American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Letter to the Editor

Prenatal Genome Instability and Their Impact on Pediatric Diseases

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To Cite This article: *Stefan Bittmann. Prenatal Genome Instability and Their Impact on Pediatric Diseases, Am J Biomed Sci & Res. 2026 29(5) AJBSR.MS.ID.003844,* **DOI:** 10.34297/AJBSR.2026.29.003844

Received: December 31, 2025; **Published:** January 13, 2026

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Genome instability refers to a high rate of mutations in the genetic material of a cell lineage, which can manifest as changes in nucleic acid sequences, chromosomal rearrangements, or aneuploidy [1,2]. This phenomenon is observed in bacteria as well as in multicellular organisms, where it plays a central role in cancer development and certain neurodegenerative diseases like amyotrophic lateral sclerosis and myotonic dystrophy in humans. The causes of genome instability are still being investigated, but factors such as external DNA damage and reduced expression of DNA repair genes are known contributors [1-14]. With human cells experiencing over 60,000 instances of endogenous DNA damage daily, impaired DNA repair mechanisms are likely significant sources of genome instability [3-5].

In most species, each individual's cells typically have a consistent number of chromosomes, known as the karyotype. However, some species exhibit high karyotypic variability. In humans, mutations that alter amino acids in the genome occur infrequently, at an average of 0.35 per generation. Occasionally, random variations or structural alterations like chromosomal translocations and deletions can disrupt the normal chromosomal count, leading to genome instability. This instability can result in aneuploidy, where cells have an abnormal number of chromosomes compared to the species' standard complement [6,7]. Causes of genome instability include DNA replication defects. During the cell cycle, DNA is most vulnerable during replication when obstacles like tightly wound chromatin, breaks, and stalled replication forks can occur. Proteins in the replisome, such as DNA polymerase and DNA ligase, play crucial roles in ensuring accurate DNA replication [8]. Mutations in these proteins can lead to replication impairment and chromosomal exchanges. Proteins like Tel1, Mec1, and Rmr3 helicase help stabilize the replication fork and prevent chromosomal recombination. ATR and ATM proteins detect and respond to different types of DNA breaks, preventing progression into mitosis by activating signalling cascades that arrest the cell in S-phase. Repair mechanisms like Break Induced Replication and homologous recombination are used to fix DNA breaks. Checkpoints in G1 and G2 phases monitor DNA damage, with genes like rad9 in yeast playing a role in cell cycle arrest and DNA repair. Cells with functional rad9 can survive by allowing repair enzymes to function properly in S/G2 phase.

Fragile sites in the genome are vulnerable to gaps and breaks when DNA synthesis is inhibited, such as during checkpoint arrest [9]. These sites can be common in mammalian genomes or rare due to mutations like DNA-repeat expansion. Rare fragile sites can cause genetic diseases like fragile X syndrome, myotonic dystrophy, Friedrich's ataxia, and Huntington's disease. Common fragile sites, found in yeast and bacteria, are characterized by trinucleotide repeats like CGG, CAG, GAA, and GCN. These repeats can form hairpins, leading to replication difficulties and breaks under stress. Repair using a sister chromatid may not be reliable due to similar DNA sequences, resulting in copy number variations. For instance, a 16th CGG repeat may be matched with the 13th CGG repeat in the sister chromatid, leading to extra copies in the final DNA sequence. Transcription-associated instability is another very important fact

of possible foetal damage on the genetic level. Transcription sites in E. coli and Saccharomyces pombe exhibit higher recombination and mutation rates. The coding strand, which is single-stranded during transcription, accumulates more mutations than the template strand due to its chemical instability. Supercoiling behind an elongating RNA polymerase can cause single-stranded breaks. Additionally, the coding strand can form DNA secondary structures that hinder replication. In E. coli, transcription of GAA triplets can lead to mismatched loops that impede replication. Replication and transcription can occur simultaneously, resulting in collisions between the replication fork and RNA polymerase complex. In S. cerevisiae, the Rrm3 helicase stabilizes stalling replication forks at highly transcribed genes. This suggests that transcription poses obstacles to replication, potentially causing single-stranded DNA breaks. Proteins act as barriers at the 3' end of transcription units in yeast to prevent further movement of the DNA replication fork.

Enhancing genetic diversity is of upmost importance for survival of human being. Genetic variability is crucial for survival, especially in regions like the Ig genes where diversity is essential. In pre-B cells, V, D, and J segments combine to form the final gene through a process catalyzed by RAG1 and RAG2 recombinases. Activation-Induced Cytidine Deaminase (AID) converts cytidine to uracil, leading to somatic hypermutation through error-prone repair by Non-homologous End Joining (NHEJ). This process generates millions of unique B-cell receptors with varying affinities for antigens, aiding in mammalian survival against infections. Neurological and neuromuscular disorders are linked to defects in DNA repair pathways or increased oxidative stress. Disorders like xeroderma pigmentosum, Cockayne's syndrome, and others result from defects in DNA repair pathways, while diseases like Huntington's and Alzheimer's are associated with increased oxidative stress and impaired base excision repair. Some disorders, such as Huntington's and Friedreich's ataxia, involve unusual expansions of repeat sequences due to genome instability. Defects in genes repairing DNA double-strand breaks are linked to diseases like ataxia-telangiectasia and Alzheimer's. Oxidative stress plays a significant role in causing genomic instability in the brain, leading to neurological diseases when pathways preventing or repairing oxidative stress are deficient.

Genome instability in cancer can occur before or after transformation, leading to various abnormalities such as extra copies of DNA, chromosomal translocations, inversions, deletions, and breaks in DNA strands [10,11]. These abnormalities contribute to the heterogeneity observed in tumour cells. Sporadic tumours are believed to arise from the accumulation of genetic errors, with an average breast or colon cancer having numerous mutations, some of which are driver mutations [12-14]. Genetic instability can result from deficiencies in DNA repair or chromosomal abnormalities, promoting tumour development by generating mutant cells that can thrive in the tumour microenvironment. The protein coding regions of the human genome, collectively called the exome, constitutes only 1.5% of the total genome. As pointed out above, ordinarily there are only an average of 0.35 mutations in the exome per generation (parent to child) in humans. In the entire genome (including non-protein coding regions) there are only about 70 new mutations per generation in humans.

The main cause of mutations in cancer is DNA damage, which can be caused by external factors such as tobacco smoke or internal factors like metabolic processes. These damages can lead to mutations through inaccurate DNA repair mechanisms. Both mutations and epigenetic alterations can contribute to cancer development. In cancer, there are typically 3-4 driver mutations and numerous passenger mutations in the protein-coding region. Additionally, a large number of mutations occur in non-protein-coding regions, with breast cancer samples having around 20,000 mutations in the entire genome and melanoma samples having around 80,000 mutations. DNA repair deficiencies in cancer can arise from mutations in DNA repair genes or epigenetic reductions in gene expression. For example, in colorectal cancers, most cases show reduced expression of the DNA repair gene MGMT due to methylation of its promoter region, rather than somatic mutations. Similarly, mismatch repair deficiency in colorectal cancer can be caused by mutations in the PMS2 gene or repression of its pairing partner MLH1 due to promoter methylation. Epigenetic deficiencies in DNA repair genes like BRCA1, WRN, FANCB, and others have been found in various cancers, with some cases showing multiple epigenetic defects simultaneously. MicroRNAs like miR-155 can also contribute to DNA repair deficiencies in cancer. Overall, epigenetic alterations play a significant role in DNA repair deficiencies in cancer.

Maintaining genomic stability is of utmost importance for cells as it ensures the correct function and survival of the organism. Changes in the genome that are not repaired can lead to a variety of diseases, including cancer. An example of the importance of genomic stability is DNA repair. Cells have various mechanisms to detect and repair damage to their DNA. One of these mechanisms is the Nucleotide Excision Repair Process (NER), which repairs UV light-induced DNA damage and helps prevent skin cancer. These points highlight why research and understanding of mechanisms for maintaining genomic stability are of extraordinary importance, especially in terms of prevention, diagnosis, and treatment of genetic and cancer-related diseases. Genomic stability is of upmost importance for a growing foetus to prevent foetal DNA from pathological mutations, which have a high impact on developing severe genetic diseases in pediatrics.

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