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Epigenetic basis of neuronal plasticity: Association with R/G-band boundaries on human chromosomes

Yoshihisa Watanabe *, Masato Maekawa

Department of Laboratory Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu 431-3192, Japan

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ABSTRACT

Epigenetic mechanisms have been suggested to have roles in neuroplasticity, in particular with regard to learning and memory formation, and in a range of neural diseases. In addition to epigenetic marks, the human genome also contains large-scale compartmentalized structures that might also influence neuroplasticity and neural disease. These structures result from variations in the amounts of GC% and in the timing of DNA replication and give rise to longitudinal differentiation (light and dark bands) along chromosomes after the appropriate staining. Here we describe our current understanding of the biological importance of the boundaries between these light and dark bands (the so-called R/G boundaries). We propose that the R/G-band boundaries on human chromosomes can be altered by epigenetic mechanisms, and that these changes may affect neuroplasticity, which is important to memory and learning, and may also have a role in the development of neural diseases associated with genomic instability.

1. Introduction: DNA sequences and chromosome bands

Considerable research effort is currently being expended on elucidating the genetic and epigenetic bases of neuroplasticity associated with learning and memory formation and with neural diseases. One aspect of this research is investigation of the relationship between large-scale chromatin structures and the epigenetic mechanisms that influence normal and abnormal mental development in humans. This review discusses the potential medical significance of one particular type of large-scale chromatin structure for conditions related to neuronal plasticity and to neural diseases associated with genomic instability.

Eukaryotic genomes contain regions with differing amounts of guanidine and cytosine residues (GC%); in mammals, these different regions have been shown to vary consistently in their replication timing patterns (Bernardi et al., 1985; Ikemura, 1985; Aota and Ikemura, 1986; Holmquist, 1989; Gardiner et al., 1990; Saccone et al., 1999; Pilia et al., 1993). Bernardi suggested the term "isochores" for regions (>300 kb) with homogenous GC contents (Bernardi et al., 1985). As isochores can show differences in staining intensity with the appropriate cytological dyes, such as Giemsa, chromosomes appear to have bands of light and dark staining regions. Giemsa dark (G) bands replicate late in S-phase and are mainly composed of AT-rich sequences (Table 1). Some Giemsa pale (R) bands are GC rich and replicate very early; these are termed T bands. The remaining R bands replicate early but have variable GC contents (Ikemura and Aota, 1988; Bernardi, 1989; Ikemura et al., 1990; Ikemura and Wada, 1991; Bernardi, 1993; Craig and Bickmore, 1993; Saccone et al., 1993). Although chromosome banding is a cytological phenomenon, the variations in sequence contents and replication timing of the bands have been used to define boundaries at the genomic level.

Epigenetic modifications, such as methylation, acetylation, or phosphorylation of histone proteins or methylation of the DNA, can cause changes to chromatin structure. These changes in chromatin structure may alter the binding of transcription factors or enhancer element binding proteins to promoter sites, thereby modifying gene transcription patterns (Gibbs et al., 2010). Consequently, regulation of changes to chromatin structure is important in the control of mRNA production (Bagot and Meaney, 2010). The epigenetic changes to chromatin structure are not permanent but can be reversed; this characteristic makes them suited to a role in memory formation. For example, the addition or removal of modifying functional groups on histones causes folding or unfolding changes in chromatin structure. In mature neurons, the addition of such functional groups to histones is transient and can be reversed in response to environmental stimuli (Bagot and Meaney, 2010).

The methylation of DNA is another epigenetic modification with a potential role in long-term memory formation. DNA methyltransferase (DNMT) enzymes, such as DNMT1, DNMT3A and DNMT3B, are highly expressed in the adult central nervous system (Fatemi et al., 2002; Feng et al., 2005; Feng et al., 2010); the activity of these enzymes, and the level of DNA methylation, is influenced by environmental cues (Feng et al., 2005). *In vitro* experiments using cortical neuronal cultures have

* Corresponding author.
E-mail address: yoshwata@hama-med.ac.jp (Y. Watanabe).

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Table 1
Characterization of chromosome bands.

Chromosome band	G/Q band	R band	T band (R subgroup)
Replication timing	Late	Early	Very early
GC%	AT-rich	Medium	GC-rich
Gene density	Low	High	Very high
Chromatin appearance	Compact	Loose	Loose

shown that the DNMT inhibitor 5-azadeoxycytidine can diminish DNA methylation levels and reduce expression of the memory-related gene, *REELIN* (Feng et al., 2005). DNMT mRNA (and its protein) has been shown to be present and active in cells of the central nervous system, indicating that changes in DNA methylation levels are involved in the normal functioning of the adult central nervous system. DNA methylation marks act either through steric inhibition of transcription factor binding or by recruiting reader proteins containing methyl-binding domains. Thus, these methylation marks may either reduce transcriptional efficiency or affect chromatin structure by recruiting histone deacetylases (Jones et al., 1998).

The *GRIK1*, *GRIA2* and *GRIA4* loci contain sequence motifs or similar sequences for the binding of the protein SATB1 (special AT-rich sequence binding protein 1) and these may be involved in controlling changes in replication timing in and around transition regions (Oda et al., 2012). Replication profiles, which correspond with chromosomal bands, are cell-type specific, and changes to these profiles identify chromosomal segments that are reorganized during differentiation (Hiratani et al., 2008). Moreover, cell pluripotency is associated with smaller replication domains and a higher density of timing transition regions that interrupt isochore replication timing (Hiratani et al., 2008).

2. Characteristic chromatin structures in chromosome band boundaries

The differences in GC contents between early and late replicating chromosomal regions are mirrored by differences in chromosomal structure at interphase and at metaphase of mitosis. In particular, early replicating regions have a looser chromatin structure than late replicating regions (Holmquist et al., 1982; Holmquist, 1989; Bernardi, 1989; Craig and Bickmore, 1993). Thus, chromosomal regions that show a transition in replication timing also show a transition in chromatin compaction. In terminally differentiated cells, such as neurons, these patterns of chromatin compaction are generally stable (Fig. 1). If a transition in chromatin compaction occurs within a gene, it might increase genomic instability and susceptibility to agents that influence gene expression. Consequently, chromatin instability and likelihood of DNA damage (including DNA rearrangements) may be greater in regions with replication transition than elsewhere in the genome (Fig. 1) (Bierne and Michel, 1994; Verbovaia and Razin, 1997; Rothstein et al., 2000; Watanabe et al., 2002, 2004, 2008, 2009; Puliti et al., 2010; Poretti et al., 2011; De and Michor, 2011).

Replication timing is often considered in terms of the interaction of transcriptional activity and chromatin structure (Hiratani et al., 2009). There is strong evidence that cellular differentiation is accompanied by coordinated changes in replication timing and transcription. These changes take place at the level of megabase-sized domains (R, G-chromosome bands) and are greater than localized alterations in chromatin structure or transcription (Hiratani et al., 2009). On the basis of these results, we propose that a key transition stage occurs during the middle of S-phase (R/G-band boundaries of human chromosomes) and that changes in replication timing that traverse this period are associated with changes in the activity of groups of promoters.

Interestingly, regions with an early to late switch in replication timing, so-called R/G-chromosomal boundaries, have been found to have a greater incidence of DNA sequences that can form non-B-DNA structures compared to other areas in the genome (Watanabe and Maekawa, 2010a, 2010b, 2013). Non-B-DNA structures are more likely to impede replication fork movement than normal chromatin. Therefore, R/G-chromosomal boundaries are genomic regions with a higher likelihood of stalled replication. Failure to complete replication has been suggested to increase the risk of genetic instability and to cause genetic mutations that have been found to be associated with many human diseases (Watanabe and Maekawa, 2010a, 2010b, 2013). It has been hypothesized that R/G-chromosomal boundaries are also more susceptible to epimutations than other parts of the genome (Watanabe and Maekawa, 2010a, 2010b, 2013).

3. Relationships between neuronal plasticity and/or neural disease and chromosomal R/G-band boundaries

Human chromosome 21 is not only responsible for Down syndrome (trisomy 21), but also carries genes associated with the development of neural diseases such as Alzheimer's disease and amyotrophic lateral sclerosis. In order to investigate the molecular pathology of neural disease, DNA replication timing on human chromosome 21q was analyzed (Watanabe et al., 2002). Three large genes, amyloid beta precursor protein (*APP*), glutamate ionotropic receptor kainite type subunit 1 (*GRIK1*) and Down syndrome cell adhesion molecule (*DSCAM*), were found to be located in regions where DNA replication timing switched from early to late S phase (Watanabe et al., 2002, 2014). Interestingly, *GRIK1* was located in a replication transition region in neural precursor cells (NPCs) but not in embryonic stem cells (ESCs); in the latter, it was located in a later replication timing region (Watanabe et al., 2014). Other large glutamate receptor genes are also located in or near transition zones in NPCs but not in ESCs where they often locate in later replication timing zones or in late replication zones. Early replicating regions tend to have “looser” chromatin structures compared to late replicating zones (Holmquist et al., 1982; Holmquist, 1989; Bernardi, 1989; Craig and Bickmore, 1993; Watanabe and Maekawa, 2010a, 2010b, 2013). Therefore, a change in relative chromatin compaction is likely to occur within a transition region of replication timing. This effect is illustrated by the four genes that encode the transmembrane AMPA glutamate receptor that mediates fast synaptic transmission in the central nervous system. Analysis of their replication timings indicated that they were clearly located in transition zones in NPCs but not in ESCs (Watanabe et al., 2014). We propose that this transition is universal in patients with neurological diseases, and that many neural genes and/or neural disease genes are located in the early/late-switch regions that correspond to the R/G-band boundaries on human chromosomes.

DNA methylation changes in three glutamate receptor genes, before and after replication transition, have been analyzed in NPCs and ESCs. A lower rate of methylation was found in the 5′-upstream genomic regions of *GRIK1*, *GRIA2* and *GRIA4* in NPCs compared to ESCs; these genes were clearly located in early replication transition zones in NPCs but not in ESCs (Watanabe et al., 2014). Thus, there was a clear relationship between replication timing and DNA methylation: earlier replication timing regions were relatively hypomethylated and later replication timing regions were hypermethylated.

One possible explanation for the different replication timing of large glutamate receptor genes and *APP* in different cell lines is that it is altered by epigenetic mechanisms (Watanabe et al., 2014). Recent studies have demonstrated that environmental factors can alter epigenetic marks in the genome that control gene expression. Thus, transition zones of DNA replication timing might be altered by epigenetic mechanisms in response to environmental factors. Such changes might be associated with the epigenetic basis of neuroplastic changes, such as the synaptic plasticity involved in learning and memory formation, and neural diseases associated with mutation of

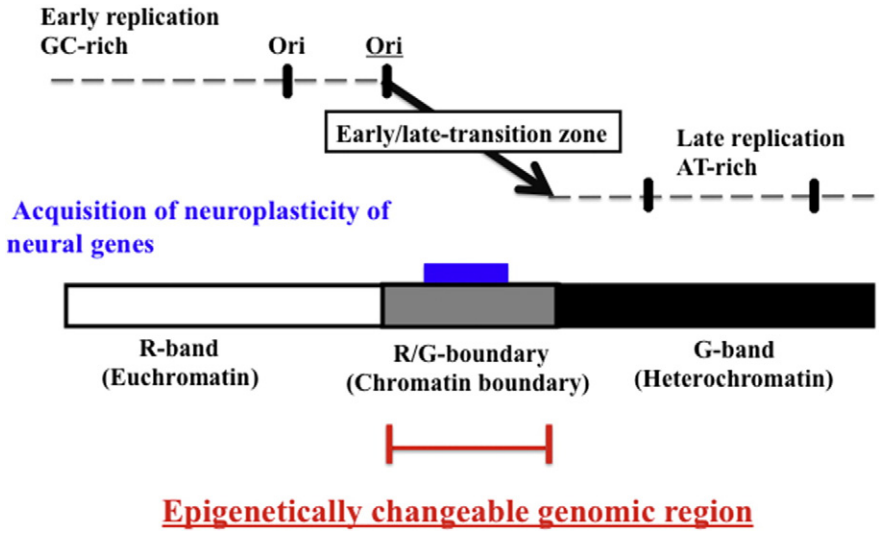

Fig. 1. Proposed model for neuroplastic changes associated with epigenetic alterations to human chromosomes. The model suggests that high-risk/high-return regions in the human genome are located in replication timing transition zones and that modification of the chromatin structure during the development of neural disease (or neuroplastic changes) affects the timing of firing of replication origins.

glutamate receptor genes or *APP*. The activation of glutamate receptors is responsible for basal excitatory synaptic transmission and for many forms of synaptic plasticity, such as long-term potentiation and long-term depression; these effects of glutamate receptor activation are thought to underlie learning and memory (Ozawa et al., 1998; Kimura et al., 2002; Debanne et al., 2003; Simeone et al., 2004; Pinheiro and Mulle, 2008; Tanzi, 2012) (Fig. 1).

It has been shown that early-life experiences in rats can induce epigenetic responses that subsequently influence behavior in adult life (Weaver et al., 2004). Exposure of young rats to maternal nursing stress alters the pattern of expression of the glucocorticoid receptor within the hippocampus, which is involved in stress responses. This study demonstrates that the epigenomic status of a gene can be modified by behavioral programming, and also that this status is potentially reversible (Weaver et al., 2004). Evidence has been reported of sustained epigenetic mechanisms for gene regulation in neurons involved in the regulation of normal and abnormal complex behavior, including depression, drug addiction and schizophrenia (Tsankova et al. 2007). Environmentally-induced epigenomic changes and neuronal function may connected by specific epigenetic mechanisms: many neural genes and/or neural disease genes are located in the R/G-band boundaries on human chromosomes, which correspond with genomic regions that are susceptible to epigenetic changes induced by various factors including the environment (Fig. 1).

In terminally differentiated cells, such as neurons, the level of chromatin compaction that is established during the final round of DNA replication is likely to be maintained. Four genes associated with neural disease (*APP*, *GRIK1*, *SOD1* and *DSCAM*) are present in early/late transition regions (Watanabe et al., 2002, 2014; Watanabe and Maekawa, 2013). Interestingly, the 5′ ends of all four genes replicate later than their 3′ ends, suggesting greater chromatin compaction at the 5′ ends. Transitions in chromatin compaction within these neural disease genes may reflect tissue-specific expression patterns and neuroplasticity. Therefore, the role of R/G bands might also be relevant in the mature neuronal state as well as in the neurodevelopmental or adult neurogenesis stage.

DNA replication in the Xq27 region of the human X chromosome is delayed in males with the fragile X syndrome (Hansen et al., 1997). This region of delayed replication extends at least 400 kb 5′ of *FMR1* and appears to merge with chromatin that shows the normal pattern of very late replication in proximal Xq27. The distal border of the delayed replication region varies among individual males, thereby defining three replicon-sized domains that can be affected in fragile X syndrome. The distal boundary of the largest region of delayed replication is located between 350 and 600 kb 3′ of *FMR1* (Hansen et al., 1997).

Duchenne and Becker muscular dystrophy are determined by two very large genes located within common fragile sites (CFSs); CSFs are specific chromosome regions that exhibit an increased frequency of breaks when cells are exposed to a DNA-replication inhibitor such as aphidicolin. Gross rearrangements within these genes are frequently observed as the causative mutations for these diseases (Mitsui et al., 2010). Furthermore, breakpoint-clustering regions within these large genes coincide with the latest-replicating region and with large nuclear-lamina-associated domains and are flanked by R/G-band boundaries and the highest-flexibility peaks (Mitsui et al., 2010).

From these various reports, we propose that this transition is present in patients with neurological disease but may also occur in other physiological conditions.

4. Mechanism of neuronal plasticity and/or neural diseases based on chromosomal R/G-band boundaries

We propose that chromatin conformation or replication timing influences the expression of neural genes and/or neural disease genes located in early/late-switch zones (Fig. 2). In our model, an increase (or decrease) in the number of early acting replication origins alters the timing of replication from mid S phase to early S phase (or mid S phase to late S phase) (Fig. 2). In addition, these changes would also cause a modification of the chromatin environment of a neural disease gene from an R/G band boundary (the boundary between euchromatin and heterochromatin) to an R band (euchromatin) or a G band (heterochromatin). In Fig. 2, the transition zone, indicated by a thick arrow, is expected to be a large region that is devoid of origins and lies between early and late-replicating domains (Ermakova et al., 1999; Letessier et al., 2011; Debatisse et al., 2012; Watanabe and Maekawa, 2010a, 2010b, 2013). This transition zone may also be genomically unstable as only replication forks that started at the edge of the early zone are predicted to continue moving over a period of hours or to

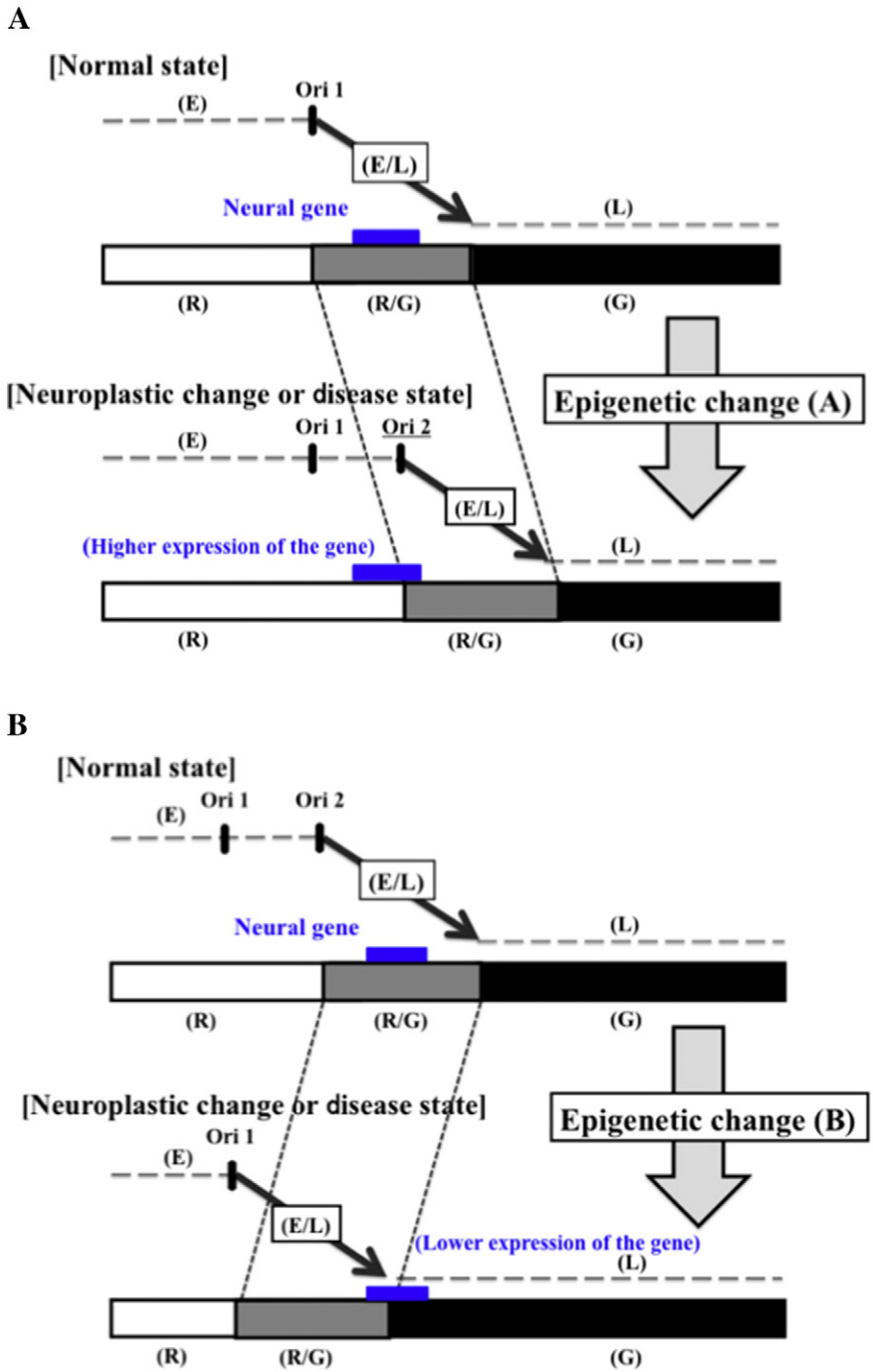

Fig. 2. Proposed mechanism for how changes in replication timing of a neural disease gene located in a transition zone affect its expression. Replication timing might switch from mid S phase to early or late S phase due to increase (A) or decrease (B) of active early replication origins at the edge of the early replication zone. Additionally, the chromatin environment of the neural disease gene might change from an R/G chromosome band boundary to an R or a G band. Stalling of the replication fork in the vicinity of neural disease genes might induce chromosomal amplification (triplet repeat expansions) or chromosome rearrangements that affect gene function, possibly through influencing the rate of expression. The position of the neural disease gene (large gene) is indicated by the blue rectangle. E, early replication zone; L, late replication zone; E/L, early/late-switch region; R, R band; G, G band; R/G, R/G band boundary; Ori, replication origin.

pause at specific sites in replication-transition regions where they meet forks initiated from adjacent later-replicating zones. A pause during replication increases the risk of DNA breaks and rearrangements (Bierne and Michel, 1994; Verbovaia and Razin, 1997; Rothstein et al., 2000; Watanabe and Maekawa, 2010a, 2010b, 2013). Therefore, the model shown in Fig. 2 also predicts that regions with a switch in replication timing have an increased risk of replication errors, such as stalling of the replication fork, and a concomitantly increased risk of chromosomal errors such as amplifications (*e.g.*, triplet repeat expansions, which are often found in mutations of neural disease genes) and rearrangements (such as translocations). Such *de novo* rearrangements might then adversely affect expression of closely positioned neural disease genes (Fig. 2). The model therefore suggests a mechanism for abnormal expression of neural disease genes that is based on replication timing patterns and chromosomal rearrangements.

5. Conclusions

In this review, we have discussed the potential significance of R/G-band boundaries in human chromosomes for disease conditions

related to neuronal plasticity and neural diseases associated with genomic instability. To explain how such disease conditions might ultimately be related to DNA replication timing, we describe a model in which R/G-band boundaries correspond to high-risk/high-return regions, which correlate with genomically unstable regions. These regions are important in the epigenetic mechanisms that regulate neuroplastic changes, such as long-term potentiation and long-term depression.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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