 66:72–74
31. Terry RD, Peck A, DeTeresa R, Schechter R, Horoupian DS (1981) Some morphometric aspects of the brain in senile dementia of the Alzheimer type. Ann Neurol 10:184–192
32. Chance SA, Casanova MF, Switala AE, Crow TJ, Esiri MM (2006) Minicolumn thinning in temporal lobe association cortex but not primary auditory cortex in normal human ageing. Acta Neuropathol 111:459–464
33. Colombo JA, Quinn B, Puissant V (2002) Disruption of astroglial interlaminar processes in Alzheimer's disease. Brain Res Bull 58:235–242
34. Armstrong RA, Cairns NJ, Lantos PL (1997) Dementia with Lewy bodies: clustering of Lewy bodies in human patients. Neurosci Lett 224(1):41–44
35. Armstrong RA, Cairns NJ, Lantos PL (1998) Clustering of Pick bodies in patients with Pick's disease. Neurosci Lett 242(2):81–84
36. Casanova MF (2003) Modular concepts of brain organization and the neuropathology of psychiatric conditions. Psychiatr Res 118:101–102
37. Rapoport SI (1988) Brain evolution and Alzheimer's disease. Rev Neurol (Paris) 144:79–90
38. Kaushal D, Contos JJ, Treuner K, Yang AH, Kingsbury MA, Rehen SK, McConnell MJ, Okabe M, Barlow C, Chun J (2003) Alteration of gene expression by chromosome loss in the postnatal mouse brain. J Neurosci 23:5599–5606
39. Rehen SK, McConnell MJ, Kaushal D, Kingsbury MA, Yang AH, Chun J (2001) Chromosomal variation in neurons of the developing and adult mammalian nervous system. PNAS 98:13361–13366
40. Yurov YB, Iourov IY, Vorsanova SG, Liehr T, Kolotii AD, Kutsev SI, Pellestor F, Beresheva AK, Demidova IA, Kravets VS, Monakhov VV, Soloviev IV (2007) Aneuploidy and confined chromosomal mosaicism in the developing human brain. PLoS One 2:e558
41. Martin O, Rubenstein JL (2001) A long, remarkable journey: tangential migration in the telencephalon. Nat Rev Neurosci 2 (11):780–790
42. Molyneaux BJ, Arlotta P, Menezes JR, Macklis JD (2007) Neuronal subtype specification in the cerebral cortex. Nat Rev Neurosci 8:427–437
43. Kornack DR, Rakic P (1995) Radial and horizontal deployment of clonally related cells in the primate neocortex: relationship to distinct mitotic lineages. Neuron 15:311–321
44. Luskin MB, Parnavelas JG, Barfield JA (1993) Neurons, astrocytes, and oligodendrocytes of the rat cerebral cortex originate from separate progenitor cells: an ultrastructural analysis of clonally related cells. J Neurosci 13:1730–1750
45. Sidman RL, Rakic P (1973) Neuronal migration, with special reference to developing human brain: a review. Brain Res 62:1–35
46. Rakic P (1988) Specification of cerebral cortical areas. Science 241:170–176
47. Mountcastle VB (1957) Modality and topographic properties of single neurons of cat's somatic sensory cortex. J Neurophysiol 20:408–434
48. Mountcastle VB (1978) An organizing principle for cerebral function. In: Edelman GM, Mountcastle VB (eds) The mindful brain. MIT Press, Cambridge, pp 7–50
49. Mountcastle VB (1997) The columnar organization of the neocortex. Brain 120:701–722

50. Kriegstein A, Noctor S, Martinez-Cerdeno V (2006) Patterns of neural stem and progenitor cell division may underlie evolutionary cortical expansion. Nat Rev Neurosci 7:883–890
51. Krubitzer L, Kahn DM (2003) Nature versus nurture revisited: an old idea with a new twist. Prog Neurobiol 70:33–52
52. Kornack DR, Rakic P (1998) Changes in cell-cycle kinetics during the development and evolution of primate neocortex. PNAS 95:1242–1246
53. Takahashi T, Nowakowski RS, Caviness VS Jr (1995) The cell cycle of the pseudostratified ventricular epithelium of the embryonic murine cerebral wall. J Neurosci 15:6046–6057
54. Hill RS, Walsh CA (2005) Molecular insights into human brain evolution. Nature 437:64–67
55. Cáceres M, Lachuer J, Zapala MA, Redmond JC, Kudo L, Geschwind DH, Lockhart DJ, Preuss TM, Barlow C (2003) Elevated gene expression levels distinguish human from non-human primate brains. Proc Natl Acad Sci U S A 100(22):13030–13035
56. Enard W, Khaitovich P, Klose J, Zöllner S, Heissig F, Giavalisco P, Nieselt-Struwe K, Muchmore E, Varki A, Ravid R, Doxiadis GM, Bontrop RE, Pääbo S (2002) Intra- and interspecific variation in primate gene expression patterns. Science 296(5566):340–343
57. Gu J, Gu X (2003) Induced gene expression in human brain after the split from chimpanzee. Trends Genet 19(2):63–65
58. Uddin M, Wildman DE, Liu G, Xu W, Johnson RM, Hof PR, Kapatos G, Grossman LI, Goodman M (2004) Sister grouping of chimpanzees and humans as revealed by genome-wide phylogenetic analysis of brain gene expression profiles. PNAS 101 (9):2957–2962
59. Khaitovich P, Muetzel B, She X, Lachmann M, Hellmann I, Dietzsch J, Steigele S, Do HH, Weiss G, Enard W, Heissig F, Arendt T, Nieselt-Struwe K, Eichler EE, Pääbo S (2004) Regional patterns of gene expression in human and chimpanzee brains. Genome Res 14(8):1462–1473
60. Khaitovich P, Weiss G, Lachmann M, Hellmann I, Enard W, Muetzel B, Wirkner U, Ansorge W, Pääbo S (2004) A neutral model of transcriptome evolution. PLoS Biol 2(5):E132
61. Thomson RY, Frazer SC (1954) The deoxyribonucleic acid content of individual rat cell nuclei. Exp Cell Res 6:367–383
62. Ueberham E, Lindner R, Kamprad M, Hiemann R, Hilger N, Woithe B, Mahn D, Cross M, Sack U, Gebhardt R, Arendt T, Ueberham U (2008) Oval cell proliferation in p16INK4a expressing mouse liver is triggered by chronic growth stimuli. J Cell Mol Med 12:622–638
63. Iourov IY, Vorsanova SG, Liehr T, Kolotii AD, Yurov YB (2009) Increased chromosome instability dramatically disrupts neural genome integrity and mediates cerebellar degeneration in the ataxia-telangiectasia brain. Human Mol Gen 18:2656–2669
64. Iourov IY, Vorsanova SG, Liehr T, Yurov YB (2009) Aneuploidy in the normal, Alzheimer's disease and ataxia-telangiectasia brain: differential expression and pathological meaning. Neurobiol Dis 34:212–220
65. Kingsbury MA, Friedman B, McConnell MJ, Rehen SK, Yang AH, Kaushal D, Chun J (2005) Aneuploid neurons are functionally active and integrated into brain circuitry. PNAS 102:6143–6147
66. Mosch B, Morawski M, Mittag A, Lenz D, Tarnok A, Arendt T (2007) Aneuploidy and DNA replication in the normal human brain and Alzheimer's disease. J Neurosci 27:6859–6867
67. Rehen SK, Yung YC, McCreight MP, Kaushal D, Yang AH, Almeida BSV, Kingsbury MA, Cabral KMS, McConnell MJ, Anliker B, Fontanoz M, Chun J (2005) Constitutional aneuploidy in the normal human brain. J Neurosci 25:2176–2180
68. Vorsanova SG, Yurov YB, Iourov IY (2010) Human interphase chromosomes: a review of available molecular cytogenetic technologies. Mol Cytogen 3:1
69. Westra JW, Peterson SE, Yung YC, Mutoh T, Barral S, Chun J (2008) Aneuploid mosaicism in the developing and adult cerebellar cortex. J Comp Neurol 507:1944–1951
70. Westra JW, Rivera RR, Bushman DM, Yung YC, Peterson SE, Barral S, Chun J (2010) Neuronal DNA content variation (DCV) with regional and individual differences in the human brain. J Comp Neurol 518:3981–4000
71. Brodsky VJ, Kusc AA (1962) Changes in the number of polyploid cells during postnatal development of rat tissue. Sci USSR 147:713–716
72. Müller H (1962) Cytophotometrische DNS-Messungen an Ganglienzellkernen des Nucleus dentatus beim Menschen. Naturwiss 49:243
73. Lapham LW (1965) The tetraploid DNA content of normal human Purkinje cells and its development during the perinatal period: a quantitative cytochemical study. Excerpta Med (Amst) Congr Ser 100:445–449
74. Lapham LW (1968) Tetraploid DNA content of Purkinje neurons of human cerebellar cortex. Science 159:310–312
75. Herman CJ, Lapham LW (1969) Neuronal polyploidy and nuclear volumes in the cat central nervous system. Brain Res 15:35–48
76. Mares V, Lodin Z, Sácha J (1973) A cytochemical and autoradiographic study of nuclear DNA in mouse Purkinje cells. Brain Res 53:273–289
77. Bernocchi G, Manfredi Romanini MG (1977) Chromatin cytochemistry as a tool for the functional interpretation of Purkinje's cells in rat cerebellum. Riv Istochim Norm Patol 21:131–142
78. Bernocchi G, Redi CA, Scherini E (1979) Feulgen-DNA content of the Purkinje neuron: "diploid" or "tetraploid"? Basic Appl Histochem 23:65–70
79. Bernocchi G (1975) Contenuto in DNA e area nucleare dei neuroni durante l'istogenese cerebellare del ratto. Instituto Lombardo (Rend Sc) 109:143–161
80. Bregnard A, Knüsel A, Kuenzle CC (1975) Are all the neuronal nuclei polyploid? Histochemistry 43:59–61
81. Brodsky VJ, Sokolova GA, Manakova TE (1971) Multiple increase of DNA in the Purkinje cells of cerebellum in ontogenesis of rats. Ontogeny (USSR) 2:33–36
82. Brodsky VY, Agroskin LS, Lebedev EA, Marshak TL, Papayan GV, Segal OL, Sokolova GA, Yarygin KN (1974) Stability and variations of amount of DNA in a population of cerebellum cells. Z Obshchei Biol 35:917–925
83. Lentz RD, Lapham LW (1969) A quantitative cytochemical study of the DNA content of neurons of rat cerebellar cortex. J Neurochem 16:379–384
84. Lentz RD, Lapham LW (1970) Postnatal development of tetraploid DNA content in rat Purkinje cells: a quantitative cytochemical study. J Neuropathol Exp Neurol 29:43–56
85. Marshak TL, Maresh V, Brodskii V (1978) Number of Purkinje cells with an increased DNA content in rat cerebellum. Kolichestvo kletok Purkin'e s uvelichennym soderzhaniem DNK v mozzhechke krysy. Tsitolog 20:651–656
86. Marshak TL, Petruchuk EM, Aref'eva AM, Shalunova NV, Brodskiĭ VI (1976) O soderzhanii DNK V kletkakh Purkin'e mozzhechka krys, spontanno infitsirovannykh virusom Kilkhema. Biulleten' eksperimental'noĭ biologii i meditsiny 82:1274–1276
87. Sandritter W, Novokova V, Pilny J, Kiefer G (1967) Cytophotometrische Messungen des Nukleins ure- und Proteingehaltes von Ganglienzellen der Ratte während der postnatalen Entwicklung und im Alter. Zeitschr Zellforsch 80:145–152
88. Magkian I, Karalova EM (1975) [Basic factors in the polyploidization of cerebellar Purkinfe cells in chick embryogenesis. III. Kinetics of RNA and DNA in Purkinje cell nuclei]. Osenovnye faktory poliploidizatsii kletok Purkin'e mozzhechka v embriogeneze kur. III. Kinetika RNK i DNK v iadrakh kletok Purkin'e. Tsitolog 17:653–659

89. Herman CJ, Lapham LW (1968) DNA content of neurons in the cat hippocampus. Science 160:537
90. Bregnard A, Kuenzle CC, Ruch F (1977) Cytophotometric and autoradiographic evidence for post-natal DNA synthesis in neurons of the rat cerebral cortex. Exp Cell Res 107:151–157
91. Nováková V, Sandritter W, Schlueter G (1970) DNA content of neurons in rat central nervous system. Exp Cell Res 60:454–456
92. Svanidze IK (1967) Cytophotometry of DNA amounts in nuclei of neurons and gliacytes of the cerebral cortex of rats at different ontogenetic stages. J Gen Biol (USSR) 28:697–708
93. Museridze DP, Svanidze IK (1972) Quantitative analysis of DNA in the neurons of the visual cortex of the brain at the early stages of postnatal ontogenesis of guinea pigs. Sov J Dev Biol 3:430–434
94. Kut AA, Iarygin VN (1965) Polipliodiia odnoiadernykh i dvuiadernykh neĭronov v verkhnem sheĭnom uzle krolika. Tsitolog 7:228–233
95. Swartz FJ, Bhatnagar KP (1981) Are CNS neurons polyploid? A critical analysis based upon cytophotometric study of the DNA content of cerebellar and olfactory bulbar neurons of the bat. Brain Res 208:267–281
96. Bregnard A, Ruch F, Lutz H, Kuenzle CC (1979) Histones and DNA increase synchronously in neurons during early postnatal development of the rat forebrain cortex. Histochemistry 61:271–279
97. Kuenzle CC, Bregnard A, Hübscher U, Ruch F (1978) Extra DNA in forebrain cortical neurons. Exp Cell Res 113:151–160
98. Cohen J, Mares V, Lodin Z (1973) DNA content of purified preparations of mouse Purkinje neurons isolated by a velocity sedimentation technique. J Neurochem 20:651–657
99. Fujita S (1974) DNA constancy in neurons of the human cerebellum and spinal cord as revealed by Feulgen cytophotometry and cytofluorometry. J Comp Neurol 155:195–202
100. Fukuda M, Bohm N, Fujita S (1978) Cytophotometry and its biological application. Progr Histochem Cytochem 11:1–119
101. Mann DM, Yates PO, Barton CM (1978) The DNA content of Purkinje cells in mammals. J Comp Neurol 180:345–347
102. Mann DM, Yates PO (1973) Polyploidy in the human nervous system: Part 1. The DNA content of neurones and glia of the cerebellum. J Neurol Sci 18:183–196
103. Morselt AF, Braakman DJ, James J (1972) Feulgen-DNA and fast-green histone estimations in individual cell nuclei of the cerebellum of young and old rats. Acta Histochem 43:281–286
104. Duijndam WA, Smeulders AW, van Duijn P, Verweij AC (1980) Optical errors in scanning stage absorbance cytophotometry. I. Procedures for correcting apparent integrated absorbance values for distributional, glare, and diffraction errors. J Histochem Cytochem 28:388–394
105. Duijndam WA, van Duijn P, Riddersma SH (1980) Optical errors in scanning stage absorbance cytophotometry. II. Application of correction factors for residual distributional error, glare and diffraction error in practical cytophotometry. J Histochem Cytochem 28:395–400
106. Fujita S, Fukuda M, Kitamura T, Satoru Y (1972) Two-wavelength-scanning method in Feulgen cytophotometry. Acta Histochem Cytochem 5:146–152
107. Brodsky VJ, Marshak TL, Mares V, Lodin Z, Fülöp Z, Lebedev EA (1979) Constancy and variability in the content of DNA in cerebellar Purkinje cell nuclei. A cytophotometric study. Histochemistry 59:233–248
108. Mares V, van der Ploeg M (1980) Cytophotometric reinvestigation of DNA content in Purkinje cells of the rat cerebellum. Histochemistry 69:161–167
109. Marshak TL, Mares V, Brodsky VY (1985) An attempt to influence DNA content in postmitotic Purkinje cells of the cerebellum. Acta Histochem 76:193–200
110. Morillo SM, Escoll P, de La Hera A, Frade JM (2010) Somatic tetraploidy in specific chick retinal ganglion cells induced by nerve growth factor. PNAS 107:109–114
111. McConnell MJ, Kaushal D, Yang AH, Kingsbury MA, Rehen SK, Treuner K, Helton R, Annas EG, Chun J, Barlow C (2004) Failed clearance of aneuploid embryonic neural progenitor cells leads to excess aneuploidy in the Atm-deficient but not the Trp53-deficient adult cerebral cortex. J Neurosci 24:8090–8096
112. Yurov YB, Iourov IY, Monakhov VV, Soloviev IV, Vostrikov VM, Vorsanova SG (2005) The variation of aneuploidy frequency in the developing and adult human brain revealed by an interphase FISH study. J Histochem Cytochem 53:385–390
113. Blaschke AJ, Staley K, Chun J (1996) Widespread programmed cell death in proliferative and postmitotic regions of the fetal cerebral cortex. Development 122:1165–1174
114. Yang Y, Geldmacher DS, Herrup K (2001) DNA replication precedes neuronal cell death in Alzheimer's disease. J Neurosci 21:2661–2668
115. Yurov YB, Vostrikov VM, Vorsanova SG, Monakhov VV, Iourov IY (2001) Multicolor fluorescent in situ hybridization on postmortem brain in schizophrenia as an approach for identification of low-level chromosomal aneuploidy in neuropsychiatric diseases. Brain Dev 23(Suppl 1):186–190
116. Gimelbrant A, Hutchinson JN, Thompson BR, Chess A (2007) Widespread monoallelic expression on human autosomes. Science 318:1136–1140
117. Loerch PM, Lu T, Dakin KA, Vann JM, Isaacs A, Geula C, Wang J, Pan Y, Gabuzda DH, Li C, Prolla TA, Yankner BA (2008) Evolution of the aging brain transcriptome and synaptic regulation. PLoS One 3(10):e3329
118. Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P, Månér S, Massa H, Walker M, Chi M, Navin N, Lucito R, Healy J, Hicks J, Ye K, Reiner A, Gilliam TC, Trask B, Patterson N, Zetterberg A, Wigler M (2004) Large-scale copy number polymorphism in the human genome. Science 305:525–528
119. Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, Hulihan M, Peuralinna T, Dutra A, Nussbaum R, Lincoln S, Crawley A, Hanson M, Maraganore D, Adler C, Cookson MR, Muenter M, Baptista M, Miller D, Blancato J, Hardy J, Gwinn-Hardy K (2003) alpha-Synuclein locus triplication causes Parkinson's disease. Science 302:841
120. Hassold T, Hunt P (2001) To err (meiotically) is human: the genesis of human aneuploidy. Nat Rev Genet 2:280–291
121. Rezaie R, Daly EM, Cutter WJ, Murphy DG, Robertson DM, Delisi LE, Mackay CE, Barrick TR, Crow TJ, Roberts N (2009) The influence of sex chromosome aneuploidy on brain asymmetry. Am J Med Genet B Neuropsychiatr Genet 150B(1):74–85
122. Bigner SH, Mark J, Bigner DD (1990) Cytogenetics of human brain tumors. Cancer Genet Cytogenet 47:141–154
123. Yamada K, Kasama M, Kondo T, Shinoura N, Yoshioka M (1994) Chromosome studies in 70 brain tumors with special attention to sex chromosome loss and single autosomal trisomy. Cancer Genet Cytogenet 73:46–52
124. Guttenbach M, Koschorz B, Bernthaler U, Grimm T, Schmid M (1995) Sex chromosome loss and aging: in situ hybridization studies on human interphase nuclei. Am J Hum Genet 57:1143–1150
125. Jacobs PA, Court Brown WM, Doll R (1961) Distribution of human chromosome counts in relation to age. Nature 191:1178–1180
126. Nowinski GP, Van Dyke DL, Tilley BC, Jacobsen G, Babu VR, Worsham MJ, Wilson GN, Weiss L (1990) The frequency of aneuploidy in cultured lymphocytes is correlated with age and gender but not with reproductive history. Am J Hum Genet 46:1101–1111
127. Ly DH, Lockhart DJ, Lerner RA, Schultz PG (2000) Mitotic misregulation and human aging. Science 287:2486–2492

128. Buckton KE, Whalley LJ, Lee M, Christie JE (1983) Chromosome changes in Alzheimer's presenile dementia. J Med Genet 20:46–51
129. King RC, Stansfiled WD (1990) A dictionary of genetics, 4th edn. Oxford University Press, New York
130. Moorhead PS, Heyman A (1983) Chromosome studies of patients with Alzheimer's disease. Am J Med Genet 14:545–556
131. Nordenson I, Adolfsson R, Beckman G, Bucht G, Winblad B (1980) Chromosomal abnormality in dementia of Alzheimer type. Lancet 1(8166):481–482
132. Thomas P, Fenech M (2008) Chromosome 17 and 21 aneuploidy in buccal cells is increased with ageing and in Alzheimer's disease. Mutagenesis 23:57–65
133. Gorman P, Roylance R (2006) Fluorescence in situ hybridization and comparative genomic hybridization. Meth Mol Med 120:269–295
134. Nordensson I, Beckman G, Adolfsson R, Bucht G, Winblad B (1983) Cytogenetic changes in patients with senile dementia. Age Ageing 12(4):285–295
135. Smith A, Broe GA, Williamson M (1983) Chromosome aneuploidy in Alzheimer's disease. Clin Genet 24:54–57
136. Ward BE, Cook RH, Robinson A, Austin JH (1979) Increased aneuploidy in Alzheimer disease. Am J Med Genet 3:137–144
137. White BJ, Crandall C, Goudsmit J, Morrow CH, Alling DW, Gajdusek DC, Tijio JH (1981) Cytogenetic studies of familial and sporadic Alzheimer disease. Am J Med Genet 10:77–89
138. Jacobs PA, Baikie AG, Court Brown WM, Strong JA (1959) The somatic chromosomes in mongolism. Lancet 1(7075):710
139. Lejeune J, Turpin R, Gautier M (1959) Mongolism: a chromosomal disease (trisomy). Bull Acad Natl Med 143:256–265
140. Lichter P, Cremer T, Tang CJ, Watkins PC, Manuelidis L, Ward DC (1988) Rapid detection of human chromosome 21 aberrations by in situ hybridization. PNAS 85:9664–9668
141. Zheng YL, Ferguson-Smith MA, Warner JP, Ferguson-Smith ME, Sargent CA, Carter NP (1992) Analysis of chromosome 21 copy number in uncultured amniocytes by fluorescence in situ hybridization using a cosmid contig. Prenat Diagn 12:931–943
142. DeLisi LE, Friedrich U, Wahlstrom J, Boccio-Smith A, Forsman A, Eklund K, Crow TJ (1994) Schizophrenia and sex chromosome anomalies. Schizophr Bull 20:495–505
143. Kaplan AR (1970) Chromosomal mosaicisms and occasional acentric chromosomal fragments in schizophrenic patients. Biol Psychiatry 2:89–94
144. Kumra S, Wiggs E, Krasnewich D, Meck J, Smith AC, Bedwell J, Fernandez T, Jacobsen LK, Lenane M, Rapoport JL (1998) Brief report: association of sex chromosome anomalies with childhood-onset psychotic disorders. J Am Acad Child Adolesc Psych 37:292–296
145. Kunugi H, Lee KB, Nanko S (1999) Cytogenetic findings in 250 schizophrenics: evidence confirming an excess of the X chromosome aneuploidies and pericentric inversion of chromosome 9. Schizophr Res 40:43–47
146. Mors O, Mortensen PB, Ewald H (2001) No evidence of increased risk for schizophrenia or bipolar affective disorder in persons with aneuploidies of the sex chromosomes. Psychol Med 31:425–430
147. Toyota T, Shimizu H, Yamada K, Yoshitsugu K, Meerabux J, Hattori E, Ichimiya T, Yoshikawa T (2001) Karyotype analysis of 161 unrelated schizophrenics: no increased rates of X chromosome mosaicism or inv(9), using ethnically matched and age-stratified controls. Schizophr Res 52:171–179
148. Callier P, Faivre L, Cusin V, Marle N, Thauvin-Robinet C, Sandre D, Rousseau T, Sagot P, Lacombe E, Faber V, Mugneret F (2005) Microcephaly is not mandatory for the diagnosis of mosaic variegated aneuploidy syndrome. Am J Med Genet A 137:204–207
149. Jacquemont S, Bocéno M, Rival JM, Méchinaud F, David A (2002) High risk of malignancy in mosaic variegated aneuploidy syndrome. Am J Med Genet 109(1):17–21
150. Kajii T, Ikeuchi T, Yang ZQ, Nakamura Y, Tsuji Y, Yokomori K, Kawamura M, Fukuda S, Horita S, Asamoto A (2001) Cancer-prone syndrome of mosaic variegated aneuploidy and total premature chromatid separation: report of five infants. Am J Med Genet 104:57–64
151. Kawame H, Sugio Y, Fuyama Y, Hayashi Y, Suzuki H, Kurosawa K, Maekawa K (1999) Syndrome of microcephaly, Dandy-Walker malformation, and Wilms tumor caused by mosaic variegated aneuploidy with premature centromere division (PCD): report of a new case and review of the literature. J Hum Genet 44:219–224
152. Limwongse C, Schwartz S, Bocian M, Robin NH (1999) Child with mosaic variegated aneuploidy and embryonal rhabdomyosarcoma. Am J Med Genet 82:20–24
153. Thiel G, Losanowa T, Kintzel D, Nisch G, Martin H, Vorpahl K, Witkowski R (1992) Karyotypes in 90 human gliomas. Cancer Genet Cytogenet 58:109–120
154. Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, Fiocco R, Foroni C, Dimeco F, Vescovi A (2004) Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. Cancer Res 64:7011–7021
155. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD, Dirks PB (2004) Identification of human brain tumour initiating cells. Nature 432:396–401
156. Singh SK, Clarke ID, Terasaki M, Bonn VE, Hawkins C, Squire J, Dirks PB (2003) Identification of a cancer stem cell in human brain tumors. Cancer Res 63:5821–5828
157. Arendt T, Mosch B, Morawski M (2009) Neuronal aneuploidy in health and disease: a cytomic approach to understand the molecular individuality of neurons. Int J Mol Sci 10:1609–1627
158. Lenz D, Mosch B, Bocsi J, Arendt T, Tarnok A (2004) Assessment of DNA replication in central nervous system by laser scanning cytometry. In: Nicolau DV (ed) Imaging, manipulation, and analysis of biomolecules, cells, and tissues II. 27–28 January 2004, San Jose, California, USA. SPIE, Bellingham, pp 146–156
159. Mosch B, Mittag A, Lenz D, Arendt T, Tárnok A (2006) Laser scanning cytometry in human brain slices. Cytometry A 69 (3):135–138
160. Arendt T, Brückner MK, Mosch B, Lösche A (2010) Selective cell death of hyperploid neurons in Alzheimer's disease. Am J Pathol 177:15–20
161. Geller LA, Potter H (1999) Chromosome missegregation and trisomy 21 mosaicism in Alzheimer's disease. Neurbiol Dis 6:167–179
162. Iourov IY, Vorsanova SG, Yurov YB (2006) Chromosomal variation in mammalian neuronal cells: known facts and attractive hypotheses. Int Rev Cytol 249:143–191
163. Iourov IY, Vorsanova SG, Yurov YB (2008) Chromosomal mosaicism goes global. Mol Cytogen 1:26
164. Potter H (1991) Review and hypothesis: Alzheimer disease and Down syndrome-chromosome 21 nondisjunction may underlie both disorders. Am J Med Genet 48:1192–1200
165. Boeras DI, Granic A, Padmanabhan J, Crespo NC, Rojiani AM, Potter H (2008) Alzheimer's presenilin 1 causes chromosome missegregation and aneuploidy. Neurobiol Aging 29:319–328
166. Granic A, Padmanabhan J, Norden M, Potter H (2010) Alzheimer Abeta peptide induces chromosome mis-segregation and aneuploidy, including trisomy 21: requirement for tau and APP. Mol Biol Cell 21:511–520
167. Iourov I, Vorsanova S, Yurov Y (2011) Genomic landscape of the Alzheimer's disease brain: chromosome instability—aneuploidy, but not tetraploidy—mediates neurodegeneration. Neurodegen Dis 8:35–37, discussion 38–40
168. Kuenzle CC (1985) Enzymology of DNA replication and repair in the brain. Brain Res 357:231–245

169. Lovell MA, Xie C, Markesbery WR (2000) Decreased base excision repair and increased helicase activity in Alzheimer's disease brain. Brain Res 855:116–123
170. Mazzarello P, Poloni M, Spadari S, Focher F (1992) DNA repair mechanisms in neurological diseases: facts and hypotheses. J Neurol Sci 112:4–14
171. Nouspikel T, Hanawalt PC (2003) When parsimony backfires: neglecting DNA repair may doom neurons in Alzheimer's disease. Bioessays 25:168–173
172. Yang AH, Kaushal D, Rehen SK, Kriedt K, Kingsbury MA, McConnell MJ, Chun J (2003) Chromosome segregation defects contribute to aneuploidy in normal neural progenitor cells. J Neurosci 23:10454–10462
173. Potter H (2005) Cell cycle and chromosome segregation defects in Alzheimer's disease. In: Copani A, Nicoletti F (eds) Cell-cycle mechanisms and neuronal death. Landes, Georgetown, pp 55–78
174. Potter H (1991) Review and hypothesis: Alzheimer disease and Down syndrome–chromosome 21 nondisjunction may underlie both disorders. Am J Human Gen 48:1192–1200
175. Cherry LM, Funk J, Lesser JM, Lesam M (1992) Gender differences and their interpretation of genetic instability in Alzheimer's disease. Mutat Res 275:57–76
176. Migliore L, Boni G, Bernardini R, Trippi F, Colognato R, Fontana I, Coppedè F, Sbrana I (2006) Susceptibility to chromosome malsegregation in lymphocytes of women who had a Down syndrome child in young age. Neurobiol Aging 27:710–716
177. Migliore L, Botto N, Scarpato R, Petrozzi L, Cipriani G, Bonuccelli U (1999) Preferential occurence of chromosome 21 malsegregation in peripheral blood lymphocytes of Alzheimer disease patients. Cytogenet Cell Genet 87:41–46
178. Migliore L, Testa A, Scarpato R, Pavese N, Petrozzi L, Bonuccelli U (1997) Spontaneous and induced aneuploidy in peripheral blood lymphocytes of patients with Alzheimer's disease. Human Genet 101:299–305
179. Percy ME, Markovic VD, Dalton AJ, McLachlan DRC, Berg JM, Rusk ACM, Somerville MJ, Chodakowski B, Andrews DF (1993) Age-associated chromosome 21 loss in Down syndrome: possible relevance to mosaicism and Alzheimer's disease. Am J Med Genet 45:584–588
180. Schupf N, Kapell D, Lee JH, Ottman R, Mayeux R (1994) Increased risk of Alzheimer's disease in mothers of adults with Down's syndrome. Lancet 344:353–356
181. Li J, Xu M, Zhou H, Ma J, Potter H (1997) Alzheimer presenilins in the nuclear membrane, interphase kinetochores and centrosomes suggest a role in chromosome segregation. Cell 90:917–927
182. Arendt T (2008) Differentiation and de-differentiation—neuronal cell cycle regulation during development and age-related neurodegenerative disorders. In: Lajtha A, Perez-Polo JR, Rossner S (eds) Handbook of neurochemistry and molecular neurobiology. Development and aging changes in the nervous system, 3rd edn. Springer, New York, pp 157–213
183. Vincent I, Rosado M, Davies P (1996) Mitotic mechanisms in Alzheimer's disease? J Cell Biol 132:413–425
184. Arendt T (2000) Alzheimer's disease as a loss of differentiation control in a subset of neurons that retain immature features in the adult brain. Neurobiol Aging 21(6):783–796