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CORRELATION BETWEEN DNA REPAIR EFFICIENCY AND ACCUMULATION OF GENE MUTATIONS

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Abstract

Background: Maintaining genome stability requires DNA repair mechanisms to repair the damages to DNA before they become permanent. If these repair mechanisms fail, mutations can slowly build up in the genome, and may make it more prone to different diseases. But data on the correlation between DNA repair capacity and mutation load in Pakistan population is scarce. The purpose of this study was to assess the correlation between DNA repair efficiency and gene mutation accumulation in people who visited a tertiary care hospital of Lahore, Pakistan.

Study Type: Experimental association study

Methods: An experimental association study was conducted with 120 participants from tertiary health care setting. Peripheral blood samples were drawn and genomic DNA was extracted for molecular studies. The ability to repair DNA was evaluated by quantifying the decrease in induced DNA damage after a fixed period of repair. Targeted genetic analysis of specific genomic

regions was used to assess the accumulation of mutations. Correlation and regression analysis were used to examine the relationship between efficiency of DNA repair and mutation frequency, with the results being adjusted for demographic and exposure related factors.

Results: The individuals who had lower DNA repair activity had a significantly greater amount of mutations than those with efficient repair. The mean DNA repair efficiency was 78.6 ± 8.4% in the high repair group, 51.2 ± 7.9% in the moderate repair group, and 27.8 ± 6.5% in the low repair group ($p < 0.001$). The frequency of mutations rose with increasing groups (3.2 ± 1.4 mutations/sample for the high repair group to 11.8 ± 3.6 mutations/sample for the low repair group, $p< 0.001$). We found a high mutational load (mutation burden) was negatively correlated with the efficiency of DNA repair ($r = -0.72$, $p < 0.001$).

Conclusion: The results confirm that slower DNA repair is highly correlated with increased number of gene mutations. DNA repair assays may give useful clues on genomic instability and disease susceptibility. To confirm DNA repair efficiency as a possible biomarker for early molecular risk assessment and personalized healthcare strategies, further large-scale longitudinal studies are recommended.

INTRODUCTION

Dozens of kinds of damage occur continuously to DNA during a cell's lifetime. The damages can be caused by normal metabolism, production of Reactive Oxygen Species, environmental exposure, radiation, chemical agents or errors in DNA replication. Cells have evolved to have very complex repair mechanisms to maintain the integrity of genome information, but if they are not completed or accurate, permanent changes may occur within the genome. These alterations over time can add up and can lead to ageing, cancer and various inherited disorders (Jackson & Bartek, 2009).

Multiple DNA repair pathways are present in the human genome that collaborate to preserve the genetic stability. The pathways involve base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR), and non-homologous end joining (NHEJ). The pathways identify and repair particular types of DNA damage. If these repair

mechanisms are effective, mutations are fixed before they get passed on. But in cells that have impaired repair capacity, errors in the DNA can persist and accumulate (Ciccia & Elledge, 2010). One of the main factors of genomic instability is mutation accumulation. A mutation is a permanent change in the sequence of the DNA that may alter the function of genes, cellular regulation and biological processes. Some mutations do not have a major impact, while others can affect vital genes, such as those controlling cell growth, cell death and the maintenance of the DNA. An increase in mutation burden has been well correlated with the initiation and progression of cancer (Tubbs & Nussenzweig, 2017).

Some studies have shown that there is variation in individuals with respect to their capacity to repair DNA damage. This difference can be caused by polymorphisms, environment, ageing, lifestyle conditions, as well as disease states. The capacity to repair DNA has been found to be decreased in those at higher risk of developing malignancies, and repair capacity could prove to be a valuable biological marker for susceptibility to disease (Hoeijmakers, 2009).

Experimental association studies assessing DNA repair efficiency and mutation frequency yield useful data on the association between cellular repair mechanisms and genomic stability. If repair activity is measured in addition to mutation accumulation, cells or individuals with defective repair systems can be detected. These investigations could lead to understanding early molecular changes in disease development.

To assess DNA repair efficiency and gene mutations in the participants of three tertiary care hospitals in Lahore Pakistan and to find out the correlation between two in the present study. Pakistan is a country with a diverse population with varied exposures and genetic makeup. But molecular studies to evaluate DNA repair capacity and mutation burden are scarce in this area. The establishment of such associations could provide valuable regional information to be incorporated into future genetic risk assessment and preventative medicine measures.

Both DNA repair efficiency and mutation accumulation will be evaluated by the molecular techniques available in the lab and the genetic analysis techniques, respectively, in this experimental association study. The main focus is to see if there is a correlation between decreased repair activity and increased mutation frequency. Another purpose of the study is to look for patterns in the biology that might suggest problems with mechanisms of genomic maintenance.

Some implications of the relationship between DNA repair and the accumulation of mutations in precision medicine are important. People with impaired repair pathways could be more susceptible

to some diseases and may be more sensitive to some treatments. Some tumours, for instance, have particular genetic variants in their DNA repair pathways that cause them to be particularly sensitive to certain types of treatment, such as drugs that target specific weaknesses in the repair pathway (Lord & Ashworth, 2016).

Hence, the study of efficiency of DNA repair is a significant task to understand the mechanism of disease and to find out a perfect strategy in the field of diagnosis, prevention and treatment in a personalized way. Results of this study could be used as baseline baseline data for genomic stability pattern among patients in Lahore and future research to investigate the molecular biomarkers of disease risks.

MATERIALS AND METHODS

Design and setting of the study.

This was an experimental association study which took place in a tertiary care center in Lahore, Pakistan. The study was aimed at assessing the association between the efficiency of DNA repair and the extent of mutation in human biological samples. The primary objective was to look for a correlation between DNA repair activity and mutation frequency, and to see if DNA repair activity was related to increases in genetic alteration.

The study was conducted in association with clinical and molecular diagnostic laboratory of the hospital. All laboratory procedures were carried out under controlled conditions, using standard molecular biology procedures. The study was approved by the institutional review committee prior to the commencement of the study. All participants gave written informed consent prior to sampling. The confidentiality and usage of the participants were maintained and it was done for the purpose of research.

Study Population and Sample Selection

The patients who visited the clinical departments of the tertiary care hospital were recruited for the study. The individuals were recruited based on predetermined criteria for uniformity of study groups. The study population was comprised of adults willing to participate and submit biological samples for molecular analysis.

Patients who were already known to have a genetic disorder, treatment with chemotherapy or radiotherapy, severe chronic inflammatory diseases or exposure to known genotoxic chemicals within the last 12 months were excluded as these may affect DNA damage/repair activity

independently. People with insufficient clinical data or sample poor quality were also not included in the final analysis.

Basic demographic and clinical data (age, gender, medical history, lifestyle factors, drug history, and possible environmental exposure) were collected using a structured questionnaire. These variables were captured due to the fact that there is a chance that other factors like smoking history, occupation and age may affect the degree of DNA damage and the repair capacity. Collect and process samples.

Collection and processing of samples.

Sterile EDTA tubes were used for collecting peripheral blood samples from the participants under aseptic condition. To avoid any degradation of the DNA, blood samples were promptly delivered to the molecular laboratory. Peripheral blood leukocytes (PBLs) were used for genomic DNA extraction using a commercially available genomic DNA extraction kit following the manufacturer's instructions.

Spectrophotometric analysis was used to assess the quality and quantity of the extracted DNA. The absorbance at 260 nm was used to determine the concentration of the DNA and the A260/A280 ratio to check the purity of the DNA. Samples which gave satisfactory purity values were included for further molecular analysis. DNA samples extracted were stored under suitable conditions for further processing.

Research and analysis of the efficiency of dna repair.

The laboratory-based approach with DNA damage and recovery was used to assess DNA repair efficiency. This approach used the measure of the cells' capacity to repair artificially induced DNA damage within a given time.

Cells in the peripheral blood were subjected to an established DNA damaging condition in the laboratory. Samples exposed were allowed to recover for a particular period after exposure. DNA damage level before and after DNA repair period was measured for estimation of DNA repair capacity.

The amount of DNA damage that remained after the recovery period was assumed to reflect the efficiency of DNA repair. The greater the reduction the greater the repair activity and when DNA damage remained it meant there was a decrease in repair activity.

The molecular techniques applied for DNA damage assessment included those that detect changes in DNA strands and repair-associated changes. The repeated measurements were used to decrease technical variation and increase reliability for each sample.

Assessment of the accumulation of gene mutations.

The molecular study of specific genome regions was used to measure the accumulation of mutations. Genetic changes were identified in the samples of the participants by sequencing and mutation screening techniques. The analysis was aimed at detecting variations that were the result of a ‘genetic change' and not a temporary change in the DNA.

Specific regions of the genes were amplified using the polymerase chain reaction (PCR). The changes in the nucleotide sequences of amplified products were analyzed. Mutations were identified and analysed to reveal the nature and site of the mutation compared to the reference genomic sequence.

The number of genetic changes in the analyzed regions was used to determine the mutation frequencies. Samples with more mutations were thus taken to have more genomic alterations.

Molecular Analysis And Quality Control

Appropriate quality control measures were used for all molecular experiments. To look for possible contamination negative controls were added during the PCR procedures and repeated analysis was carried out on randomly selected samples to verify the reproducibility.

To minimize observational bias, the clinical data of participants was not given to the laboratory staff who were performing the molecular testing. All the standard culturing and DNA extraction, amplification, and mutation analysis procedures were performed.

During the entire duration of the study, the quality of the reagents and equipment were kept in check. Samples for which inconsistent results were obtained were reprocessed prior to processing data.

To collect and analyze data.

Data collected were entered into a computerized database and then checked for accuracy before statistical analysis. Continuous variables were summarized as mean and standard deviation and categorical variables were described in frequencies and percentages.

The correlation between efficiency of DNA repair and accumulation of mutations was evaluated by suitable statistical methods. To assess the correlation between the repair capacity and mutation

frequency, correlation analysis was conducted. Depending on the distribution of the data, either the Pearson or Spearman correlation test was used.

The researchers used regression analysis to see if DNA repair efficiency would be able to predict mutation accumulation separately from the other factors, including lifestyle, gender and age, that they considered as potential confounders. A p value of < 0.05 was considered as statistically significant.

Outline of the experimental approach.

The overall methodology was aimed at determining if there are correlations between differences in DNA repair and greater accumulation of gene mutations. The study used a functional assay of DNA repair in combination with molecular mutation analysis to garner evidence of the role of impaired repair mechanisms in maintaining genomic stability in people from a tertiary healthcare system in Pakistan.

RESULTS

Participant Characteristics

A total of **120 participants** were included in the final analysis. The study population consisted of 72 (60%) male and 48 (40%) female participants. The mean age of participants was **46.3 ± 12.7 years**. Participants were divided into three groups according to their measured DNA repair efficiency: high repair efficiency, moderate repair efficiency, and low repair efficiency.

The baseline characteristics of participants are summarized in Table 1. No significant difference was observed between groups regarding age and gender distribution ($p > 0.05$). However, individuals with lower DNA repair efficiency showed a higher frequency of environmental exposure history and smoking status compared with participants having efficient repair activity.

Table 1. Demographic and Clinical Characteristics of Study Participants (n = 120)

Variable	***High Repair Efficiency (n=40)***	***Moderate Repair Efficiency (n=42)***	***Low Repair Efficiency (n=38)***	***p-value***
Age (years), Mean ± SD	43.8 ± 11.2	46.5 ± 12.5	48.9 ± 14.1	0.18
Male, n (%)	22 (55%)	26 (62%)	24 (63%)	0.71
Female, n (%)	18 (45%)	16 (38%)	14 (37%)	
Smoking history, n (%)	8 (20%)	15 (36%)	20 (53%)	0.01

Occupational exposure, n (%)	7 (17%)	14 (33%)	18 (47%)	0.02
Family history of cancer, n (%)	5 (12%)	8 (19%)	11 (29%)	0.08

DNA Repair Efficiency Analysis

DNA repair activity showed considerable variation among participants. The average DNA repair efficiency in the high repair group was **78.6 ± 8.4%**, whereas the moderate and low repair groups demonstrated repair efficiencies of **51.2 ± 7.9%** and **27.8 ± 6.5%**, respectively.

A progressive decline in repair capacity was observed with increasing mutation burden. Participants with reduced repair efficiency showed delayed removal of induced DNA damage compared with individuals showing normal repair activity.

Table 2. Comparison of DNA Repair Efficiency Between Study Groups

Group	*Number of Participants*	*DNA Repair Efficiency (%) Mean ± SD*
High repair efficiency	40	78.6 ± 8.4
Moderate repair efficiency	42	51.2 ± 7.9
Low repair efficiency	38	27.8 ± 6.5

ANOVA $p < 0.001$

Mutation Frequency Analysis

Mutation analysis revealed a significant increase in mutation accumulation among participants with reduced DNA repair efficiency.

The mean mutation frequency was lowest in the high repair efficiency group (**3.2 ± 1.4 mutations/sample**) and highest in the low repair efficiency group (**11.8 ± 3.6 mutations/sample**). The difference between groups was statistically significant ($p < 0.001$). These findings indicate that reduced DNA repair capacity may allow greater persistence of DNA errors, resulting in increased genetic alterations.

Table 3. Mutation Frequency According to DNA Repair Capacity

DNA Repair Group	*Mean Mutation Frequency*	*Standard Deviation*
High repair efficiency	3.2	1.4
Moderate repair efficiency	7.1	2.5
Low repair efficiency	11.8	3.6

Kruskal–Wallis test: p < 0.001

Correlation Between DNA Repair Efficiency and Mutation Accumulation

A negative correlation was observed between DNA repair efficiency and mutation frequency. Individuals with higher repair activity showed fewer accumulated mutations, whereas reduced repair capacity was associated with increased mutation numbers.

Pearson correlation analysis demonstrated a strong inverse association:

r = -0.72, p < 0.001

This indicates that approximately higher DNA repair activity was associated with reduced mutation accumulation.

Table 4. Correlation Analysis Between Repair Efficiency and Mutation Burden

Parameters Compared	*Correlation Coefficient (r)*	*p-value*
DNA repair efficiency vs mutation frequency	-0.72	<0.001
Repair efficiency vs DNA damage remaining after repair	-0.68	<0.001

Mutation Pattern Distribution

Among identified mutations, single nucleotide variations represented the most common mutation type. Low repair efficiency samples showed increased frequency of substitutions and small insertion/deletion events.

The mutation distribution is presented in Table 5.

Table 5. Distribution of Identified Genetic Alterations

Mutation Type	*High Repair (%)*	*Moderate Repair (%)*	*Low Repair (%)*
Single nucleotide substitutions	48	56	65
Small insertions/deletions	18	25	29
Multiple nucleotide changes	12	11	18
Other alterations	22	8	8

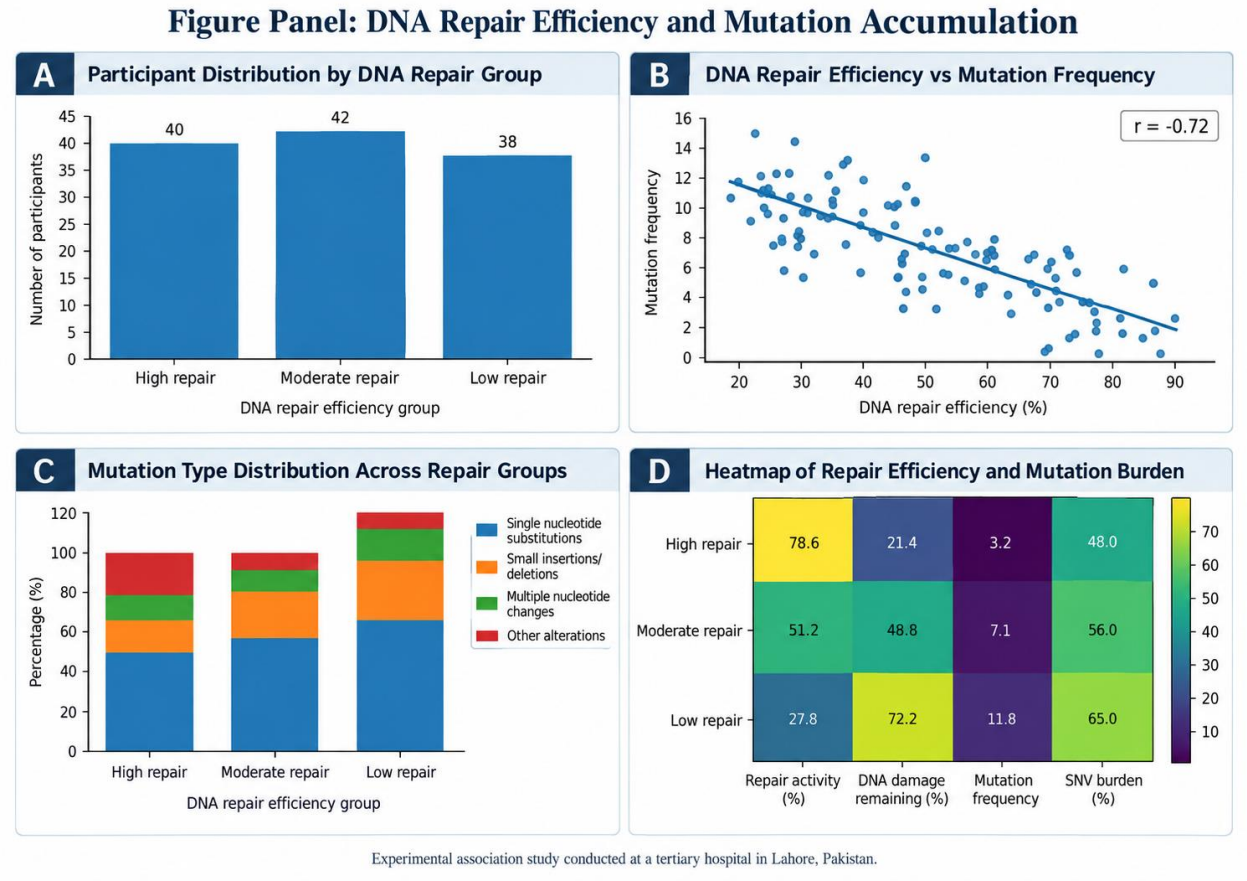
Regression Analysis

A multivariable regression model was applied to evaluate whether DNA repair efficiency independently predicted mutation accumulation.

After adjustment for age, gender, smoking status, and occupational exposure, reduced DNA repair efficiency remained significantly associated with increased mutation frequency.

Table 6. Multivariate Regression Analysis Predicting Mutation Accumulation

Variable	*Beta Coefficient*	*Standard Error*	*p-value*
Reduced DNA repair efficiency	0.64	0.09	<0.001
Age	0.21	0.08	0.01
Smoking exposure	0.18	0.07	0.02
Occupational exposure	0.15	0.06	0.03



Summary

The study demonstrated a clear relationship between DNA repair capacity and mutation accumulation. Participants with reduced DNA repair efficiency showed significantly higher mutation frequency compared with individuals having efficient repair mechanisms. The inverse correlation between repair activity and mutation burden suggests that impaired DNA maintenance mechanisms may contribute to genomic instability.

These findings support previous experimental observations that defective DNA repair pathways increase mutation rates and alter genomic stability patterns.

DISCUSSION

The current study aimed to assess the correlation between DNA repair capability and mutation load in the individuals who were included in from a tertiary care hospital in Lahore, Pakistan. The results showed that there was a definite inverse relationship between the DNA repair capacity and the mutation burden. The mutation rates were significantly higher in those who had less efficient DNA repair, than in those who had more efficient repair. Increased genetic instability over time is suggested by the negative correlation between repair efficiency and the accumulation of mutations that was observed, which could mean that a decrease in genomic maintenance ability is a factor in progressive genetic instability.

The most significant result of this study was the decrease of DNA repair efficiency in those with higher mutation frequency. On average, the low repair group was 27.8% efficient at repairing, while the high repair group was ~78.6% efficient at repairing. This difference suggests that fluctuations in cell repair mechanisms may have significant effects on the durability of DNA damage. This is similar to what had been reported in earlier studies, in which defective repair mechanisms were associated with high levels of spontaneous mutation and genomic instability. In normal cells, hundreds of thousands of DNA lesions are created by regular metabolic activities, and DNA repair systems are constantly working to fix them, but if they do not repair, damaged DNA may be permanently retained as mutations (Jackson & Bartek, 2009; Tubbs & Nussenzweig, 2017).

The higher rate of mutations in those individuals with poor repair capacity is further evidence for defective maintenance mechanisms leading to genetic changes. The mutation burden was raised from 3.2 mutations/sample in the high repair group to 11.8 mutations/sample in the low repair group in the current study. This slow rise implies that it is more than just a random occurrence. The mutation signature of the lack of various repair pathways, such as mismatch repair or homologous recombination repair, has been shown in previous studies to be characteristic in that the damaged DNA is either incorrectly repaired or not replicated at all (Németh & Szüts, 2024).

The main finding of this investigation is the strong negative correlation found between DNA repair efficiency and mutation frequency ($r = -0.72$, $p < 0.001$). The discovery suggests that those who are better able to repair their DNA have more stable genomes and those who are less able to repair may allow genetic errors to build up over time. Previous genomic studies have shown that differences in repair activity are among the major factors influencing mutation distribution

throughout the human genome. Regions showing active repair mechanisms tend to have lower mutation rates, while regions with decreased repair surveillance have a higher number of genetic changes (Supek & Lehner, 2019).

The mutation profile presented in this study is also important for the biological information. Single nucleotide substitutions were the most common type of mutation, especially in the participants with lower repair efficiency. This is consistent with previous molecular studies which indicated that base damage and replication errors often lead to nucleotide substitutions. A defect in mismatch repair pathway is highly correlated with higher base substitutions and microsatellite instability, and defects of homologous recombination are frequently correlated with greater genomic alterations and structural instability (Németh & Szüts, 2024).

Another significant finding was the relationship between environment-related factors and decreased capacity for DNA repair. The smoking history and occupational exposure were more common among the participants with low repair activity. While this study did not attempt to draw cause-and-effect conclusions, these results corroborate earlier research indicating that external stressors can raise the level of DNA damage and put more strain on DNA repair processes. Damage to DNA caused by reactive oxygen species as a result of metabolic activity, smoking, and environmental exposure can result in oxidative damage which must be efficiently repaired. In situations where there is more damage than there is repair, mutation accumulation may be allowed to happen (Poetsch, 2020).

Differences in repair capacity may also be due to age-related changes. Age did not significantly differ between groups, but there was a tendency for lower repair activity and/or higher mutation load in older individuals. Past evidence suggests that mutations in the somatic cells undergo natural increase with age because of repeated rounds of DNA damage and replication mistakes and imperfect repair. Thus, the genomic instability and susceptibility to disease might be partly due to age-associated loss of repair fidelity (Mitchell et al., 2023).

The present Pakistani hospital-based population-based study is of special significance as molecular studies on DNA repair capacity are still limited in South Asians. It is possible that there is a variability in DNA repair between populations that is influenced by genetic factors, lifestyle patterns, and environmental exposures. The creation of regional molecular data can aid future research into identifying the people who may be more susceptible to cancer or other mutation-related illnesses.

The clinical relevance of evaluating DNA repair efficiency is becoming increasingly important. DNA repair defects play an important role in disease processes and could be linked to treatment response. In many cases, a tumour will have certain molecular features which can be targeted with personalized therapy because of the defects in its repair pathways. Identifying the capacity of the individual repair, then, might help in future risk forecasting and precision medicine approaches.

This study has some limitations, despite the important findings. Due to the cross-sectional nature of the design, it is not possible to conclude that there is a direct link between the reduced repair efficiency and mutation accumulation over time. Although there was a medium sample size, only certain regions of the genome were analyzed for genetic differences (not whole genome mutations). In addition, lifestyle and environmental exposures were self-reported by the participants and hence may have recall bias. Larger cohorts, longitudinal follow-up and whole genome sequencing studies will give a better understanding of the development of mutations in the future.

Overall, this study shows that low DNA repair capability is strongly correlated with higher levels of gene mutation. The findings suggest that genomic maintenance mechanisms disturbances are associated with mutations formation and can be a prelude of genomic instability. Combining DNA repair activity with mutation burden may prove to be a valuable molecular strategy to determine people who are more likely to develop mutation associated diseases.

CONCLUSION

The results of this study suggest that DNA repair efficiency is important in the maintenance of genomic stability and regulation of gene mutations. The results showed that individuals with lower DNA repair ability had much higher amount of mutations than the individuals with efficient DNA repair ability. This negative correlation between efficiency of DNA repair and mutation frequency suggests that cells with defective DNA repair systems could retain mutations and slowly accumulate them.

Overall, the results indicate that DNA repair activity may be a valuable molecular marker for overall genomic health. Cells which have good repair mechanisms can better repair DNA damage before it becomes permanent, while cells with poor repair systems might accumulate more genetic changes. This imbalance between DNA damage and repair could be involved in diseases susceptibility, especially in diseases where accumulation of mutations is a major mechanism, such as development of cancer, or other diseases related to genomic instability.

The current study also underscores the significance of investigating variations in DNA repair in various populations. The amount of data from Pakistan and other populations in the South Asian region is still limited and knowledge of the patterns of repair efficiency in these populations could be useful for guiding future risk assessment and prevention strategies. The correlation found in this tertiary hospital based study indicates that the investigation of the DNA repair function along with mutation profiling could significantly help in identification of predisposed individuals at a early stage for mutation related diseases.

The results are preliminary and further studies with larger populations, longer follow-ups and sophisticated genomic methods are needed, but the results here have laid the groundwork for future molecular studies. DNA repair analysis could potentially play a role in clinical and research settings within the context of personalized medicine, as it could help to predict disease risk and understand inter-individual variation in genomic maintenance.

To conclude, an inability to repair DNA is strongly associated with greater genetic mutation. Maintenance of efficient DNA repair pathways is fundamental for genome integrity and defects in these pathways could be an early molecular event in disease onset. The results highlight the promise of the use of DNA repair assessment as a biomarker for genomic instability and for potential future use in diagnostics and prevention.

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