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**Gallbladder cancer epidemiology, pathogenesis and molecular genetics: recent update**

Sharma A *et al*. GBC recent update

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**Abstract**

Gallbladder cancer is a malignancy of biliary tract which is infrequent in developed countries but common in some specific geographical regions of developing countries. Late diagnosis and deprived prognosis are major problems for treatment of gallbladder carcinoma. The dramatic associations of this orphan cancer with various genetic and environmental factors are responsible for its poorly defined pathogenesis. An understanding to the relationship between epidemiology, molecular genetics and pathogenesis of gallbladder cancer can add new insights to its undetermined pathophysiology. Present review article provides a recent update regarding epidemiology, pathogenesis, and molecular genetics of gallbladder cancer. We systematically reviewed published literature on gallbladder cancer from online search engine PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>). Various keywords used for retrieval of articles were Gallbladder, cancer Epidemiology, molecular genetics and bullion operators like AND, OR, NOT. Cross references were manually searched from various online search engines (http://www.ncbi.nlm.nih.gov/pubmed,<https://scholar.google.co.in/>, http://www.medline.com/home.jsp). Most of the articles published from 1982 to 2015 in peer reviewed journals have been included in this review.

**Key words:** Gallbladder cancer; Epidemiology; Molecular genetics; Pathogenesis

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**Core tips:** The Gallbladder cancer is a fatal malignancy which displays considerable differences in certain ethnicities and geographic regions. Indo-Gangetic plains of India, Mapuche Indians in Chile and South America are most affected regions with this cancer. Because of this cancer is largely unstudied as compare to other cancers Present review provides a comprehensive summery of the studies conducted regarding its Epidemiology, Pathogenesis and molecular genetics. This will be helpful for the researchers to understand the current scenario of research work and how much success we have gained till now. Based on which future research work can be planned in appropriate directions.

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**Introduction**

Gallbladder cancer (GBC) is a rare biliary tract malignancy in most western countries, but is much widespread in some other regions of the world. Moreover this carcinoma is infrequent in developed countries but more common in some developing countries, characterized by its lack of symptoms at initial stage leading to difficulties in treatment.

The extensive variation in geography, ethnicity, and cultural differences in the incidence of gallbladder cancer suggests the role of key genetic and environmental factors associated with the development and progression of the disease[[1](#_ENREF_1),2].The lack of a serosal layer of gallbladder adjacent to the liver thus enabling hepatic invasion and metastatic progression is one of the major cause of its miserable prognosis[[3](#_ENREF_1)].The present review provides a recent update of studies regarding epidemiology, pathogenesis and molecular genetics of gallbladder cancer as available in literature.

**Epidimiology of Galllbladder cancer**

Gallbladder cancer shows an unusual geographic distribution worldwide with substantial geographic variation. Data from Mapuche Indians from Valdivia, Chile, South America shows the rate of gallbladder cancer as: 12.3/100,000 for males and 27.3/100,000 for females[[3](#_ENREF_4)]. The native people is these countries exceed for gallbladder cancer mortality rates from cervical (8.0/100,000), breast (8.7/100,000), pancreatic (7.4/100,000), and ovarian cancers (7.3/100,000)[[3](#_ENREF_4)]. American Indians in New Mexico, USA, have also very high average annual rate of GBC (8.9/100,000)[4], [Surveillance, Epidemiology End-Results Program (SEER) The Four Most Common Cancers for Different Ethnic Populations 2013. Bethesda, MD: National Cancer Institute; 2013].

Although the worldwide occurrence of gallbladder cancer is less than 2/100,000 individuals, but this has been recorded with extensive variance[5]. The residents of Indo-Gangetic belt particularly females of northern India (21.5/100000) and south Karachi Pakistan (13.8/100,000) have been reported as one of the highest affected regions[[4](#_ENREF_4)].Gallbladder cancer is also found in high frequency in Eastern Europe include Poland (14/100,000 in Poland), Czech Republic, and Slovakia and Asia whereas south Americans of Indian descent (3.7 to 9.1 per 100000), Israel (5/100000) and Japan (7/100000) have shown intermediate prevalence of gallbladder cancer[[4](#_ENREF_6),[6](#_ENREF_6)].The residents of Andean-area, North American Indians and Mexican-Americans are specially predisposed of GBC[[6](#_ENREF_6)]. The majority of the world has decreasing mortality trends in gallbladder cancer but GBC frequency is constantly rising in Shanghai, China which is substantial cause of mortality[[7](#_ENREF_7)]. Although Gallbladder cancer is more common in females still in some countries like Korea, Iceland and Costa Rica, higher mortality rate has been reported for males as compare to females[[8](#_ENREF_8)]. The data from National Cancer Institute; Surveillance, Epidemiology and End Results (SEER) Program (<http://seer.cancer.gov/>) has revealed only little turn down in incidence over the past few decades.

### Etiological factors for GBC pathogenesis

The development of gallbladder cancer has been linked to various genetic and environmental factors. Chronic infection of gallbladder or/and environmental exposure to specific chemicals, heavy metals, and even many dietary factors, have been found to be associated with GBC formation. The dramatic association of GBC with female gender and certain geographical regions (mostly developing countries) has been proposed to be influenced by various female hormones, cholesterol cycling and salmonella infections in existing literature[[9](#_ENREF_9),[10](#_ENREF_10)]. Worldwide GBC affects females 2-3 times more commonly than males, but bias varies greatly in different parts of the world mostly in high prevalent regions of GBC[[4](#_ENREF_4),[6](#_ENREF_6)]. To some extent, the female hormone estrogen causes increased cholesterol super saturation in bile and hence involved in gallstone mediated GBC pathogenesis[[11](#_ENREF_11)]. Although the female gender GBC can be linked with the role of female hormones. However an article published previously has questioned the association of hormone receptor expression to tumor differentiation[[12](#_ENREF_12)]. So the extent of female hormones contribution in Gallbladder cancer is still not certain and requires more investigation.

Other well-known GBC associated risk factors such as porcelain gallbladder, Mirizzi's syndrome and bile reflux has also been playing a major role as a predisposing factors of this disease[[9](#_ENREF_9)]. Family history of gallstones, tobacco consumption, chemical exposure, residence in Gangetic belt and high concentrations of secondary bile acids, excessive intake of fried foods (reused oil), increases the risk for GBC[[13](#_ENREF_13)]. Present data suggest that gallstones are a major risk factor for GBC but their role as a cause for gallbladder cancer is still not certain. A review article by Shrikhande *et al*[[14](#_ENREF_14)]has also supported the fact that the populations reporting high incidence of gallbladder cancer with associated gallstones, prophylactic cholecystectomy should be done only after correlating with the epidemiological profile of the place. Convincing evidence also exists for the presence of gallstones as strongly associated factor for gallbladder cancer etiology[[7](#_ENREF_7)]. Most of the etiological factors are summarized in Table 1[6,7,10,13,15-50].

### Familial and Linkage Studies

Swedish family-cancer database and Utah cancer registry (UCR) has reported the first ever data for familial clustering of GBC[[51](#_ENREF_51)]. This study has provided the first data on familial clustering of gallbladder cancer based on medically confirmed records, in which it was estimated that 26% of gallbladder cancers are familial. The significant risk in 3rd degree relatives and the disease manifestation in several high risk pedigrees as reported in previous studies gives a strong indication for genetic susceptibility to GBC[[51](#_ENREF_51)]. The high risk heritable factors are likely to contribute to a large extent to this cancer further modulated by environmental factors. The nationwide Swedish Family-Cancer Data base from the Swedish Cancer Registry (10.2 million individuals from the year 1961-1998), has reported maternal transmission favoring over paternal in familial gallbladder cancers[[52](#_ENREF_52)]. Furthermore, the clustering of gallbladder cancer within families is suggestive of a critical role of genetics in its development[[19](#_ENREF_19)]. Carcinoma gallbladder was detected in two siblings from Brazil as reported by Trajber *et al*[[53](#_ENREF_53)]. Role of allele specific mutations in pathogenesis of carcinoma gallbladder has also been reported[[54](#_ENREF_54)]. Another report by Pandey *et al*[[55](#_ENREF_55)]has shown higher frequency of carcinoma gallbladder in patients with A+ and AB+ blood groups to which the reason is still unknown.

## **Genetic and molecular alteration reported in gallbladder carcinoma**

The present existing information regarding genetic and molecular alterations in GBC is still very much limited. Like other neoplasms, GBC is a multifactorial disorder involving multiple genetic alterations[[56-58](#_ENREF_56)]. Abnormality in tumor suppressor genes, oncogenes, and DNA repair genes, presence of microsatellite instability (MSI) and epigenetic alterations mainly caused by aberrant promoter methylation of gene areas are some of the various well known factors reported till now. The serious of genetic alteration leading to gallbladder cancer formation is still not established clearly. Some of the molecular alterations reported so far are enumerated in Tables 2-4.

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### Genetic Alterations in GBC

***KRAS***

KRAS act as initial key player in numerous signal transduction mechanisms and associated pathways. Many pathogenic mutations have been reported in *KRAS onco*gene in Gallbladder cancer tissue[[58-63](#_ENREF_58)]. K*RAS* gene mutations identified in GBC mostly affects codons 12, 13 and 61. In north India *KRAS* codon 13 mutation is more common (about one third) than codon 12 and 61[[64](#_ENREF_64)]. However many other studies have not detected any mutations in this gene[[65](#_ENREF_65),[66](#_ENREF_66)]. Any activating point mutations in *KRAS* oncogene can give rise to abnormal growth signals which is one of the hallmarks of cancer. The previous reports have co-related a condition called anomalous arrangement of the pancreatico-biliary duct with presence of gallbladder cancer as patients harboring this condition have a higher frequency of *KRAS* gene mutation as compare to normal condition[[65](#_ENREF_65),[67](#_ENREF_67),[68](#_ENREF_68)]. However mutation of *KRAS* gene has not been detected in gallbladder carcinomas associated with an adenoma[[69](#_ENREF_69)] (Table 2).

***TP53***

TP53 is a well-known tumor suppressor gene and has various mechanisms of anticancer function and plays significant role in maintenance of genome integrity, apoptosis, genomic stability, and inhibition of angiogenesis etc. Loss of *TP53* function allows deregulated survival of genetically impaired abnormal cells which can lead to neoplastic conversion of later on[[70](#_ENREF_70)]. *TP53* mutations are relatively more common in later stages of the disease[[63](#_ENREF_63),[66](#_ENREF_66),[71-73](#_ENREF_71)]. Most of the *TP53* mutations associated with GBC are missense mutations that produce a non-functional protein with an increased half-life. The existing literature has reported mutations of the *TP53* gene in between approximately 27% to 70% of gallbladder carcinomas[[74](#_ENREF_74)]. Many codons of the *TP53* codons are affected by pathogenic mutations of this gene. Functional molecular studies have discovered that mutations in exons 5 and 8 of *TP53* gene causes deregulation of this gene[[75](#_ENREF_75)]. Details are shown in various existing literature is shown in Table 2[54,60,63,64,76-86].

***C-ERB-B2***

The oncogene *c-erb-B2* is a homologue for epidermal growth receptor, encoding a protein with tyrosine kinase activity. The immunohistochemical (IHC) expression of c-erb-B2 has been found positive between 10%-46% of gallbladder cases. However its expression has been found to be absent in dysplasia or adenomas as shown by previous reports[[87](#_ENREF_87),[88](#_ENREF_88)]. Animal model studies in transgenic mice have shown that *erbB2* overexpression in the basal layer of the biliary tract epithelium led to the development of GBC in all (100%) of mice. Moreover, the expression of HER2⁄neu was positively observed in 28% of GBCs which was directly correlated with advanced stage of cancer[[89](#_ENREF_89)]. Therefore, it can be hypothesized that some oncogene is associated with in Gallbladder cancer progression.In a study from India, C-erbB2 was frequently expressed in well differentiated and stage II to stage IV in about 9.4% of GBC cases[[90](#_ENREF_90)]. A recent report showed HER2/neu overexpression occurred in 14% of the advanced gallbladder cancer cases, and this subgroup was expected to be benefited from HER2/neu pathway inhibitors[[91](#_ENREF_91)]. Therapeutic targeting of *EGFR/HER2* pathways boosts the anti-proliferative effect of gemcitabine in biliary tract and gallbladder carcinomas as shown by a previous study[[92](#_ENREF_92)]. Based on facts it can be concluded that *C-ERB-B2* expression can become a marker for a poor prognosis.

**High Throughput mutation studies in GBC**

High throughput research has made large scale repetition of experiments feasible as it automates the experiments thus it has now become possible to study how all 21,000 genes potentially contribute to cell function or disease. But in case of gallbladder cancer there are very limited high throughput studies. One of the pioneer studies published in nature genetics using high throughput approach by Chinese population has found recurrent mutations in ErbB pathway[[93](#_ENREF_93)]. Javle *et al*[[94](#_ENREF_94)]has found 26 missense mutations with more common *TP53* and *PIK3CA* mutations in GBC tumor using NGS technology. Mutation profiling of gallbladder cancer tissue in Indian population has found *PIK3CA* and *KRAS* mutations as most common among this ethnicity[[95](#_ENREF_95)]. The variability in the results is an indicator of intra-tumoral heterogeneity of cancer, which describes the observation of different tumor cells showing distinct morphological and molecular profiles including variable gene expression but ultimately leading to a common phenotype. The high throughput mutation studies in GBC are presented in Table 3[93-96].

**GENE EXPRESSION STUDIES IN GBC**

### In order to identify potential biomarkers for GBC progression, many studies have been performed to find out the differential gene expression profiles between normal and tumor cells. Existing data various greatly, despite of same grade and stage of the included study subjects. Table 4[97-101] and Table 5[54,66,75,84,86,90,102-180] are summarizing global and single gene expression studies reported in GBC respectively.

###  Loss of Heterozygosity and Microsatallie instability

### Loss of heterozygosity (LOH) is a common genetic alteration in cancer genome. The events like heterozygous deletion of one of the two alleles, or duplication of a maternal or paternal chromosome or chromosomal region and concurrent loss of the other allele gives rise to LOH. The studies focused to detect loss of heterozygosity (LOH) in GBCs have shown frequent heterozygous allelic loss which spans in 18 different chromosomal regions[[57](#_ENREF_57)]. Cytogenetic locations involved in frequent loss of heterozygosity *i.e.* 3p, 8p, 9p, and 22q regions have also been identified in GBC from different populations; which have also been reported in several other cancers like Retinoblastoma, melanoma, Squamous cell carcinoma of larynx[[181-183](#_ENREF_181)]. In particular, gallbladder tumor shows numerous site of allelic loss in the short arm of chromosome 3, which harbors several known or putative tumor suppressor genes[[109](#_ENREF_109),[181](#_ENREF_181)]. High degree of microsatellite instability (MSI) in 10% of GBC cases was observed as reported in research article published by Goldin *et al*[[184](#_ENREF_184)]. A different pattern of allelic loss has also been detected in Japanese population. In this report the allelotype analysis of gallbladder carcinoma revealed an interesting associated with anomalous junction of pancreatico-biliary duct[[68](#_ENREF_68)]. Table 6[54,57,66,68,109,112,185-193] enlists various studies conducted in GBC regarding LOH and MSI.

**Methylation and Gallbladder Cancer**

Understanding of DNA methylation patterns of gallbladder tumors can prove to be important biomarkers to refine the diagnosis and prognostic information which ultimately helps in appropriate therapeutic selection. Hypermethylation in gene promoter regions is a common epigenetic mechanism for the inactivation of tumor suppressor genes. One of the important research article published previously has found an important link between methylation and survival. In this study methylation of genes *p73, MGMT,* and *DCL1* was significantly associated with survival of gallbladder cancer patients[[194](#_ENREF_194),[195](#_ENREF_195)]. The study was conducted in a series of 109 advanced gallbladder cancer cases. However genes like *CDH13* and *FHIT* did not show any significant tendency with respect to gallbladder cancer patient’s survival[[194](#_ENREF_194),[195](#_ENREF_195)]. Multivariate analysis found *MGMT* gene to be an independent prognostic factor for survival found, representing the important role of epigenetic process in gallbladder carcinogenesis[[195](#_ENREF_195)]. The recent report showed that promoter methylation of specific genes like *CDH1, CDKN2A-p16*, *REPRIMO* (tumor suppressor gene family) and *UCHL1* (also known as PGP9.5) have important role in gallbladder carcinogenesis[[196](#_ENREF_196)]. Other studies conducted on GBC have shown variable methylation pattern of a number of genes Table 7[81,82,193-208].

In addition, with the help of advanced technologies like high resolution allele stratification (allelotyping analysis) investigated very high frequencies of 3p (100%), 8p (100%), 9q (88%), 22q (92%) sites in gallbladder cancer that lead to positional identification of tumor suppressor genes associated with GBC malignancies and pathogenesis[[57](#_ENREF_57),[58](#_ENREF_58),[109](#_ENREF_109),[209](#_ENREF_209)]. Moreover, some well-known tumor suppressor genes that are present in chromosomes like 3p*,* 5q, 8p,13q and 18qcan also influence the gallbladder cancer formation[[57](#_ENREF_57),[58](#_ENREF_58),[109](#_ENREF_109),[209](#_ENREF_209)].

### Candidate Genes for Gallbladder Cancer Susceptibility

The merely successful mechanism for identifying low or moderate penetrance cancer genes, is the analysis of genes involved in candidate loci. Therefore, these genes are also termed as candidate genes. The candidate gene analysis is done via case-control study, in which allele frequencies in cancer patients and healthy controls are compared and obtained results are analyzed statistically. Candidate modifier genes are selected on the basis of biological plausibility. Most studies are based on genes that encode proteins, thought to be involved in carcinogenesis, such as those involved in apoptosis, cell-cycle control, DNA repair, xenobiotic metabolism, hormonal and inflammatory pathway or other risk factors. Moreover, known genes account for a small proportion of the heritability of gallbladder cancer, and it is likely that many genes with modest effects are yet to be found.

A study by Wang *et al*[[210](#_ENREF_210)] from china suggested about CCK-induced impaired gallbladder emptying in patients having gallstones. Most of the candidate genes identified so far are related to the classical rate limiting enzymes and proteins of lipid metabolism, steroidogenesis, lipid transport, bile acid synthesis, bile canalicular transport, gallbladder contractility, cell cycle, DNA repair and Inflammatory pathway[[211-233](#_ENREF_210)]. Till now there are very limited studies in GBC which are independently replicated which includes *OGG1*rs1052133, *TP53*rs1042522, *GSTM1* null polymorphism and *CYP1A1*rs1048943 polymorphism[[48](#_ENREF_48)]. No definitive conclusions can be drawn due to limited number of studies. Hence there is a great need to explore genes related to GBC susceptibility. Table 8[30,214-273] shows an overview of candidate gene studies reported in GBC.

The only one genome-wide association study conducted in gallbladder cancer identified a SNP (rs7504990) in *DCC* genewhich was associated with six times gallbladder cancer risk in the Japanese population. It has also been reported that reduced expression of *DCC* gene (deleted in colorectal cancer, 18q21.3) was designated to be associated with the greater aggressiveness of the disease which include increased proliferation, poorly differentiated histology, and metastasis through loss of adhesiveness[[234](#_ENREF_234)]. However genome wide association study (GWAS) identified SNPs was replicated in Indian population and the study found no individual association of *DCC*rs7504990 but haplotype analysis of *DCC* gene found the cumulative effect of Grs2229080-Ars4078288-Crs7504990 Ars714 haplotypes in Gallbladder Cancer predisposition[[235](#_ENREF_235)].

## **Molecular Pathogenesis of GBC**

Gallbladder carcinoma develops through a serious of events before converting in to invasive malignancy. Any exposure to carcinogens may convert normal gallbladder epithelium to condition called metaplasia which subsequently forms dysplasia to carcinoma *in situ* (CIS), and finally proceeding to invasive carcinoma in about 15 years[[274](#_ENREF_274),[275](#_ENREF_275)]. The multistage pathogenesis of gallbladder carcinoma begins with gallstones giving rise to a condition called chronic cholecystitis, which increases to risk to gallbladder cancer formation. More than 90% of patients with gallbladder carcinoma show dysplasia and CIS[[274](#_ENREF_274),[275](#_ENREF_275)]. There is an unusual asymmetric thickening of the gallbladder wall with infiltration to surrounding structures in gallbladder cancer. Maximum cases reported in carcinomas of gallbladder are adenocarcinomas (80%-95%). Adenocarconomas can further be of papillary, tubular, mucinous, or signet cell type. Some other types which are present in very low frequency include: squamous cell carcinoma (16%), undifferentiated or anaplastic carcinoma (2%-7%), and adeno-squamous carcinoma (1%-4%)[[276](#_ENREF_276)]. Most of GBCs (60%) are found in the fundus, near about 30% in the body, and 10% in the neck region.

Tumor Markers in GBC

Till date there is no reliable tumor marker developed which can be employed in diagnosis of gallbladder cancer. The only two markers *i.e.* carcino-embryonic antigen (CEA) and carbohydrate antigen 19-9 are most often elevated in advanced stages with a low specificity. So most often they are not used in stand-alone diagnosis of GBC[[277](#_ENREF_277)]. However, there are other tumor markers like CA125, CA199, CEA (carcino-embryonic antigen), cancer antigens (CA) and CA242, which are for diagnosis of different other types of cancer (*e.g.*, gastric, liver, pancreatic), have also been researched in diagnosis of gallbladder cancer but the obtained results are highly inconsistent[[278-280](#_ENREF_278)]. In addition some previous reports have shown CA 242, RCAS1 (receptor binding cancer antigen expressed on SiSo cells) CA15-3, Mac-2BP (macrophage galactose-specific lectin-2 binding protein), Fragments of cytokeratin-19 (CYFRA 21-1) are frequently present in blood of cancer patients and shown to be associated with GBC with variable sensitivity and specificity[[277](#_ENREF_277),[281](#_ENREF_281),[282](#_ENREF_282)].

**Conclusion and future directions**

Various lines of evidence suggest role for various environmental risk factors in Gallbladder carcinoma. Despite of many articles regarding genetic predisposition of gallbladder cancer there is no established genetic marker. Also, very limited Genome wide association studies (GWAS) have been conducted in gallbladder cancer till now.

### The evidence-based model of gallbladder carcinogenesis and its dissemination by Barreto *et al*[[283](#_ENREF_283)] serves as a basic platform for elucidation of molecular mechanisms involved in cancer development which based on recent data can be improved by discovery of other signature mutations using high throughput studies. Technological advancement can be helpful more understanding of pathogenic mechanisms underlying neoplastic conversion of gallbladder cancer muscosa. The tumor markers available for diagnosis GBC has also not of very high specificity and not discovered until advanced stage of the disease leading to complexity of the treatment. Exome sequencing of gallbladder cancer tissue has found ERBB pathway as most dysregulated pathway in this disease. Although the studies have been published in highly distinguished journals but they need to be validated before clinical implication. Moreover, limited studies with small sample size are not robust enough to conclude anything. Regardless of improvement in technologies in research field there is no accountable betterment in the prognosis of GBC patients. The future therefore should be engaged towards good quality research focused on early diagnosis and refinement of prognostic information to ultimately improve the management strategies of gallbladder cancer. Present review provides a comprehensive summery of the studies conducted regarding its Epidemiology, Pathogenesis and molecular genetics under a single umbrella. This will be helpful for the researchers to understand the current scenario of research work and how much success we have gained till now. Based on that future research work can be planned in appropriate directions.

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**Table 1 Etiological factors for gallbladder cancer pathogenesis**

|  |  |
| --- | --- |
| **Major Independent Etiological factors** | **Dependent Etiological factors** |
| Age[[6](#_ENREF_6)] | Tobacco consumption[[15](#_ENREF_15)] |
| Sex[[6](#_ENREF_6)], BMI[[16](#_ENREF_16)] | Mustard oil[[17](#_ENREF_17)] Argemone oil (AO) and butter yellow (BY)[[18](#_ENREF_18)]  |
| Family history[[7](#_ENREF_7), [19](#_ENREF_19)]  | Early age at first pregnancy[[20](#_ENREF_20)]  |
| Cholelithiasis [[6](#_ENREF_6),[22-24](#_ENREF_22)]  | Use of Oral contraceptives [[15](#_ENREF_15),[25](#_ENREF_25),[26](#_ENREF_26)] |
| Chronic cholecystitis, porcelain gallbladder[[27](#_ENREF_27), [28](#_ENREF_28)] | Red Chili pepper[[29](#_ENREF_17),30] |
| Chronic infection by *Salmonella* species, *S. paratyphi* or *S. typhican*[[6](#_ENREF_6),[10](#_ENREF_10),[31-34](#_ENREF_31)]  | Occupational exposure, Benzene[[17](#_ENREF_17),35] |
| Helocobacter pylori [[36](#_ENREF_36),[37](#_ENREF_37)] | Secondary bile acids[[13](#_ENREF_13),[38-40](#_ENREF_38)] |
| High parity[[20](#_ENREF_20),[21](#_ENREF_21),[24](#_ENREF_24),[26](#_ENREF_26)] | Xanthogranulomatous cholecystitis[[41](#_ENREF_41)] |
| Anomalous pancreatobiliary duct junction [[42](#_ENREF_42), [43](#_ENREF_43)]  | Heavy metals[[44](#_ENREF_44),[45](#_ENREF_45)] |
| Porcelain gallbladder[[46](#_ENREF_46)] Gallbladder polyp[[47](#_ENREF_47)]  | Genetic factors[[48](#_ENREF_48)] |
| Obesity[[49](#_ENREF_49)] | Free radical oxidation products[[50](#_ENREF_50)]  |

Table 2 Mutations detected in gallbladder cancer by low throughput methods

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Studied gene** | **Type of study** | **Methods used** | **Studied****Population** | **Ref.** |
| *KRAS* | Mutation at codon-12 (8%) | PCR-RFLP | India | [[64](#_ENREF_64)] |
| Mutation at codon-12 (29%-30%) | PCR-RFLP | Chile | [[76](#_ENREF_76),[77](#_ENREF_77)] |
| Mutation at codon-12 (0% to 59%) | PCR-RFLP, Direct sequencing | Japan | [[60](#_ENREF_60),[78](#_ENREF_78),[79](#_ENREF_79)] |
| Mutation at codon-12(50%-80%) | ELMA,SAB,PCR-SSCP, Direct sequencing | Japan | [[63](#_ENREF_63),[80](#_ENREF_80)] |
| *INK4A (p16)* | Mutation, deletion | PCR-RFLP, direct sequencing, IHC | Japan, Chile | [[54](#_ENREF_54),[79](#_ENREF_79),[81](#_ENREF_81),[82](#_ENREF_82)] |
| *D310 mtDNA* | Mutation (Displacement loop) | PCR-based assay, direct sequencing | Chile | [[83](#_ENREF_83)] |
| *TP53* | Mutation, overexpression, LOH | PCR-RFLP, direct sequencing, IHC | Greece, Japan, Chile | [[84-86](#_ENREF_84)] |

Table 3 Mutations studies in gallbladder cancer by high throughput methods

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Platform** | **Number of samples** | **Study population** | **Research planned** | **Key findings** | **Ref.** |
| Sequenom Mass ARRAY technology | 49 FFPE | India | 390 mutations in 30 genes | *PIK3CA* (4%), *KRAS* (2%), *CTNNB1* (4%), *TP53* (18%) | [[95](#_ENREF_95)] |
| Mass spectroscopy-basedNext-generation sequencing (NGS) | 57 FFPE15 FFPE | MD Anderson Centre | 159 mutations in 33 genesNGS of 182 cancer-related genes | 14 hotspot mutations in 9 cases including (*KRAS, NRAS, PIK3CA, IDH1, ALK, MET*)26 mutations in 15cases(*P53, STK11, RICTOR,TSC2, FGF3-TACC* fusion, *FGF10* amplification)Preponderance of mutations involving the PI3 kinase pathway | [[94](#_ENREF_94)] |
| Whole Exome and transcriptome Sequencing | 29 Fresh Frozen | Japan | 64 non silent mutations signatures | *EGFR,ERBB3,PTEN,ARID2,MLL2,**MLL3, APOBEC,TERT**APOBEC*-associated mutation signature were observed in GBC | [[96](#_ENREF_96)] |
| Exome sequencing and targeted gene sequencing | 57 Fresh Frozen | China | Whole exome sequencing | *TP53* (47.1%), *KRAS* (7.8%) and*ERBB3* (11.8%)ERBB pathway genes mostly mutated | [[93](#_ENREF_93)] |

FFPE: Fresh frozen paraffin embedded.

Table 4 Summary of global gene expression studies in gallbladder cancer

|  |  |  |
| --- | --- | --- |
| **Biological sample used**  | **Platform / Studies key findings** | **Ref.** |
| 17 gallbladder tissue specimens (6 advanced GBC , 6 early GBC cancers and 5 normal control | Oligonucleotide Microarray platform  Unregulated genes: 2270 Downregulated genes: 2412 | [[97](#_ENREF_97)] |
| 5-Normal biliary epithelial scrapings, 11- surgically resected biliary carcinomas, 9-biliary cancer cell lines  | Oligonucleotide Microarray platformunregulated genes : 282 genes downregulated genes: 513 | [[98](#_ENREF_98)] |
| 37 biliary tract carcinomas (15 bile duct, 11 gallbladder, 11 of ampulla of Vater) | cDNA array platform 118 genes were identified with a prognostic value | [[99](#_ENREF_99)] |
| 12 advanced gallbladder carcinoma tissue 3 samples of normal control gallbladder epithelium | Oligonucleotide Array platform Upregulated: (TOPO II-alpha, cyclin B2, CDC28, ubiquitin-conjugating enzyme E2C), and one metabolism-related: (gamma-glutamyl hydrolase) | [[100](#_ENREF_100)] |
| 34 biliary tract cancers including13 intrahepatic (IHC), 12extrahepatic (EHC), 9 (GBC) | Oligonucleotide Array platform 1281 genes with deregulated expression pattern | [[101](#_ENREF_101)] |

Table 5 Summary of single gene expression studied reported in gallbladder cancer

|  |  |  |  |
| --- | --- | --- | --- |
| **Studied single genes** | **Expression pattern** | **Studied Population** | **Ref.** |
| *TP53* | Expression (20%-70%) | India, Slovenia, Greece, Taiwan, Japan, Chile | [[75](#_ENREF_75),[84-86](#_ENREF_84),[102-106](#_ENREF_102)] |
| *p16* | Overexpression | South Korea | [[107](#_ENREF_107)] |
| *FHIT* | Expression loss (45%-75%) | Japan, Chile | [[108](#_ENREF_108),[109](#_ENREF_109)] |
| *ERBB2* | Over-expression (25%-64%) | India, Japan, China, South Korea | [[66](#_ENREF_66),[103](#_ENREF_103),[110](#_ENREF_110),[111](#_ENREF_111)] |
| expressed in 9.4%casesofwell differentiated and stage II to stage IV tumors | India | [[90](#_ENREF_90)] |
| *RB* | 20% cases allelic loss4%-14%- loss of expression | Japan | [[54](#_ENREF_54),[112](#_ENREF_112)] |
| *CDKN1A* | Reduced expression 49% cases | Japan | [[113](#_ENREF_113)] |
| *Cyclin D1, Cyclin E* | Over-expression (41%-49%) | Japan | [[114](#_ENREF_114),[115](#_ENREF_115)] |
| *COX2* | Over-expressed | Slovenia, Japan, Chile | [[104](#_ENREF_104),[116](#_ENREF_116),[117](#_ENREF_117)] |
| *BCL2* | Over-expressed | Japan | [[118](#_ENREF_118)] |
| *CKIT* | Expression 45% | Japan | [[119](#_ENREF_119)] |
| *SOX-4* | Overexpression | China | [[120](#_ENREF_120)] |
| *Chemokine (C-X-C motif) ligand 12* | Increased expression | South Korea | [[121](#_ENREF_120)] |
| *CXCR4, CXCR7* | Increased expression | China | [[122](#_ENREF_122)] |
| *hedgehog pathway components (Shh, Ptch1 and Gli1)* | *Shh:* 81.7% of cases expressed*Ptch1:* 75.3% of cases*Gli1:* 70.0% of cases | China | [[123](#_ENREF_123)] |
| *CD56, CD99* | Altered expression | South Korea | [[124](#_ENREF_124)] |
| *CD97, CD55* | *CD97*: 69.6% of cases expressed*CD55:* 65.2% of cases | China | [[125](#_ENREF_125)] |
| *HMGA2 and CD9* | *HMGA2* positive expression*CD9* negative expression | China | [[126](#_ENREF_126)] |
| *cholecystokinin type-A* | 44.1% of cases expressed | India | [[127](#_ENREF_127)] |
| *vascular endothelial growth factor-A* | 53.6% of cases expressed | China | [[128](#_ENREF_128)] |
| *VEGF-C, VEGF-D* | *VEGF-C:*64.0% of cases*VEGF-D:* 62.0% of cases | China | [[129](#_ENREF_129)] |
| *Tumor endothelial marker 8 protein* | Increased expression | India | [[130](#_ENREF_130)] |
| *L1 cell adhesion molecule* | Increased expression | SouthKorea | [[131](#_ENREF_131)] |
| *Tissue factor pathway inhibitor-2* | down-regulated | China | [[132](#_ENREF_132)] |
| *HIF-1α* | Increased expression | China | [[133](#_ENREF_133)] |
| *VHL* | Reduces expression |
| *ERCC1(excision repair cross-complementing 1)* | high expression in best differentiated tumors | Chile | [[134](#_ENREF_134)] |
| *NF-E2-related factor 2 (Nrf2)* | Increased expression | China | [[135](#_ENREF_135)] |
| *CD34 , CA15-3* | highly expressed in stroma and in epithelium | Italy | [[136](#_ENREF_136)] |
| *ADAM-17* | over-expression | China | [[137](#_ENREF_137)] |
| *Cdx2* | aberrant expression | Japan | [[138](#_ENREF_138)] |
| *TLR4* | expressed in glandular and luminal epithelium | China | [[139](#_ENREF_139)] |
| *MiRNA* | loss of Dicer and Drosha expression | China | [[140](#_ENREF_140)] |
| *Inducible Nitric Oxide Synthase iNOS* | Expressed | China | [[141](#_ENREF_141)] |
| *Prostate stem cell antigen (PSCA)* | down-regulated | Japan, China | [[142](#_ENREF_142)] |
| *OCT-4* | down-regulated | China | [[143](#_ENREF_143)] |
| *hTERT/Telomerase* | expressed in 56.66% cases | India | [[144](#_ENREF_144)] |
| *Aquaporins (AQPs)* | positive expression | Japan | [[145](#_ENREF_145)] |
| *Ornithine decarboxylase (ODC) and glutamate decarboxylase 65 (GAD65)* | Overexpression | China | [[146](#_ENREF_146)] |
| *Alpha-methylacyl coenzyme A (racemase) AMACR* | overexpression | Taiwan | [[147](#_ENREF_147)] |
| *Sonic Hh (Shh)* | Elevated expression | Japan | [[148](#_ENREF_148)] |
| *TGF-β induced miR-182* | overexpression | China | [[149](#_ENREF_149)]  |
| *SLP-2* | overexpression | China | [[150](#_ENREF_150)]  |
| *TMPRSS4* | Higher expression | China | [[151](#_ENREF_151)] |
| *zinc finger X-chromosomal protein* | suppressed | China | [[152](#_ENREF_152)] |
| *multidrug resistance-associated protein 2 (MRP2)* | overexpressed | South Korea | [[153](#_ENREF_153)] |
| *HuR* | overexpressed | Taiwan | [[154](#_ENREF_154)] |
| *miR-155* | overexpressed | Japan | [[155](#_ENREF_155)]  |
| *LAPTM4B-35* | overexpressed(76%) | China | [[156](#_ENREF_155)] |
| *p27 ,P21* | *p21*(75% cases) and *p27* (25% cases) | Jordan | [[157](#_ENREF_157)] |
| *Thymidylate synthase (TS)* | low expression | Japan | [[158](#_ENREF_158)] |
| *CD146* | Elevated expression | China  | [[159](#_ENREF_155)] |
| *AEG-1* | highly expressed (63.4%) | Shanghai | [[160](#_ENREF_160)] |
| *CCKAR* | expression increased (76.6%) | India | [[127](#_ENREF_127)] |
| *Nemo-like kinase (NLK)* | overexpression of *NLK* | China | [[161](#_ENREF_161)] |
| *C-erbB2* | overexpression (9.4%) | India | [[90](#_ENREF_90)] |
| *Phospho-mTOR expression* | positive expression (64.1%) | Chile | [[162](#_ENREF_162)] |
| *human telomerase reverse transcriptase (hTERT)* | expression increased | India | [[163](#_ENREF_163)] |
| *Phosphoglycerate kinase 1 (PGK1)* | Decreased expression (54.7%) | China | [[164](#_ENREF_164)] |
| *Notch 1 and Notch 3* | Positive expression | China | [[165](#_ENREF_165)] |
| *CCK-A*  | Decreased expression | India | [[166](#_ENREF_166)] |
| *3-phosphoinositide-dependent protein kinase 1 (PDK1)* | positively expressed | China | [[167](#_ENREF_167)] |
| *Zinc finger X-chromosomal protein (ZFX)* | Over-expression | China | [[151](#_ENREF_151)] |
| *miR-138* | Over expression | Shanghai | [[168](#_ENREF_168)] |
| *HSP gp96* | Expression (90.7%) | China | [[169](#_ENREF_169)] |
| *Long non-coding RNA-LET* | overexpression | China | [[170](#_ENREF_170)] |
| *Survivin* | higher expression (2.9- fold) | India | [[171](#_ENREF_171)] |
| *Long non-coding RNA CCAT1* | overexpressed | China | [[172](#_ENREF_172)] |
| *TEM8* | Expression increased | India | [[130](#_ENREF_130)] |
| *Fhit,MIh1,P53* | Reduced expression of Fhit and Mlh1 protein and Overexpression of *P53* | Japan | [[108](#_ENREF_108)] |
| *NDRG2,CD24*  | NDRG2 down-regulation, CD24 up-regulation | China | [[173](#_ENREF_173)] |
| *IL-6* | overexpressed | China | [[174](#_ENREF_174)] |
| *SLP-2*  | overexpression | China | [[150](#_ENREF_150)]  |
|  *BCL6, p19(ARF)* | *BCL6* overexpression *, p19* (ARF) Low expression | Taiwan | [[175](#_ENREF_175)] |
| *VEGF-A* | high expression of *VEGF-A* | Chile | [[176](#_ENREF_176)] |
| *MALAT1* | Upregulation of MALAT1 | China | [[177](#_ENREF_177)] |
| *miR-182* | Upregulation of miR-182 | China | [[149](#_ENREF_149)]  |
| *miR-155* | High expression level of miR-155 | Japan | [[155](#_ENREF_155)]  |
| *p53,S100A4, p27, p16, RB, Smad4, FHIT, E-cadherin and PML*  | *p53* and *S100A4* overexpressed,loss of p27, p16, RB, Smad4, *FHIT, E-*cadherin and *PML* expression | South Korea | [[178](#_ENREF_178)] |
| *PEG10, TSG101* | *PEG10* and *TSG101* overexpressed | China | [[179](#_ENREF_179)] |
| *CK7,CK20* | *CK7* (69.05%), *CK20* (28.57%) expressed | Greece | [[180](#_ENREF_180)] |

Table 6 Loss of heterozygosity and microsatellite instability studies reported in gallbladder cancer

|  |  |  |
| --- | --- | --- |
| **Studied reported in respective population** | **LOH /** **MSI** | **Ref.** |
| Chilean | LOH reported in : 3p, 6q, 7q, 8p, 9p, 9q, 11q, 12q, 17p, 18q, 19p, 22q, and Xq | [[57](#_ENREF_57)] |
| Japan | LOH reported in : 2p, 4p, 4q, 8q,9q, 10p,14p,14q,16p, 19p, 21p and Xp [Maximum deletion- 2p24, 14q22 and 21q22] | [[68](#_ENREF_68)] |
| Chilean, Japan | p53, 9p.8p, *DCC, KRAS*, p16, 16q24, 3p,9q, 22q and *p161NK4* | [[54](#_ENREF_54),[66](#_ENREF_66),[109](#_ENREF_109), [112](#_ENREF_112),[185](#_ENREF_185)] |
| Greece | *BAT-26* | [[186](#_ENREF_186)] |
| Chile, Japan | MSI reported (20%-33%) | [[187](#_ENREF_187),[188](#_ENREF_188)] |
| India | E-cadherin (*CDH1*) 2p, 2q, 6q, 7q,17p  | [[189](#_ENREF_189)] |
| India | Fragile histidine triad *(FHIT*) MSI-H 17.5% LOH :27.5% | [[190](#_ENREF_190)] |
| Japan | High incidences of LOH at 1p36 (19/36:53%), 9p21 (12/32:38%), 13q14 (20/36: 56%), 16q24 (31/54: 61%), and 17p13 (15/36: 42%) | [[191](#_ENREF_191)] |
| Chile | *FHIT* gene locus (3p14.2) | [[109](#_ENREF_109)] |
| India | LOH at 8 loci, that is 3p12, 3p14.2, 5q21, 9p21, 9q, 13q, 17p13, and 18q for tumor suppressor genes (*DUTT1, FHIT, APC, p16, FCMD, RB1, p53,* and *DCC* genes) | [[192](#_ENREF_192)] |
| India | genomic instability at 2p, 2q, 6q, 7q, and 17p loci | [[189](#_ENREF_189)] |
| Chile | *DUTT1* (3p12), *FHIT* (3p14.2), *BLU*, *RASSF1A*, *SEMA3B* and *hMLH1* (3p21.3) | [[193](#_ENREF_193)] |

LOH: loss of heterozygosity; MSI: microsatellite instability.

**Table 7 Aberrant promoter methylation gene studies summary in gallbladder cancer**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Gene**  | **Full name** | **Function** | **Meth Freq (%)** | **Population** | **Ref.** |
| *CDH1* | Cadherin 1, type 1,E-cadherin (epithelial) | Tissue invasion (cell-cell adhesion) | 11-65 | Japan, Chile | [[194-200](#_ENREF_194)] |
| *FHIT* | Fragile histidine triad gene | Regulation of DNA Replication, and apoptosis | 30-57 | Chile | [[81](#_ENREF_81),[193-195](#_ENREF_193),[199](#_ENREF_199)] |
| *APC* | Adenomatous polyposis coli | Tumor suppressor gene(Cell migration, adhesion and apoptosis) | 26-35 | Chile, United States | [[81](#_ENREF_81),[194](#_ENREF_194),[195](#_ENREF_195),[198](#_ENREF_198),[199](#_ENREF_199)] |
| *hMLH1* | Human homologs ofMutL gene of bacteria | Mismatch repair | 0 -14 | Chile, United States | [[81](#_ENREF_81),[193-195](#_ENREF_193),[199](#_ENREF_199)] |
| *p16* | Cyclin-dependent kinaseinhibitor 2A | Cell cycle regulation | 15-60 | Chile, United States, Germany | [[81](#_ENREF_81),[82](#_ENREF_82),[195](#_ENREF_195),[197-199](#_ENREF_197),[201](#_ENREF_201),[202](#_ENREF_202)] |
| *p15* | Cyclin-dependent kinase inhibitor 2B | Cell cycle regulation | 22-44 | Chile | [[81](#_ENREF_81),[198](#_ENREF_198)] |
| *DAPK1* | Death-associated protein kinase 1 | Serine-threonine kinase | 8-61 | Japan, Chile | [[81](#_ENREF_81),[197](#_ENREF_197),[198](#_ENREF_198)] |
| *DLC1* | Deleted in liver cancer 1 | GTPase-activating protein | 39 | Chile | [[81](#_ENREF_81)] |
| *RASSF1* | RAS association domain family protein 1A | Signal transduction | 0-36 | Japan, Chile South Korea | [[81](#_ENREF_81),[193](#_ENREF_193),[197](#_ENREF_197),[198](#_ENREF_198),[203](#_ENREF_203)] |
| *MGMT* | O-6-methylguanine-DNAmethyltransferase | Methyltransferase | 13-30 | Chile, United States | [[81](#_ENREF_81),[195](#_ENREF_195)] |
| *CDH13* | CDH13 Cadherin 13, H-cadherin(heart) | Tissue invasion (cell-cell adhesion) | 44-70 | Chile | [[81](#_ENREF_81),[198](#_ENREF_198)] |
| *TIMP3* | Metallopeptidase inhibitor 3 | Degradation ofextracellular matrix | 0-39 | Chile | [[81](#_ENREF_81),[198](#_ENREF_198)] |
| *GSTP1* | Glutathione S-transferase pi 1 | Conjugation of hydrophobicand electrophilic compounds | 13 | Chile | [[198](#_ENREF_198)] |
| *RARβ2*  | Retinoic acid receptor, beta | Encodes retinoic acid receptor beta | 4-44 | Chile, United States | [[81](#_ENREF_81),[198](#_ENREF_198)] |
| *REPRIMO* | TP53 dependent G2 arrest mediator candidate | Cell cycle regulation (p53 mediator) | 62 | Chile | [[204](#_ENREF_204)] |
| *SHP1* | Protein tyrosine phosphatase,non-receptor type 6 | Regulate cell growth,differentiation, mitotic cycle | 80 | Chile | [[198](#_ENREF_198)] |
| *3-OST-2* | Heparan sulfate (glucosamine)3-O-sulfotransferase 2 | Osulfotransferase | 72 | Chile | [[198](#_ENREF_198)] |
| *RUNX3* | Runt-related transcription factor 3 | TGF-beta signal pathway | 22-32 | Chile | [[197](#_ENREF_197),[198](#_ENREF_198)] |
| *RIZ1* | PR domain containing 2, with ZNF domain | Histone/protein methyltransferase | 26 | Chile | [[198](#_ENREF_198)] |
| *HPP1* | Transmembrane protein with EGF-like and two follistatin-like domains 2 | TGF-beta signal pathway | 20 |  | [[198](#_ENREF_198)] |
| *P73* | Tumor protein p73 | Induction of apoptosis andcell cycle regulation | 14-28 | Chile, United States | [[81](#_ENREF_81),[198](#_ENREF_198)] |
| *SOCS-1* | Suppressor of cytokine signaling 1 | JAK-STAT pathway | 12 | Chile | [[198](#_ENREF_198)] |
| *DCR2* | Tumor necrosis factor receptor superfamily, member 10d | TNF-receptor superfamily | 6 | Chile | [[198](#_ENREF_198)] |
| *SEMA3B* | Sema domain, immunoglobulin domain (Ig), short basic domain, secreted,(semaphorin) 3B | Induction of apoptosis | 92 | Chile | [[193](#_ENREF_193)] |
| *DUTT1* | Human homolog ofDrosophila Roundabout(ROBO1) | Cell migrationand metastasis | 22 | Chile | [[193](#_ENREF_193)] |
| *BLU* | Zinc finger, MYND-typecontaining 10 | Cell cycle regulation | 26 | Chile | [[193](#_ENREF_193)] |
| *p14* | Ribonuclease P/MRP 14 kDa subunit | Cell cycle regulation | 40 | Germany | [[201](#_ENREF_201)] |
| *MASPIN* *THBS1**HLTF* | Mammary serine protease inhibitorThrombospondin 1Helicase-like transcription factor | Tumor suppressor genePlatelet aggregation, angiogenesis, and tumorigenesisRegulate transcription | 70%52%16% | India | [[205](#_ENREF_205)] |
| *MYC* | V-Myc Avian Myelocytomatosis Viral Oncogene Homolog transcription factor | Cell cycle progression, apoptosis and cellular transformation | 80 % | Brazil | [[206](#_ENREF_206)] |
| *APC CDKN2A ESR1 PGP9.5**SSBP2* | Adenomatous polyposis coliCyclin-dependent kinase inhibitor 2AEstrogen receptor 1Protein gene product 9.5Single-stranded DNA-binding protein 2 | Tumor suppressor geneCell cycleTranscription factorNeural and/or nerve sheath differentiationMicrosatellite instability | 71%-95% | United States | [[207](#_ENREF_207)] |
| *PGP9.5* | Protein gene product 9.5 | Neural and/or nerve sheath differentiation | 27.2% | South Korea | [[208](#_ENREF_208)] |
| *MLH1, CDKN2A**FHIT**APC**CDH1* | MutL homolog 1Cyclin-dependent kinase inhibitor 2AFragile histidine triad proteinAdenomatous polyposis coliCadherin-1 | Mismatch repairCell cyclePurine metabolismTumor suppressor genesCell cycle | 5%35%21%25%66% | Chile | [[194](#_ENREF_194)] |

**Table 8 Candidate gene studies (Low susceptibility genes) in gallbladder cancer**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Pathway involved** | **Gene** | **Polymorphism** | **Population** | **Ref.** |
| DNA repair pathway genes | *XPC* | (rs2228000) Ala499Val | China | [[236](#_ENREF_236)] |
| (rs2228001) Lys939Gln | China |
| *ERCC2* | (rs1799793) Asp312Asn | North Indian | [[232](#_ENREF_232)] |
| (rs13181) Lys751Gln | North Indian |
| *MSH2* | (rs2303426) IVS1+9G>C |
| (rs2303425) -118T>C |
| *OGG1* | (rs2072668) 748-15C>G |
| *TP53* | (rs1042522) Pro72Arg | Chilean, Hungary, Japanese | [[237-239](#_ENREF_237)] |
| *XRCC1* | (rs1799782) Arg194Trp | North Indian Shanghai, China | [[222](#_ENREF_222),[231](#_ENREF_231)] |
| (rs25487) Arg399Gln |
| *APEX1* | (rs3136820) Asp148Glu | Shanghai, China | [[222](#_ENREF_222)] |
| *RAD23B* | (rs1805335) IVS5-15A>G | [[223](#_ENREF_223)] |
| (rs1805329) EX7+65C>T |
| *FEN1* | FEN1-69G > A and haplotypes | China | [[240](#_ENREF_240)] |
| Hormonal pathway genes | *CCKAR* | (rs1800857) IVS1-5T>C | North Indian | [[227](#_ENREF_227)] |
| CCK and CCKAR | (rs2071011G>C,rs915889C/T,rs3822222C/T,rs1800855T/A | Shanghai, China, | [[241](#_ENREF_241)] |
| *ESR1* | (rs2234693) IVS1-397T>C | Shanghai, China, North India | [[241](#_ENREF_241)-243] |
| (rs3841686) IVS5-34->T |
| (rs2228480) Ex8+229G>A |
| (rs1801132) Ex4-122G>C |
| (rs9340799 ) IVS1-351A>G |
| *ESR2* | (rs1256049 )Val328Val | Shanghai, China |
| *PGR* | Ins/Del | North India |
| *AR* | (CAG)n | Shanghai, China | [[244](#_ENREF_244)] |
| *COMT* | (rs4633) His62His | Shanghai, China | [[224](#_ENREF_224)] |
| (rs4818) Leu136Leu |
| *CYP1A1* | (rs2606345) IVS1+606G>T |
| *CYP1B1* | (rs10012)Arg48Gly |
| *CYP19A1* | (rs1065778) IVS4-76A>G | Shanghai, China | [[224](#_ENREF_224)] |
| (rs700518) Val80Val |
| (rs2304463) IVS7-106T>G |
| (rs700519) Arg264Cys |
| (rs1065779) IVS9-53G>T |
| (rs4646) Ex11+410G>T |
| *HSD3B2* | (rs1819698) Ex4-133C>T | Shanghai, China | [[224](#_ENREF_224)] |
| (rs1361530) Ex4-88C>G |
| *HSD17B3* | (rs2066479) Gly289Arg |
| *HSD17B1* | (rs2830) Ex1-486G>A |
| *SHBG* | (rs6259) Ex8+6G>A |
| *SRD5A2* | (rs523349) Ex1-17G>C |
| *RXR-a* | (rs1536475) IVS6+70A>G | Shanghai, China | [[245](#_ENREF_245)] |
| (rs1805343) IVS1-27A>G |
| *RXR-b* | (rs2744537) G392T |
| (rs2076310) C51T |
| *INS* | (rs689) A-6T | Shanghai, China | [[245](#_ENREF_245)] |
| *PPARD* | (rs2016520) Ex4+15C>T | Shanghai, China |
| *PPARG* | (rs3856806) His477His | Shanghai, China |
| Inflammatory pathway genes | *CR1* | (rs2274567) His1208Arg | North Indian | [[230](#_ENREF_230)] |
|  | ( rs12144461 ) Intron 27, HindIII |
| *IL1RN* | 86-bp VNTR | North Indian | [[220](#_ENREF_220)] |
| *PTGS2* | (rs689466) -1195G>A | [[233](#_ENREF_233)] |
| (rs20417) -765G>C |
| (rs5275 ) +8473T>C | north Indian Shanghai, China | [[233](#_ENREF_233),[246](#_ENREF_246)] |
| *IL1B* | (rs16944 ) -1060T>C | Shanghai, China north Indian | [[220](#_ENREF_220),[247](#_ENREF_247)] |
| *IL10* | rs1800871)- 7334T>C | Shanghai | [[247](#_ENREF_247)] |
| (rs1800872) -6653A>C | Shanghai |
| *IL-8* | (rs10805066) *IL8* -13985C>G | China | [[248](#_ENREF_248)] |
| *EGF* | (rs4444903) +61A>G | north Indian | [[221](#_ENREF_221)] |
| *TGFb1* | (rs1800469 )-509C>T | Shanghai, north Indian | [[219](#_ENREF_219),[221](#_ENREF_221),[247](#_ENREF_247)] |
| *TNF-α* | (rs1800629) -308G>A |
| *IL6* | (rs1800795) 236C>G) |
| *IL8* | (rs10805066) -13985C>G | China | [[248](#_ENREF_248)] |
| *MMP-2* | (rs2285053) -735 C>T | north Indian | [[249](#_ENREF_249)] |
| (rs9340799) -1306 C>T |
| *MMP-7* | (rs11568818) -181 A>G |
| *MMP9* | (rs2250889) P574R |
| (rs 17576) R279Q |
| (rs 17577) R668Q |
| *TIMP2* | (rs8179090) -418 G>C |
| Metabolic pathway genes | *MTHFR* | (rs1801133) Ala222Val | Indian | [[228](#_ENREF_228)] |
| *APOB* | (rs17240441) 35\_43del9 | Indian | [[217](#_ENREF_217)] |
| *NAT2* | (rs1799929) NAT2\*5A(rs1799930) NAT2\*6Brs1799931, NAT2\*7A | Indian | [[216](#_ENREF_216)] |
| *GSTT1* | Null polymorphism | Indian | [[215](#_ENREF_215)] |
| *GSTP1* | (rs1695) Ile105Val |
| *CYP17* | (rs743572 ) Ex1+27T>C | Shanghai Indian (265) | [[250](#_ENREF_250),[251](#_ENREF_251)]  |
| *GSTM1* | Null polymorphism | Indian, Chilean Hungary Japanese | [[215](#_ENREF_215),[237](#_ENREF_237),[238](#_ENREF_238)] |
| *CYP1A1* | (rs4646903) CYP1A1\*2A | Indian, Chilean Hungary Japanese | [[218](#_ENREF_218),[237](#_ENREF_237),[239](#_ENREF_239)] |
| (rs1048943) Ile462Val (\*2C) | China, Chilean, Hungary Japanese | [[224](#_ENREF_224),[237-239](#_ENREF_237)] |
| *Cyp1a1 cyp1b1* | CYP1A1-MspI, CYP1A1-Ile462Val, and CYP1B1-Val432Leu | India | [[252](#_ENREF_252)] |
| *LDLR* | (rs5930) EX10+55G>A | Shanghai | [[253](#_ENREF_253)] |
| (rs6413504) IVS17\_42A>G | Shanghai |
| (rs14158) EX18+88G>A |
| *LPL* | (rs263 ) IVS5-540C>T |
| *ALOX5* | (rs2029253 ) IVS3+100G>A |
| *ApoB* | rs693 ) Thr2515Thr | Indian Chilean | [[30](#_ENREF_30),[217](#_ENREF_217)] |
| *ABCG8* | (rs11887534 ) Asp19His | North Indian Shanghai China | [[229](#_ENREF_229),[254](#_ENREF_254)] |
| *CETP* | (rs708272 )TaqIB | Chilean Shanghai China | [[30](#_ENREF_30),[254](#_ENREF_254)] |
| (rs1800775) -629C>A | Shanghai China | [[254](#_ENREF_254)] |
| *LRPAP1* | (rs11267919)752\_177\_752\_176 *I* 37 | North Indian Shanghai China | [[214](#_ENREF_214),[254](#_ENREF_254)] |
| *CYP7A1* | (rs3808607) -204 A>C | North Indian | [[255](#_ENREF_255)] |
| *CYP7A1* | (rs3824260) -469 T>C | North Indian |
| *CYP17* | (rs743572)A/G | North Indian | [[250](#_ENREF_250),[251](#_ENREF_251)]  |
| *ApoB* | (rs676210 ) Pro2739Leu | Shanghai | [[253](#_ENREF_253)] |
| (rs673548 ) IVS23-79T>C |
| rs520354 )IVS6+360C > T |
| (rs1367117) Thr98Ile |
| (rs440446 ) IVS1+69C>G |
| *CYP2C19* | (rs4244285) CYP2C19\*2,(rs4986893) CYP2C19\*3 | Japanese | [[256](#_ENREF_256)] |
|  | *ADRB3* | (rs4994)A/G | North Indian | [[257](#_ENREF_257)] |
| Apoptosis pathway  | *CASP8* | (rs3834129 ) -652 6N ins/del | North Indian | [[258](#_ENREF_258)] |
| (rs1045485 ) Asp302His |
| (rs3769818 A) IVS12-19 G>A |
| Nuclear Receptors | *Lxr-alpha, Beta* | LXR-α (rs7120118) and LXR-β (rs35463555 and rs2695121) | North Indian | [[259](#_ENREF_259)] |
| Cancer Stem cell gene | *CD44* | CD44 (rs13347) C>T, CD44 (rs353639)A>C,CD44 (rs187116) G>A,CD44 (rs187115) T>C | North Indian | [[260](#_ENREF_260)] |
| *NANOG,ALCAM,**EpCAM,SOX-2,OCT-4,NANOG* | NANOG (rs11055786)T>C,ALCAM (rs1157)G>AEpCAM (rs1126497)T>C,SOX-2(rs11915160)A>COCT-4 (rs3130932)T>G,NANOG (rs11055786)T>C | North Indian | [[261](#_ENREF_261)] |
| Prostate stem cell antigen | *PSCA* | (rs2294008) T/C and rs2978974) | India, Japan | [[262](#_ENREF_262),[263](#_ENREF_263)] |
| miRNA | *hsa-miR-146a* | (rs2910164 ) G>C | North Indian | [[264](#_ENREF_264)] |
| *hsa-mir-196a2* | (rs11614913) C>T |
| *hsa-mir-499* | (rs3746444)T>C |
| *miR-27,miR-570,miR-181* | miR-27a (rs895819)A>G,miR-570(rs4143815)G>C,miR-181a(rs12537)C>T | North Indian population | [[265](#_ENREF_265)] |
| GWAS-associated genes | *DCC* | (rs7504990)C>T | Japan | [[234](#_ENREF_234)] |
| ( rs2229080) C>G | North Indian | [[235](#_ENREF_235)] |
| (rs4078288) A>G |
| (rs7504990) C>T |
| (rs714) A>G |
| Wnt signaling pathway | *SFRP4, DKK2, DKK3,APC,AXIN-2,Β-CATENIN,GLI-1* | SFRP4 (rs1802073) G>T,DKK2 (rs17037102) C>TDKK3 (rs3206824) C>T,APC(rs4595552)A/TAPC( rs11954856) G>T,AXIN-2 (rs4791171)C>Tβ-CATENIN (rs4135385) A>G,GLI-1(rs222826) C>G | North Indian | [[266](#_ENREF_266)] |
| Other genes  | *KRAS* | codon 25 Gln25His | Eastern India | [[267](#_ENREF_267)] |
| *ACE I/D* | (rs4646994) 289 bp del | North Indian | [[268](#_ENREF_268)] |
| *DNMT3B* | (rs1569686 ) -579 G>T | North Indian | [[269](#_ENREF_269)] |
| *TLR2* | -196-174del | North Indian | [[270](#_ENREF_270)] |
| *TLR4* | (rs4986791) Thr399Ile | North Indian |  |
| Adrenergic receptors *(ADRA)* | ADRA2A C-1291G, ADRβ3 T190C or Trp64Arg, and ADRβ1 C1165G or Arg389Gly | North Indian | [[271](#_ENREF_271)] |
| Death Receptors and their ligands *(DR4)* | DR4 (rs20575, rs20576 and rs6557634), FAS (rs2234767) FASL (rs763110) | North Indian |  |
| *PlCE1* | (rs2274223) A>G and. (rs7922612) T>C | North Indian | [[272](#_ENREF_272)] |
| *Vitamin D receptor (VDR)* | FokI C>T | China | [[273](#_ENREF_273)] |