Pancreatic cancer (PaCa), although not very common, shows the highest mortality rate associated with any specific cancer. Throughout the world, the incidence and mortality rates for PaCa are almost equal indicating that there are very few survivors; the five-year survival rates are less than 5% and according to the WHO, PaCa ranked eighth in world cancer mortality in 2005. Moreover, at the time of presentation, most PaCa patients harbor multiple metastases, which limit treatment options. In addition, present chemotherapeutic regimens are largely unsuccessful. An improved understanding of the molecular pathogenesis of PaCa is urgently needed to identify new targets and strategies for effective therapy. Recent advances in the area of genomics have made it possible to identify important PaCa genes. However, it is equally important to validate these genes in order to confirm their role(s) in PaCa initiation and progression. Since PaCa has a high rate of local invasion and early metastatic spread, the study of PaCa genes may also reveal pathways(s) for tumor invasion and metastasis. Amplification of oncogenes and deletion of tumor suppressor genes are two important mechanisms for tumor initiation and progression. In studies from several laboratories, several localized novel copy number alterations (CNAs) were identified in PaCa cell lines and primary pancreatic tumor tissues by using a combination of high resolution array-based comparative genomic hybridization (aCGH) and gene expression microarrays (GEM). For my thesis, I have selected two homozygous deletions located at 6q25.3 and 18q23, which were identified in the PaCa cell lines MiaPaCa2 and Colo357 respectively for further validation as novel tumor suppressor loci in PaCa. The thesis is divided into six chapters. Chapter one includes general introduction and review of literature of common cancers and PaCa incidence and mortality statistics. This chapter also outlines a brief review of literature of current understanding of diagnostic and therapeutic markers used in PaCa and lack of efficient therapeutic options. Further, this chapter summarizes genomic approach for identification of novel therapeutic markers. Finally, the

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Chapter describes the importance of aCGH and GEM as potential technology for identification of potential tumor suppressors genes and oncogenes.

Chapter two describes review of literature regarding CNAs validated for identification of novel deregulated genes in common cancers as well as in PaCa. This chapter also provides review of literature regarding deletion at 6q25.3. Further, this chapter includes detailed review of ARID1B gene and its role in cancer initiation and progression. The chapter describes studies on ARID1B, its normal cellular functions such as maintenance of stem cell, cellular differentiation, DNA repair, cell cycle regulation, etc. This chapter also describes involvement of SWI/SNF components in normal cellular function and cancer. Also, a brief review of ARID1B as a possible TSG in PaCa is included. Subsequently, the chapter provides a review of literature of chromosomal deletion located at 18q23 with respect to PaCa. PARD6G gene is located in this locus. The gene is known to be a component of polarity complex. The Chapter describes the review of literature for cell polarity structure and its components. PARD6G is a component of “par” complex of cell polarity; role of “par” complex with respect to cell migration and its regulation through various cell signaling pathways is also described. Current understanding of the involvement of polarity complex components in cancer initiation and progression is given in this chapter and the possible role of PARD6G as a TSG in PaCa is described. Finally, the chapter outlines rationale of this study and outlines the specific objectives.

Chapter three describes the materials used in this study and a detailed description of the methodology followed for each experiment in this study.

Chapter four describes the result of the study regarding ARID1B and PARD6G as possible TSGs. This chapter is divided into two sections. Section I provides the results of ARID1B and describes the genomic (mutation screening of ARID1B) and epigenetic (Bisulfite genome sequencing and Azacytidine mediated transcript quantification) approach to determine

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possible role of *ARID1B* as putative tumor suppressor. Secondly, the chapter describes generation of stable expressing clones of *ARID1B* and their subsequent characterization with respect to growth, colony formation, wound healing, etc. to analyze the function of this gene in MiaPaCa2. Section II describes the results of *PARD6G* gene in PaCa cells. This section provides the results of *PARD6G* mutation screening in PaCa cells. Further, this section deals with promoter analysis of this gene and describes the *in silico* analysis of the putative promoter region followed by functional analysis of the putative promoter region using a luciferase reporter construct. The results of reporter assay indicate a probable transcriptional activator and a probable transcription repressor region. Further, *in silico* analyses of both regions indicate presence of possible transcription factor binding elements.

Chapter five discusses the results of *ARID1B* and *PARD6G* gene with respect to current understanding of function of both the genes. Finally, chapter six outlines the summary of the results obtained and provides conclusion drawn from the results.

**Summary**