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IN SILICO ANALYSIS OF TP53 PATHWAY GENES IN HUMAN FERTILITY

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The TP53 gene, first described in 1979, was identified as a tumor suppressor gene in 1989, when it became clear that its product, the p53 nuclear phosphoprotein, was frequently inactivated in many different forms of cancers. Nicknamed "guardian of the genome", TP53 occupies a central node in stress response networks. The p53 protein has a key role as transcription factor in limiting oncogenesis through several growth suppressive functions, such as initiating apoptosis, senescence, or cell cycle arrest. The p53 protein is directly inactivated in about 50% of all tumors as a result of somatic gene mutations or deletions, and over 80% of tumors demonstrate dysfunctional p53 signaling. Beyond the undeniable importance of p53 as a tumor suppressor, an increasing number of new functions for p53 have been reported, including its ability to regulate energy metabolism, to control autophagy, and to participate in various aspects of differentiation and development. Recently, studies on genetic variations in TP53 among different populations have led to the notion that the p53 protein might play an important role in regulating fertility. Although the important interaction between p53 and LIF is crucial for embryo implantation, current evidence suggests that not only LIF, but other genes may be important in the reproductive stages of decidualization and implantation. To further test this hypothesis, we constructed a network with 18 TP53 related genes involved in decidualization and implantation processes. Eighteen genes (AKAP5, CALCA, CYP27B1, IGFBP7, IL1B, ESR1, LIF, MDM2, MEN1, PLA2G4A, PLAU,PPARD, PTGS2, SOD1, SPP1, TP53, UBE2A and VDR) related to decidualization and implantation were compiled from the Gene Ontology website database using the AmiGO browser. Association among these genes was tested using the STRING 9 software which tests available known and predicted gene/protein interactions. This “two-step” approach was chosen to minimize the possibility of false associations during the STRING analysis due to co-existence of words. An additional analysis to verify if these 18 genes belong to a specific functional cluster was performed using GeneDecks V3 software. Thirteen of them were functionally clustered as having an involvement in the reproductive system (CYP27B1, ESR1, LIF, MEN1, PLA2G4A, PLAU, PPARD, PTGS2, SOD1, SPP1, TP53, UBE2A and VDR). More specifically, six genes (CALCA, IL1B, LIF, PTGS2, SOD1 and SPP1) were associated with embryo implantation ($p=1x10^{-12}$) and seven (CYP27B1, LIF, PLA2G4A, PPARD, PTGS2, SPP1 and VDR) with decidualization ($p=1x10^{-16}$). This analysis illustrates the importance of multiple genes in these specific stages of human fertility and opens a wide range of possibilities for genetic variation studies in genes not yet being investigated with regard to fertility.