Plants are organisms that do not have the capacity of movement. Constantly, they are exposed to an array of biotic and abiotic stresses that affect their ability to grow and reproduce. Water deficit stress is one of the most frequent abiotic stresses that plants have to cope with. It significantly affects the productivity of many agronomically important plants. We initiated studies to identify genes that might confer tolerance to water deficit stress in Upland cotton (*Gossypium hirsutum* L.). Acala 1517-99 was chosen for these studies because this cultivar was developed in the arid and semi-arid Southwest of the U.S. and may possess some level of ability to withstand water deficit stress. Seed was planted on May 7, 2008 and irrigated immediately for emergence. Under normal irrigation regime the well watered treatment was irrigated on June 17, 2008, while the drought stress treatment was implemented by delayed irrigation in the field. Plant measurements were taken on June 27, 2008. Cotton plants in the drought stress treatment exhibited significant growth reduction in plant height, fresh weight and number of fruiting branches. On June 26, 2008, leaf tissues (third leaf from the top) of well watered and drought stressed field cotton plants in three replicates were harvested for RNA isolation using an improved quick RNA extraction method. RNA samples were bulked in an equal molar ratio based on treatments for cDNA synthesis and hybridized to Affymetrix GeneChip® Cotton Genome Arrays. The cotton GeneChip is comprised of 23,977 probe sets representing 21,854 cotton transcripts. A total of 111 drought responsive genes were identified in the GeneChip Cotton Genome arrays, including 89 genes being down-regulated and 21 genes being up-regulated under drought stress conditions. The differentially expressed genes were used to construct hierarchical clusters and our preliminary analysis indicated that some of these genes were involved in transcription, lipid metabolism, and cell wall and praline biosynthesis, while many others were stress-related heat shock protein genes. 25 drought responsive genes were selected for validation using quantitative (q) real time RT-PCR and the relative expression levels of 18 genes were consistent between microarray analysis and qRT-PCR. The identified drought responsive genes will be useful for marker development, candidate gene discovery, and improvement of drought tolerance in cotton.