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REVIEW ARTICLE

LOSS OF Y CHROMOSOME, AN ALARM TOWARDS AGGRESSIVE BLADDERCANCER IN MEN: IT'S DETECTION AND DIAGNOSIS

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Abstract

In comparison to the other chromosomes, it is said that the Y chromosome is a bit poor in genes- being more than 50% of its sequence composed of repeated elements. Moreover, research says that the Y genes are in continuous decay probably due to the lack of recombination of this chromosome. Earlier assumptions carried a notion that the Y chromosome only played a role in guiding the development of the male sex organs in a foetus. However, detailed research studies over the past few years have revealed the fact that apart from only sex determination, the Y chromosome may actually protect men from aggressive bladder cancer. To examine the significance of Y chromosome losses in bladder cancer, fluorescence in situ hybridization (FISH) was used to determine its prevalence and associations with known parameters of malignancy. Detection of mosaic loss of Y chromosome (mLOY) is yet another important issue which is required for the proper diagnosis of the diseases in men. They usually include Next-generation sequencing (NGS) and Multiplex PCR-based assays.

Introduction:-

It was once thought that the Y chromosome had little other function after controlling the development of male reproductive organs in the foetus. However, in recent years, several research findings have called this assumption into question. The latest evidence comes from a new study that suggests, the Y chromosome may actually protect men from advanced aggressive bladder cancer.

Most biological females have two X chromosomes in each cell, while most biological males have one X chromosome and one Y chromosome. However, as a man ages, some of his cells can naturally lose his Y chromosome. More than half of men in their early 90s have lost the Y chromosome in some of their blood cells.

The new study, conducted in both mice and humans, found that loss of the Y chromosome in bladder cancer cells allows the tumors to escape the immune system and grow uncontrollably. Meanwhile,loss of the Y chromosome

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appears to make bladder cancer more susceptible to immunotherapy drugs called immune checkpoint inhibitors, researchers reported June 21 in Nature.

The lead investigator of this study, Dan Theodorescu, M.D., Ph.D., and the Director of Cedars-Sinai's Samuel Oschin Comprehensive Cancer Institute, said that, it's surprising that the loss of the Y chromosome has such a biological impact on the immune system. He also added that, based on current or prior scientific findings, this would have been completely unexpected.

"Numerous studies have shown that loss of the Y chromosome puts men at a higher risk of developing and dying from cancer, but it's not yet understood why...", said Konstantin Salnikov of NCI's Division of Cancer Biology, who was unaware of this implication. Being involved in the field of research, he assures that the results of a new study partially funded by NCI (National Cancer Institute) may answer that question, and that may help scientists begin to solve the long-standing mystery of why men develop more rates of cancer than women, he added.

Y Chromosome: The Genotypic Component Determining Male

Stucture Of The Y Chromosome:

The Y is one of the smallest chromosomes in the human genome (approximately 60 Mb), accounting for approximately 2–3% of the haploid genome. Cytogenetic observations based on chromosome banding studies led to the identification of distinct Y regions, namely the pseudoautosomal regions (split into two regions, PAR1 and PAR2) and the euchromatic and heterochromatic regions [Figure 1].

Pseudoautosomal regions (PARs): PAR1 is located at the end of the short arm (Yp) and PAR2 is located at the tip of the long arm (Yq). PAR1 and PAR2 constitute approximately 2600 kb and 320 kb of DNA, respectively. In the pseudoautosomal region, specifically PAR1, during meiosis in a male, the Y chromosome pairs with the pseudoautosomal region of the X chromosome and exchanges genetic material. Therefore, genes located in PARs are inherited like autosomal genes. The euchromatic region is distal to PAR1 and consists of a paracentromeric region of the short arm, a centromere, and a paracentromereic region of the long arm. Finally, the heterochromatic region includes distal Yq, which corresponds to Yq12. This region is primarily composed of two highly repetitive sequence families, DYZ1 and DYZ2, containing approximately 5000 and 2000 copies, respectively, making them genetically inactive and length polymorphic in different male populations.

It is believed that although PAR1 and PAR2 constitute 5% of the total chromosome, the majority (95%) of the Y chromosome is formed by the so-called "Non-Recombining Y" (NRY). These include euchromatic and heterochromatic regions of the chromosome. Although heterochromatic regions are considered to be genetically inactive, euchromatic regions contain many highly repeated sequences, but some genes responsible for the important biological functions described here also included.

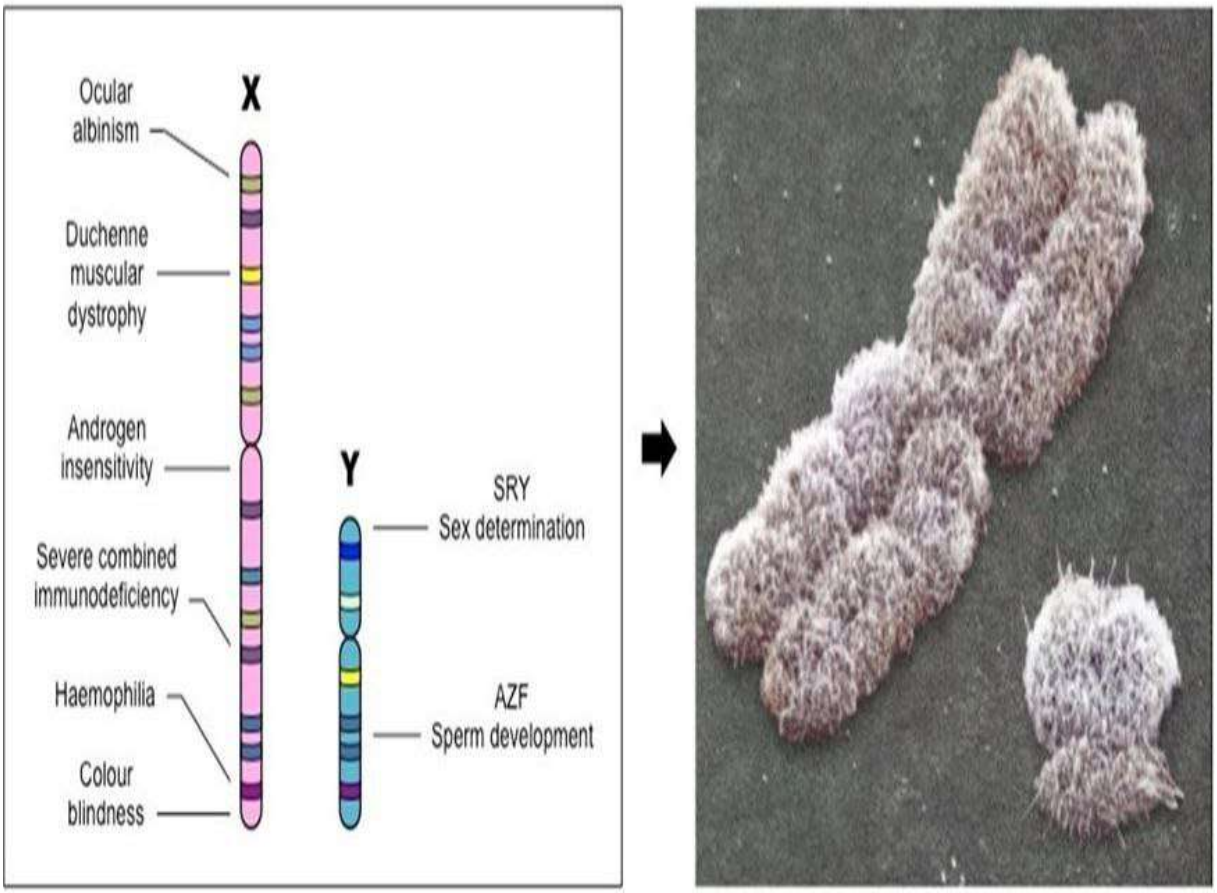

Figure 1A:- Genetic comparison of X & Y chromosomes. **Figure 1B:-** Micrograph of X & Y chromosomes.

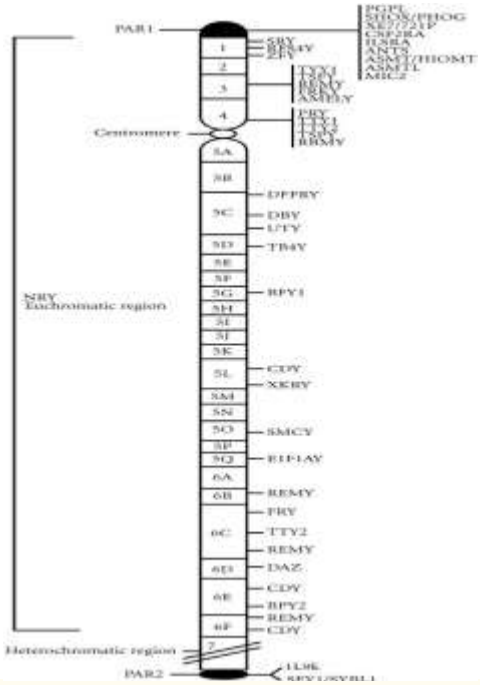

Figure 1C:- Schematic representation of the Y chromosome. Genes in the two pseudoautosomal regions (PAR1 and PAR2) as well as those in the nonrecombining Y region (NRY) are illustrated.

SRY Gene: The Sex Determiner:

The first evidence that the Y chromosome is involved in determining male sex is that patients with XY or XXY syndrome (Klinefelter syndrome), or XYY syndrome (Jacobs syndrome) develop testes, whereas patients with XX or XO syndrome (Turner syndrome) develop ovaries[1]. Subsequent studies showed that mouse XX, which has a male phenotype, carries a small portion of the Y chromosome, indicating that the master gene responsible for determining male sex is located on her Y chromosome, confirmed the idea[2]. In 1990, a gene involved in testicular determination called SRY (sex-determining region on the Y chromosome) was finally identified [3]. SRY was cloned by isolating a small fragment of translocated Y from an XX transsexual patient. This gene is located on the short arm of the Y chromosome near the border of the pseudoautosomes. It consists of a single exon encoding a 204-amino acid protein with a conserved DNA-binding domain (HMG box: High Mobility Group), suggesting that this protein regulates gene expression. This gene has been shown to be essential for the initiation of testicular development and differentiation of the indifferent bipotent gonads into the testicular pathway. Furthermore, it was hypothesized that SRY is a master gene controlling the testis determination cascade. A number of genes and loci have been suggested to interact with the SRY protein, including: WT-1 (Wilm's tumor gene), SF-1 (steroidogenic factor 1), and SOX-9. However, the question of how, if at all, these genes are regulated by SRY remains an open question which is yet to be resolved.

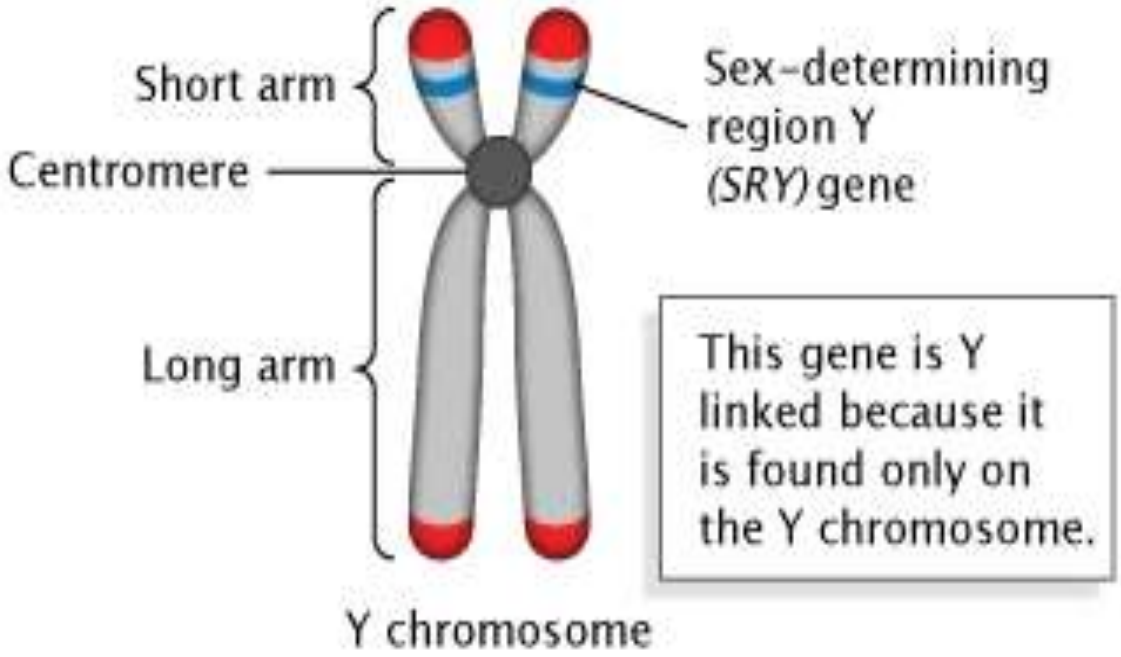

Figure 2:- A diagrammatic representation of Y chromosome showing the regions of the SRY gene.

Mosaic loss of Y Chromosome

In somatic cells of elderly men, loss of the Y chromosome (LoY) is often observed. On the other hand, LoY is significantly elevated in tumor tissue and is associated with a generally poorer prognosis. It is largely unknown what the underlying causes and long-term effects of LoY are. Consequently, male patient tumors have been classified, based on the loss or retention of the Y chromosome (LoY or RoY, average LoY fraction: 0.46) by analyzing genomic and transcriptomic data of 13 cancer types (2375 patients). From nearly nonexistent (glioblastoma, glioma, thyroid carcinoma) to 77% (kidney renal papillary cell carcinoma), the frequencies of LoY varied. LoY tumors had higher levels of genomic instability, aneuploidy, and mutation burden. Furthermore, we discovered that the oncogenes MET, CDK6, KRAS, and EGFR amplified in multiple cancer types, and that the gatekeeping tumor suppressor gene TP53 mutated in three cancer types (colon adenocarcinoma, head and neck squamous carcinoma, and lung adenocarcinoma) more frequently in LoY tumors. At the transcriptome level, we found that the tumor suppressor gene GPC5 was down-regulated in LoY of three cancer types and that MMP13, which is known to be involved in invasion, was up-regulated in LoY of three adenocarcinomas. Additionally, it was discovered that a smoking-related mutation signature was enriched in LoY tumors related to lung and head and neck cancer. Surprisingly, a correlation was found between the frequencies of LoY and the sex bias in cancer type-specific

incidence rates, supporting the theory that LoY raises the risk of cancer in men and more aggressively targeting the bladder, as per recent research results.

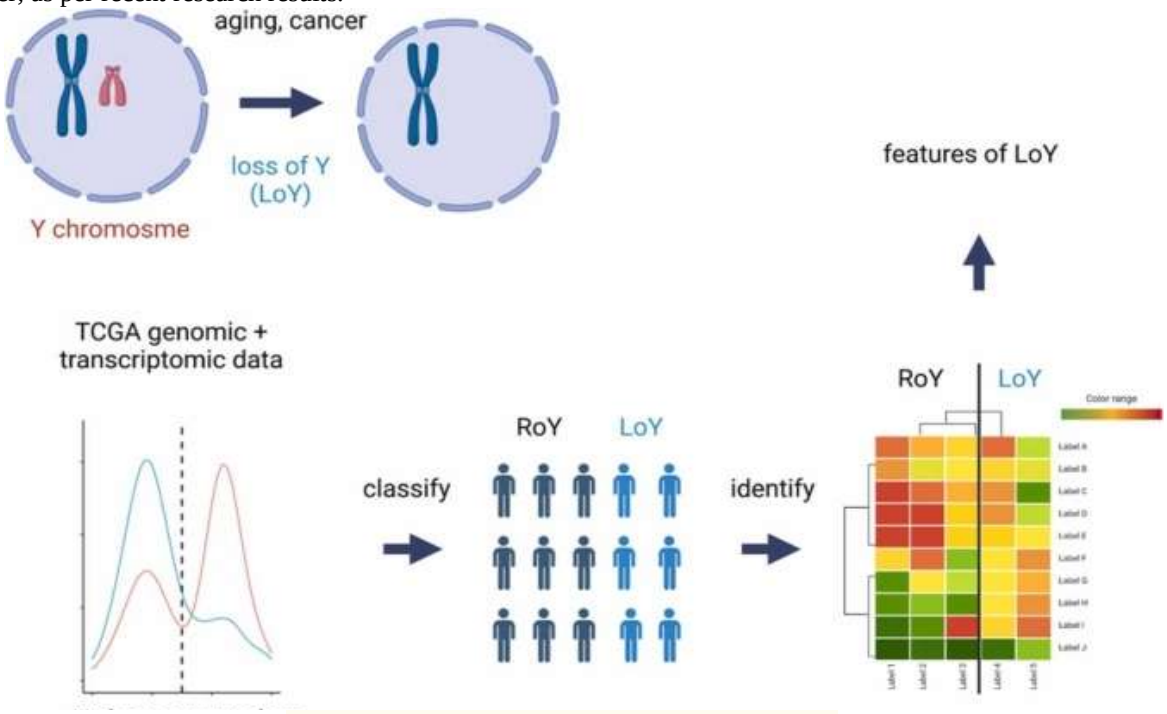

Figure 3:- Figure showing loss of Y chromosomes.

The onset of bladder cancer

Statistical records show that up to 40% of older men with bladder cancer lack the Y chromosome in their tumors.

Given that men are three to five times more likely than women to develop bladder cancer, the researchers investigated the possibility of a link between Y chromosome loss and bladder cancer. In order to investigate that possibility, a large group of men with bladder cancer were examined by the researchers. They discovered that men whose tumors expressed little to no Y chromosome genes (known as Y-negative tumors) lived shorter lives than men whose tumors expressed a lot of Y chromosome genes (known as Y-positive tumors). The researchers used mouse bladder cancer cells that had a Y chromosome (Y-positive) and those that did not (Y-negative) to investigate why. They discovered that when the two cell groups were placed into male mice devoid of immune systems, the cells grew at the same rate in lab dishes. Y-negative cells on the other hand grew twice as quickly when the researchers implanted the cells into male mice with healthy immune systems. That was the first indication, Dr. Theodorescu said, that Y-negative cells were more adept at eluding the immune system.

Moreover, the discovery that PD-L1, a protein that inhibits T cells—immune cells that are primarily in charge of locating and eliminating cancer cells—was present in greater quantities in Y-negative tumors in both men and mice provided the researchers with yet another hint. It is true that T cells in Y-negative tumors showed less activity than T cells in Y-positive tumors. Not only that, but T cells in Y-negative tumors showed signs of exhaustion, a phenomenon that occurs when T cells run out of steam trying to rid.

The Molecularbackground behind bladder cancer

Understanding the molecular mechanisms of bladder cancer genesis has advanced significantly in recent years. The formation of a premalignant abnormal urothelial patch is an early stage in the development of carcinoma. This patch can harbor different types of urothelial carcinoma and act as a breeding ground for multifocal synchronous and metachronous tumors. There are two different molecular pathways at play. FGFR3 mutations or, in certain situations, mutations in the RAS genes are linked to low-grade papillary carcinoma. pRB and p53 alteration, on the other hand, is characteristic of high-grade in situ/muscle-invasive carcinoma. When these important genes, which are essential for controlling the cell cycle, stop working, more mutations and gene deletions build up and cause an aggressive phenotype.

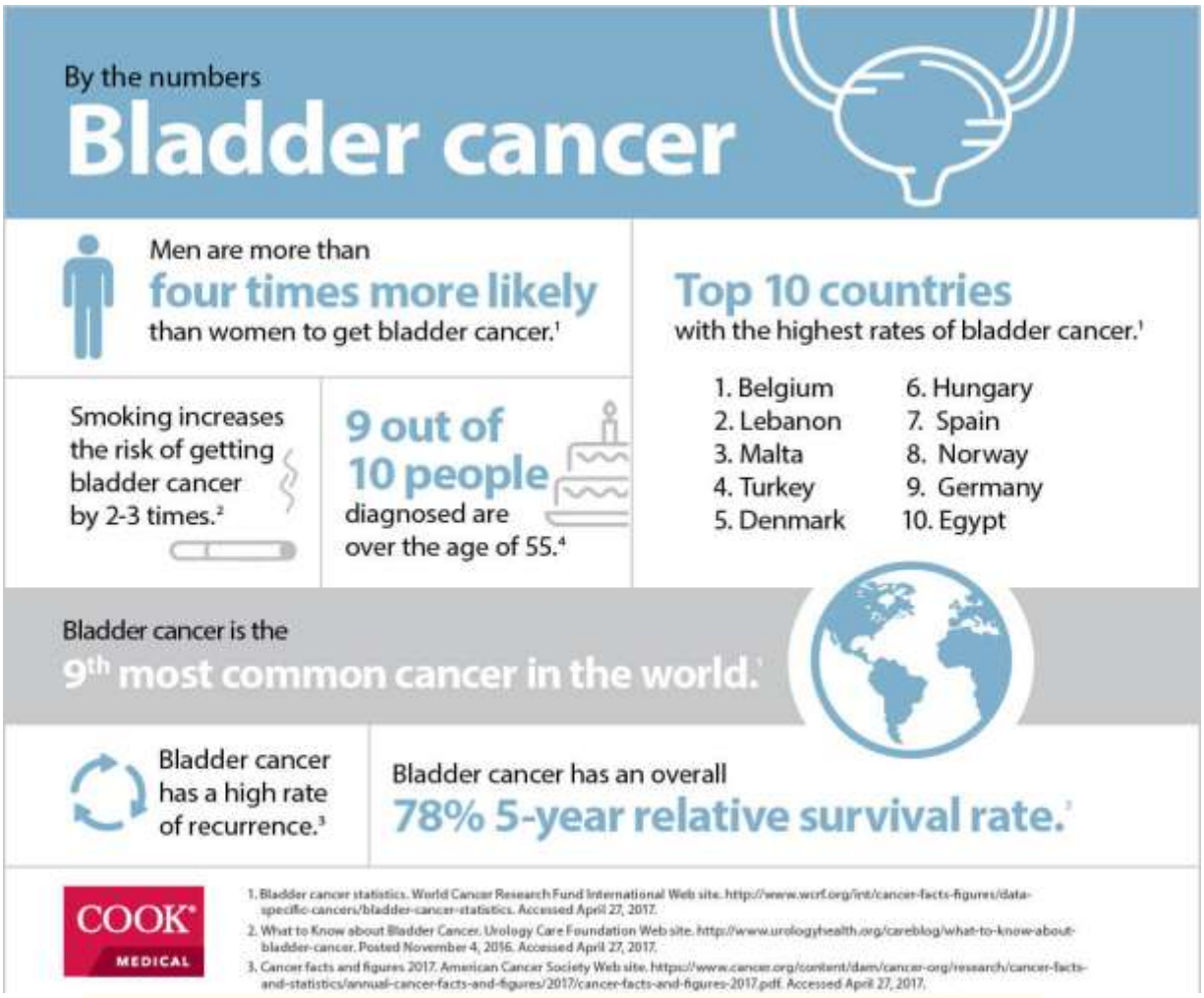

Figure 4:- A record chart showing people all over the world suffering from bladder cancer.

Overview Of The Fgfr Signaling Pathway:

Receptor tyrosine kinases (RTKs), which are made up of approximately 20 families of homologous proteins and nearly 60 distinct members in humans, are significant signal transducers in the cell membrane [4]. There are four homologous human receptors in the FGFR family that have been identified: FGFR1, FGFR2, FGFR3, and FGFR4. A membrane-spanning segment, a split tyrosine kinase domain, and three extracellular immunoglobulin (Ig)-like domains are present in all FGFRs. As high-affinity FGFR agonists, fibroblast growth factors (FGFs), a broad family of related growth factors, work in tandem with heparin sulfate proteoglycans (HSPGs) [5, 6]. The most researched splicing isoforms of FGFRs involve the third immunoglobulin-like domain of the receptors, which leads to additional differentiation of ligand specificity along with changed biological properties [7]. The first half of the third Ig domain for FGFR2 and FGFR3 is composed of an invariant exon (IIIa). The second half of the third Ig domain, which is spliced, yields either the IIIb isoform (exons 7 and 8) or the IIIc isoform (exons 7 and 9). In general, mesenchymal tissues express the IIIc isoforms of FGFRs, while tissues of epithelial origin express the IIIb isoforms [8].

Tyrosine residues in the cytoplasmic kinase domain of the receptor dimerize in the plasma membrane when FGF/HSPG binds to FGFR. This is followed by trans-autophosphorylation of the receptor monomers. Tyrosine phosphorylation causes PKC to become activated by causing the Src homology (SH2) domain of phospholipase C gamma (PLCγ) to bind to the receptor. Through the FRS2 and GRB2 adaptor proteins, activation also triggers PI3K–AKT and RAS–MAPK signaling. Furthermore, JAK/STAT and Jun N-terminal kinase pathways are triggered by FGFRs. Angiogenesis, anti-apoptosis, cellular migration and proliferation, and wound healing are all caused by FGFR signaling (Fig. 5) [9].

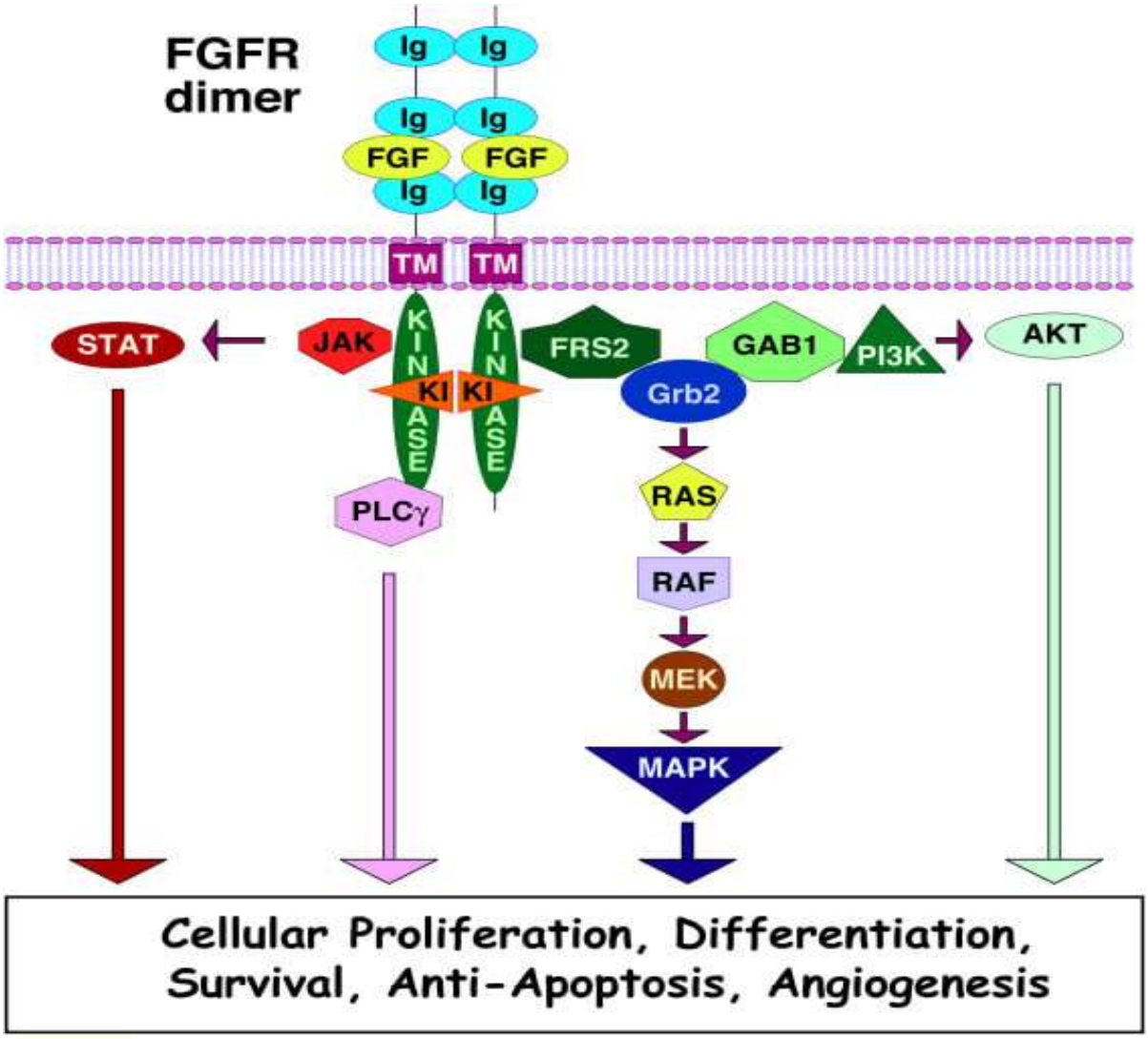

Figure 5:- FGFR signaling pathways. FGF ligand binds to FGFR monomers, leading to the dimerization and subsequent tyrosine autophosphorylation of the receptor. This event leads to activation of FGFRs and various downstream proteins, resulting in cellular proliferation, differentiation, survival, anti-apoptosis and angiogenesis.

FGFR Mutations:

Missense mutation acquisition is a significant tumorigenic mechanism that also involves activation of the aberrant FGF/FGFR axis. Autosomal dominant diseases are caused by particular germline point mutations of FGFR3, which result in constitutive activation of the receptor [10]. It is true that FGFR3 mutations like S249C, R248C, and Y373C cause the formation of disulphide bonds, which in turn set off a number of cancer-related downstream signaling pathways[11]. This results in constitutive receptor dimerization and ligand-independent phosphorylation [12,13]. There is more stability with this dimer, according to several studies[14]. Some mutations, such as G370C, S371C, and G380R, have also been examined in HEK293T cells, showing that the mutant receptors could dimerize both in the presence and absence of ligand [15]. Moreover, consistent transcriptional activity and constitutive ligand-independent hyperactivation of the MAPK signaling pathway were observed in all mutants [15]. The upregulation of transcription factors, such as ETV5, resulting in the hyper-expression of TAZ and YAP1, and consequently the transcription of anti-apoptotic and pro-proliferative genes, has been shown in some studies on TERT-NHUC cells expressing FGFR3 mutants, which lends support to this proposal [16,17]. The same FGFR3 missense mutations have been linked to both cervical and bladder carcinomas and multiple myeloma in more recent research [18]. Out of the 132 bladder tumors that Billerey and colleagues examined, 48 (or 36.4%) had FGFR3 mutations.

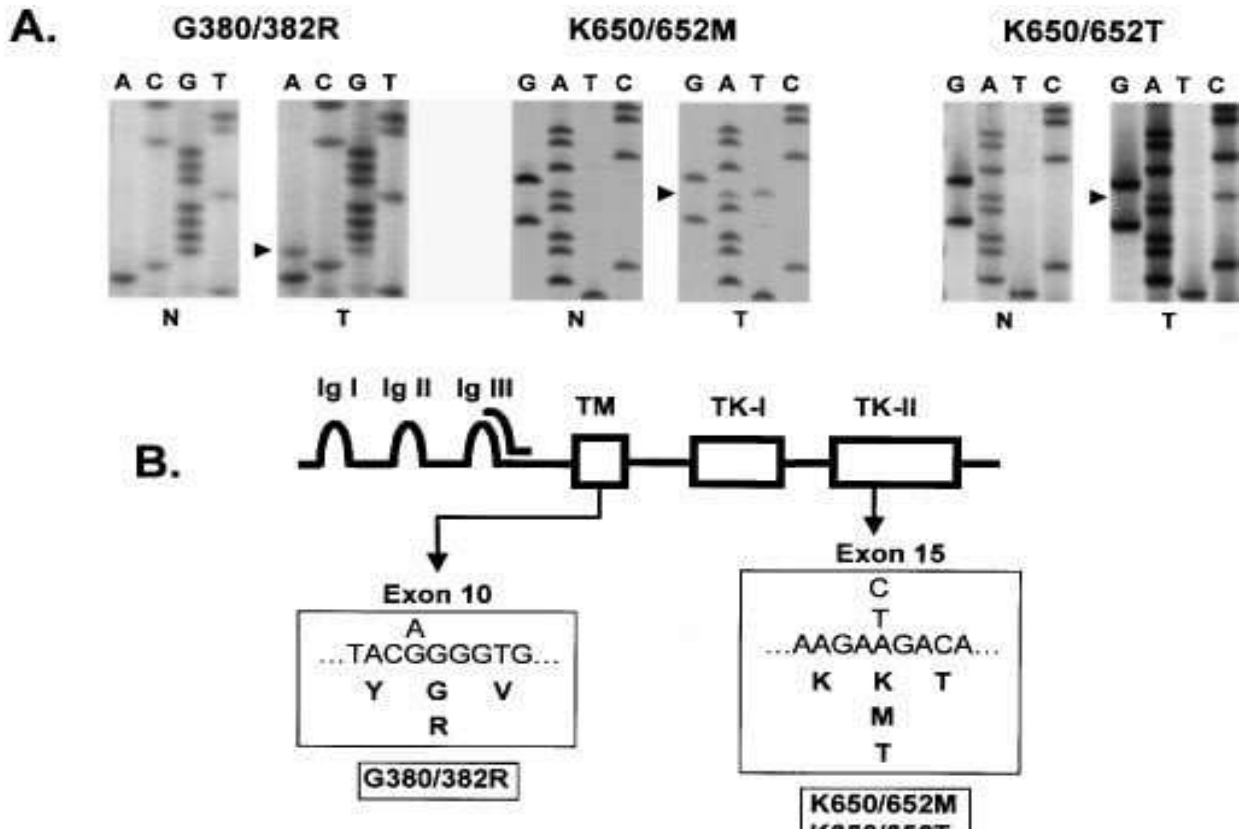

Figure 6:- Identification of novel FGFR3 mutations in bladder cancer.

(A) Novel somatic FGFR3 mutations were identified by PCR-SSCP followed by direct DNA sequencing. The tumourshown on the left side has a G to A transition in exon 10, which changes the sequence of codon 380/382 from GGG (Gly) to AGG (Arg). The tumour in the middle has an A to T transversion in exon 15, which changes the sequence of codon 650/652 from AAG (Lys) to ATG (Met). The tumour on the right side has an A to C transversion in exon 15, which alters the sequence of codon 650/652 from AAG (Lys) to ACG (Thr). Arrowheads indicate the positions of the mutations. The FGFR3b isoform, which is expressed in epithelial cells, contains two amino acids more than the FGFR3c isoform expressed in bone. Therefore, the G380R, K650M and K650T mutations in FGFR3c are equivalent to the G382R, K652M and K652T mutations in FGFR3b. Note in addition: while the present study was under evaluation, the K650/652M mutation in bladder cancer was reported by Kimura et al.26 N, sequence of normal DNA; T, sequence of tumour DNA.

(B) Schematic diagram of the FGFR3 protein. The areas within the two exons, in which the new missense mutations occurred, are shown in greater detail. The nucleotide substitutions are shown above, the amino acid substitutions are shown at the bottom of the Figure.

p53 The Guardian Of Genome & Its Role In Carcinogenesis:

Through the induction of stress response mechanisms that maintain genome integrity, p53 plays a role in mitigating cellular stressors such as hypoxia, DNA damage, and oncogene activation. The p53 protein is well-known for being the “tumor suppressor p53” because it significantly inhibits the development and spread of cancer when it functions normally [19,20]. Therefore, mutations in the p53 gene, TP53, are necessary for carcinogenesis to occur and can significantly affect p53 function. This contributes to the fact that p53 is one of the proteins that is most commonly mutated in all cancers; up to 53% of all cancers have p53 mutations.

It is well known that p53 binds to different DNA response elements in target sequences to function as a transcription factor. Over 100 p53 response genes have been found, including the p21 encoding gene CDKN1A, the apoptosis genes BAX, PERP, and BBC3, the angiogenesis gene THBS1, and many more [21]. The DNA-binding domain of the p53 protein is the most important domain for mediating its interaction with response elements among all the

other domains. Because they are unable to interact with DNA components involved in the progression of tumors, such as proto-oncogenes, base mutations in the DBD sequence (also known as mis-sense mutations) are associated with tumorigenesis. In somatic cells, these mutations develop either on their own or as a result of DNA damage. The degree to which a mutation can influence the development of a tumor, however, varies depending on the specific residue and gene region that is mutated. Not all mutations impact p53 function in the same way. The degree of p53 binding is also determined by the response element sequence in the target genes. Certain tumor types have mutations that cause p53 agonists like Mdm2 and Mdm4 to become more functional. This leads to the inhibition of p53 activity regardless of whether the cell contains normal quantities of wild-type p53. Mdm2 is a ubiquitin ligase that, in healthy cells, binds to p53 and directs proteasomal degradation of the protein to keep p53 at a low level. Additionally, MDM2 binds to the p53 mRNA to control translation [22].

Single base substitutions in the coding sequence account for the majority of p53's "tumor associated mutations" [23]. In addition, over 200 single nucleotide polymorphisms in TP53 have been found; these have no discernible impact on the activity of p53 or the development of tumors. The most extensively researched and frequently mutated tumor suppressor gene, p53 is distinct in that it exhibits a broad range of residual activity as a direct result of the mutated residue [24]. Uncertainty surrounds the molecular basis of the majority of p53 mutations. Therefore, a deeper comprehension of these mechanisms may result in more effective clinical treatment for cancers containing p53 mutations. It is now necessary to conduct additional research to fully comprehend the roles of the "guardian of the genome" because other mechanisms, like micro RNAs, have been suggested as being involved in p53-mediated gene regulation. The variety of mutations that TP53 can carry has led to an abundance of online resources that provide details on TP53 mutations, including the domain that contains the mutated residue, the approximate loss of function, and potential associations with different types of cancer. The IARC TP53 mutation database, the p53 Knowledgebase, the TP53 Web Site, and the Database of germline p53 mutations are a few of the most well-known.

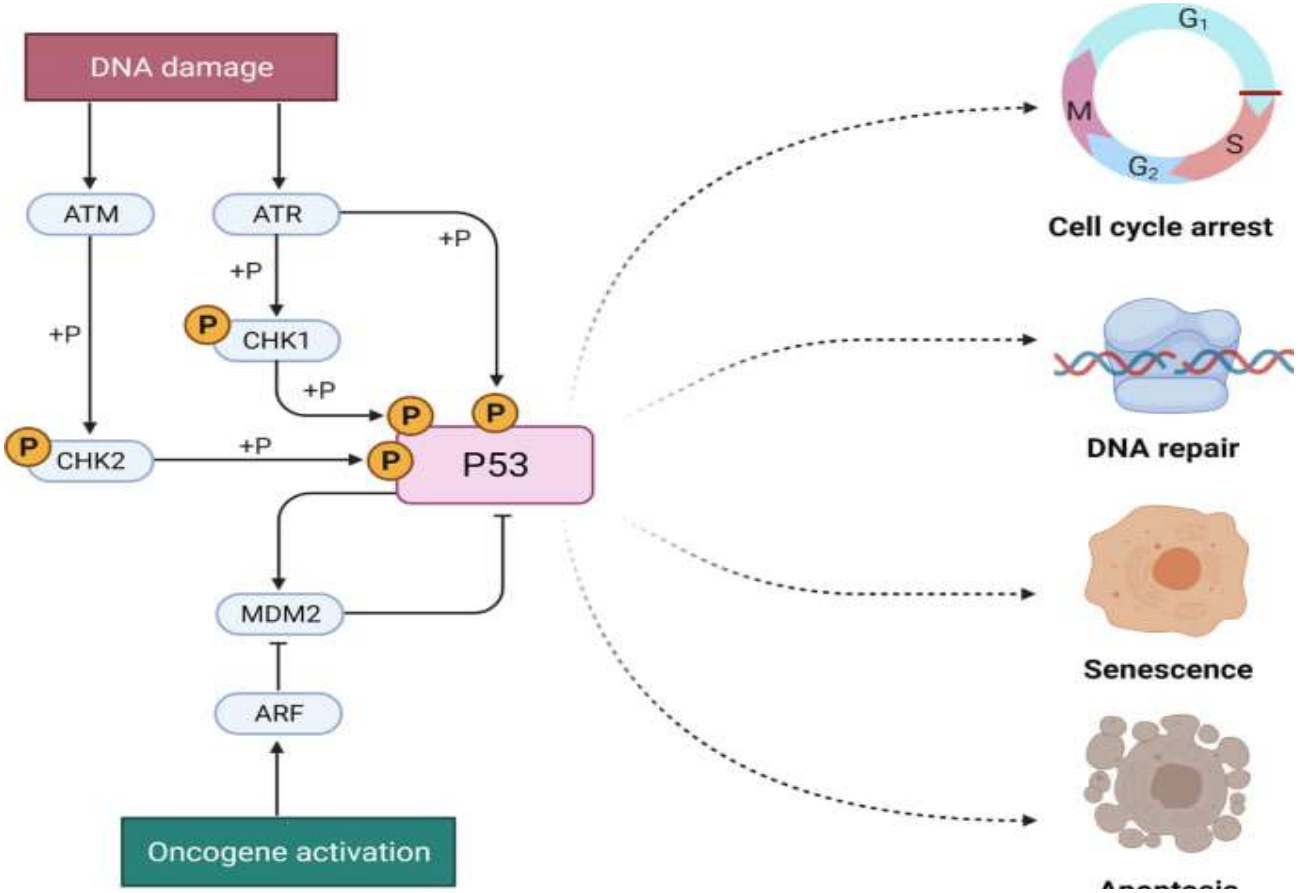

Figure 7:- Role of p53 in tumor suppressor function. The DNA damage signal sensed by ATM/ATR and oncogene activation leading to MDM2 inhibition resulting in the activation of secondary sensor p53 to orchestrates, cell cycle arrest/DNA repair/senescence/apoptosis.

Detection and Diagnosis
The techniques usually used for the detection of the loss of Y chromosome and the onset of bladder cancer are –

Fluorescent In-Situ Hybridization (FISH):
It is perhaps the most reliable method for identifying specific DNA sequences, diagnosing genetic disorders, mapping genes, and identifying novel oncogenes or genetic abnormalities causing different kinds of cancers is fluorescence in situ hybridization, or FISH. In fluorescence inverted microscope (FISH) analysis, target sequences of the sample DNA are annealed to fluorescent reporter molecules via DNA or RNA probes. Recently, the technique has been extended to allow simultaneous screening of the entire genome using multicolor whole chromosome probe techniques like spectral karyotyping or multiplex FISH, or via an array-based approach utilizing comparative genomic hybridization. In the fight against genetic diseases, FISH is now acknowledged as a dependable diagnostic and discovery tool, having completely transformed the field of cytogenetics.

Principle:
The fundamental idea is to use a nucleic acid probe to hybridize the nuclear DNA of either interphase cells or metaphase chromosomes attached to a microscopic slide. Either a hapten is used to indirectly label the probes, or a fluorophore is added to directly label them. Following denaturation, the labeled probe and the target DNA are combined to enable the annealing of complementary DNA sequences. If the probe was indirectly labeled, the non-fluorescent hapten will need to be seen through an additional enzymatic or immunological detection system step. Finally, fluorescence microscopy is used to assess the signals. Fluorochrome, which produces colored signals at the hybridization site, is a component of the enzymatic detection system. The basis of the immunological detection system is the binding of antibodies to particular antigens, which is subsequently shown by fluorochromes under ultraviolet light or a colored histochemical reaction visible under a light microscope.

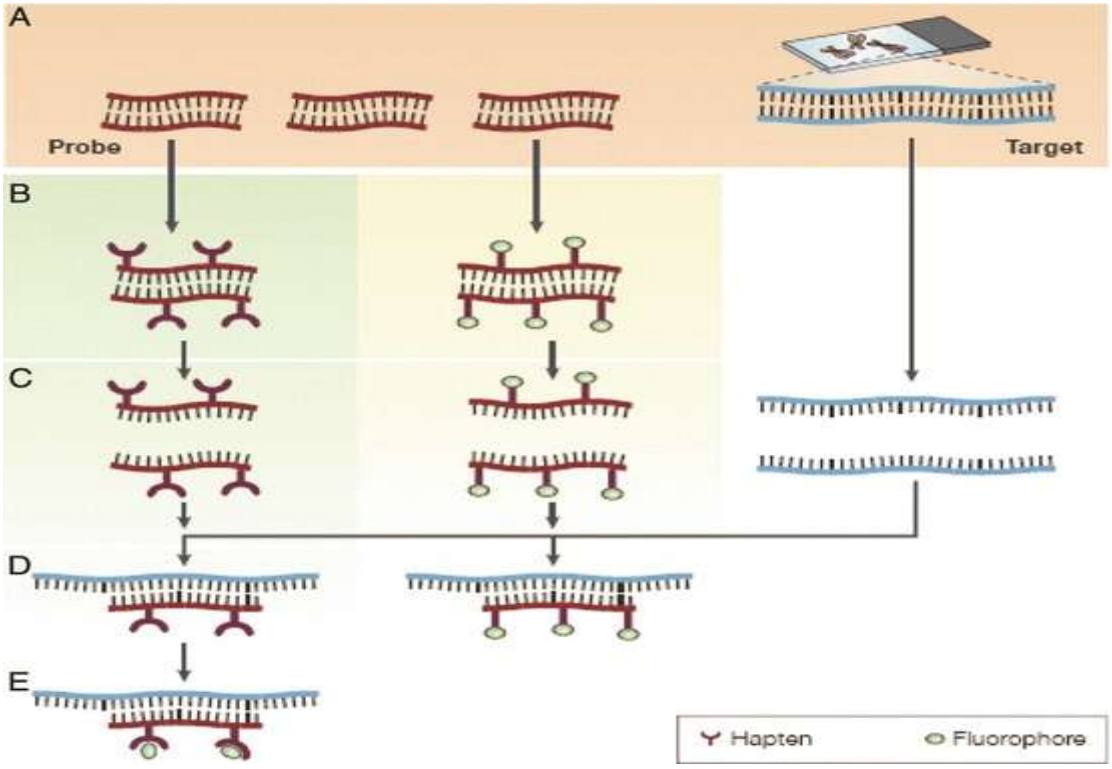

Figure 8:- The principles of fluorescence in situ hybridization. (a) The basic elements are a DNA probe and a target sequence. (b) Before hybridization, the DNA probe is labeled indirectly with a hapten (left panel) or directly labeled via the incorporation of a fluorophore (right panel). (c) The labeled probe and the target DNA are denatured to yield single-stranded DNA. (d) They are then combined, which allows the annealing of complementary DNA sequences. (e) If the probe has been labeled indirectly, an extra step is required for visualization of the nonfluorescent hapten that uses an enzymatic or immunological detection system. Finally, the signals are evaluated by fluorescence microscopy.

Next-Generation Sequencing (NGS):

Sequencing multiple genes at a very high depth of coverage is made possible by Next-Generation Sequencing (NGS). The identification of distinct molecules that can be employed as drug targets or as molecular markers implicated in the progression and/or survival of tumors forms the basis of targeted therapy. Single-gene diagnosis is losing efficacy in light of the ongoing identification of novel molecules that may be targets or the causes of mechanisms underlying treatment resistance. Genome characterization is now necessary for precision medicine. Multiplex analysis with high analytical sensitivity is now possible.

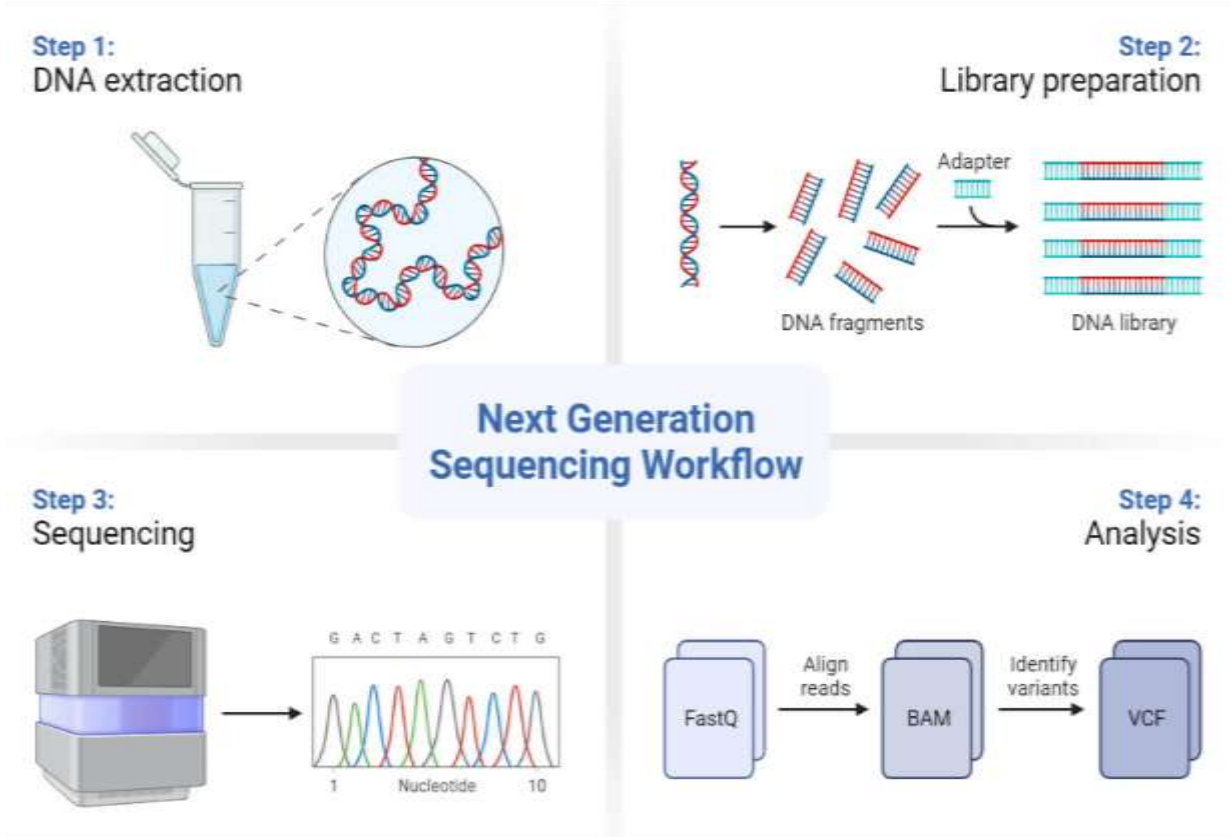

Figure 9:- Figure showing basic procedure of Next Generation Sequencing (NGS).

Multiplex-Pcr Based Assay:

Using distinct primer pairs for each target, multiplex PCR allows for the simultaneous detection of several targets in a single reaction well. Multiple simultaneous detections and separations of probes are necessary for this technique. A variety of fluorophores-based probe technologies are available. The fields of clinical diagnostics, forensic science, and life science research all use multiplex PCR. Comparative analyses are now considered standard practice in many realms of research and testing due to the advent of PCR detection systems with simultaneous multi-target detection and improvements in probe chemistries. Multiplex PCR is widely used in numerous fields, such as SNP genotyping, pathogen detection, forensic studies, food analysis, mutation and polymorphism analysis, gene deletion analysis, template quantitation, linkage analysis, and RNA detection.

As per in this field of study and analysis, it has been concluded well that Multiplex-PCR assays can be a useful tool for staging and monitoring purposes in patients with bladder cancer.

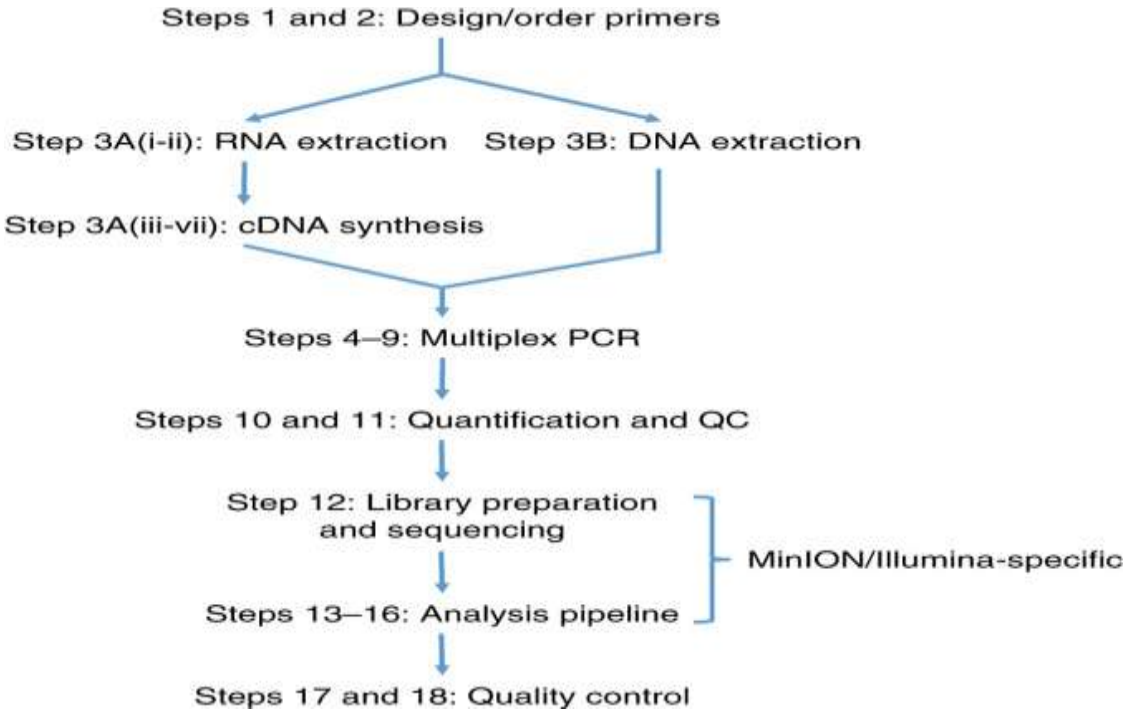

Figure 10:- A word-diagrammatic representation of the flow chart showing Multiplex PCR.

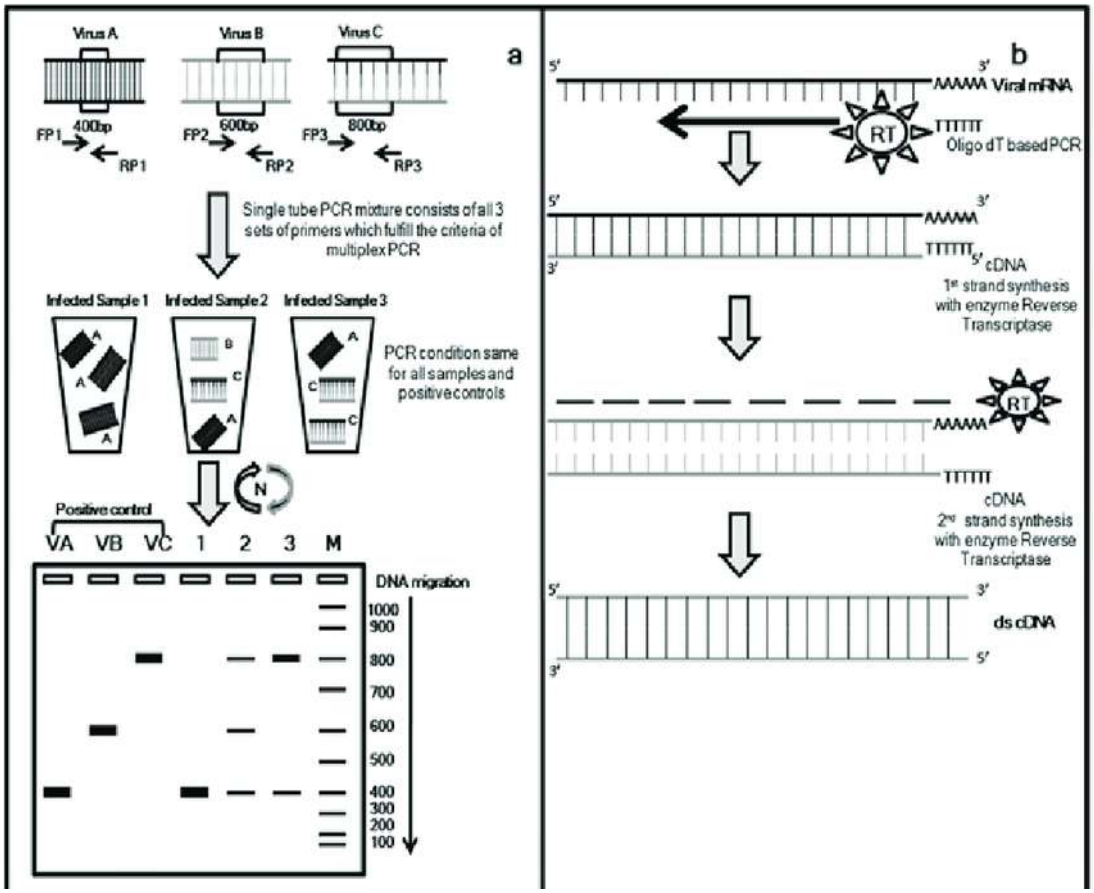

Figure 11:- Multiplex PCR procedure.

Cystoscopy:
During a cystoscopy procedure, the doctor looks for abnormalities inside the bladder and urethra, the tube that exits the body. To see inside the bladder, a doctor gently inserts a cystoscope through the urethra. A thin, tube-shaped device with a light and a viewing lens is called a cystoscope. It might also have a tool to remove tissue samples for a biopsy or extremely tiny bladder tumors. Cystoscopy aids in the diagnosis and occasionally the treatment of bladder cancer as well as other diseases.

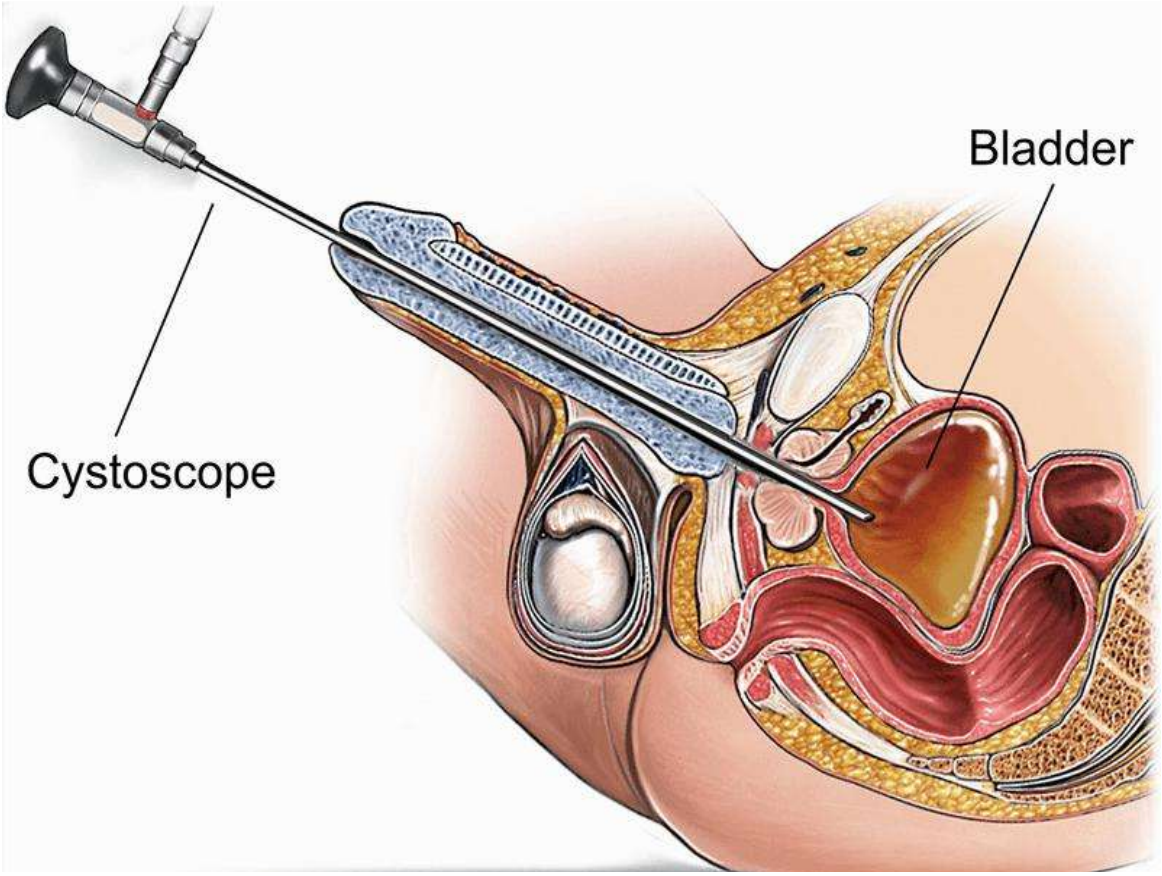

Figure 12:- Schematic representation showing the method of Cystoscopy through male penis.

Conclusion:-

The rising incidence and high recurrence rate of bladder cancer have made it a significant social issue in recent decades [25,26]. According to statistical data, the number of bladder cancer cases increased globally between 2002 and 2012, from 375 point 000 to approximately 430 point 000 [27,28]. At the same time, patient mortality increased, rising from 145 point 000 in 2002 to 165 point 000 in 2012 [29,30,31]. Cases of bladder cancer are distributed quite differently worldwide. Data suggests that two thirds of bladder cancer cases occur in developing nations [32,33].

1073 patients with bladder tumors were admitted to the Urology Clinic between 2013 and 2015. Relatively proportionate was the annual distribution. Therefore, using this diagnostic, 369 patients (34.39 percent) were admitted in 2013, 381 patients (35.51 percent) were admitted in 2014, and 323 patients (30.10 percent) were admitted in 2015 (Fig.13).

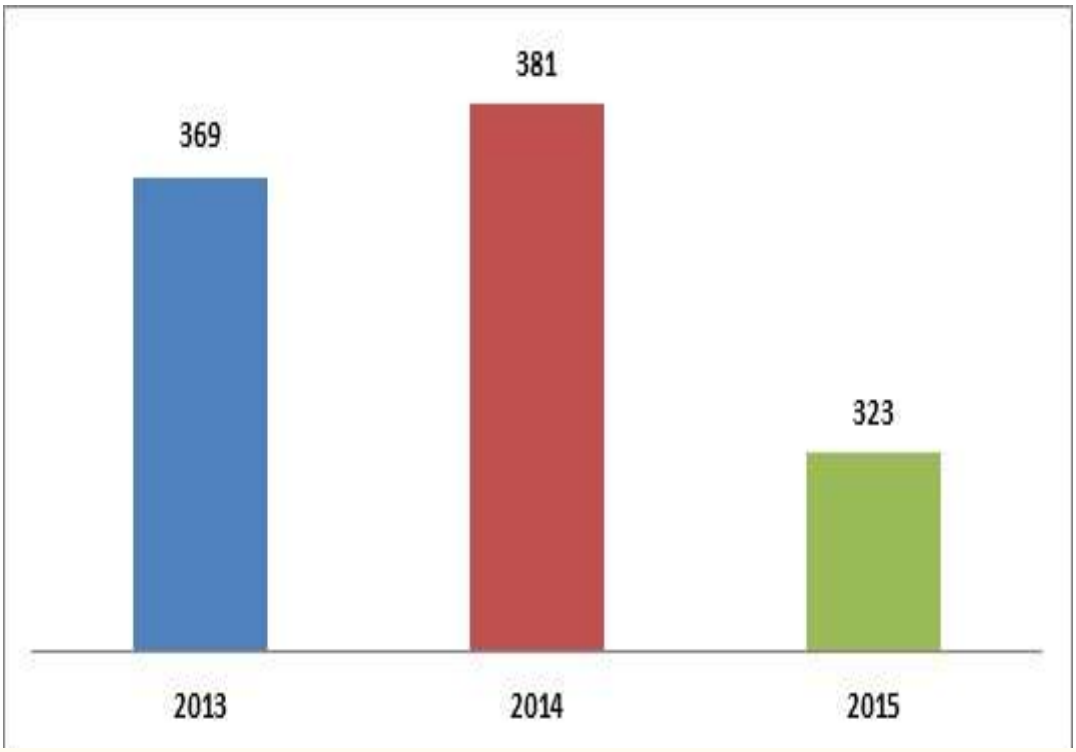

Figure 13:- Yearly distribution of patients with urinary bladder tumors.

As for the gender distribution, we found that, in line with previous research, men were significantly more likely than women to develop bladder tumors. Therefore, of the 1073 bladder cancers that were detected, 741 (69.06 percent) were diagnosed in men and 332 (30.94 percent) in women; the men/women ratio was 2.23/1 (Fig.14).

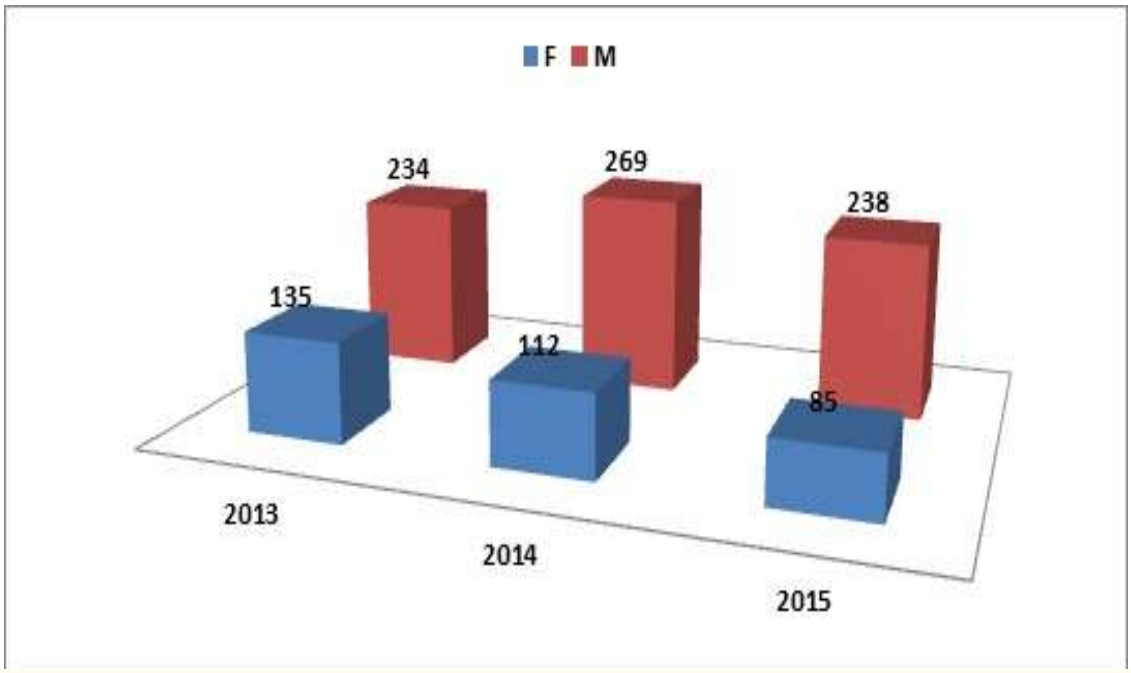

Figure 14:- Sex distribution of urinary bladder tumors.

By analyzing the distribution of bladder tumor cases according to the age groups, we observed that the incidence of bladder cancer increased with the patient age (Fig.15).

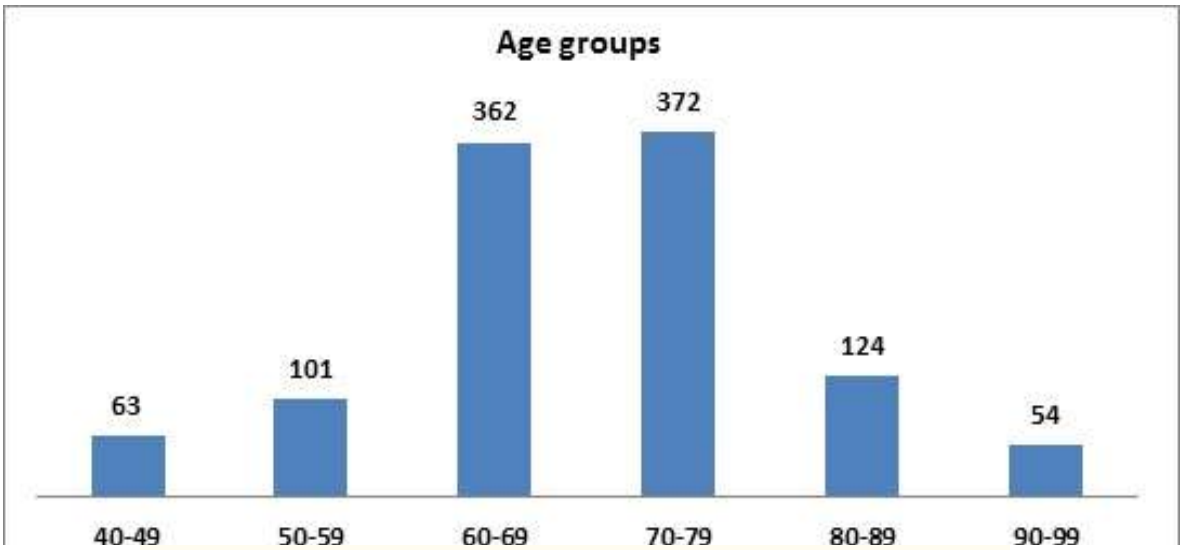

Figure 15:- Distribution of urinary bladder tumors according to the patients' age.

An effective form of immunotherapy that helps reenergize worn-out T cells for attack is immune checkpoint inhibitory therapy. Treating mice with an immune checkpoint inhibitor slowed the growth of Y-negative tumors much more than Y-positive tumors. The team wondered if this would help mobilize the T cells against Y-negative tumors if loss of the Y chromosome causes T cell exhaustion. T cells also exhibited less fatigue in the Y-negative tumors. Moreover, men with Y-negative tumors lived longer than men with Y-positive tumors, according to data from a 2016 clinical trial using the immune checkpoint inhibitor atezolizumab (Tecentriq) for bladder cancer. "Y chromosome loss may... be a biomarker for informing us that these [tumors] will be more sensitive to checkpoint inhibitors, but we are still in the early stages of understanding this process," said Dr. Salnikow. Currently, Dr. Theodorescu and his associates are creating an examination that searches for Y chromosome loss in cancerous growths.

Author's contributions:
MPK performed the selection of literature, drafted the manuscript. RG and MM prepared the figures and collected the related references. MPK, RG and MM carried out the design of this review. Dr. SKB and Dr. SRK reviewed the whole work and manuscript. All authors contributed to this manuscript. All authors read and approved the final manuscript.

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