**Phenotypic relevance of genes associated with increased risk of radiation-induced fatigue in patients being treated for prostate cancer**

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**REASON FOR JOURNAL DESIGNATION:**

This study investigates the pathobiology of a common cancer treatment complication (Radiotherapy-induced prostate cancer fatigue) through analysis of recently available bioinformatic genomic data. This analysis is also the continuation of a previous study that was published on Cancer Bioinformatics (1).**ABSTRACT**

Radiotherapy-Induced Fatigue (RIF) is a common and debilitating complication of cancer treatment. Its underlying pathophysiology is poorly understood. We conducted an ontological analysis and a review of all literature to identify possible implicated pathways of a set of 35 genes previously associated with development of RIF in men with prostate cancer. Findings suggest alterations in genes associated with neural, immunological, mitochondrial, muscular, and metabolic pathways. Additionally, certain genes were associated with specific phenotypes, such as increased ionization radiation sensitivity and altered DNA repair frequency. Although prominent physiologic mechanisms were revealed from our analysis, it must be noted that many of the 35 RIF-associated genes are currently very poorly characterized, warranting further investigation. Nevertheless, this study demonstrates an arguably comprehensive method of approaching known genomic alterations underlying any complex phenotype or disease, to correlate feasible pathophysiology.

**KEYWORDS:**

(3-6 words): Gene, Phenotype, Attributions, Cancer, Radiotherapy, Fatigue

**MANUSCRIPT TYPE:**

Original Research

**INTRODUCTION:**

Fatigue is among the most common and troubling side effects of many forms of cancer treatment including radiation therapy (1, 2). Cancer treatment-related fatigue (CTRF) is reported to occur in up to 80% of cancer patients, with 30% of the cases becoming chronic (3), and is associated with reduced quality of life, functional capacity and physical well-being (4).

While CTRF is common, like other regimen-related toxicities, it does not occur uniformly across all patients. Rather, it impacts an at-risk population. The desirability of being able to prospectively identify at-risk individuals has prompted a number of studies; some focused on biologic indicators and others on symptom clusters. While the pathoetiology of CTRF is incompletely understood, it has become increasingly clear that its development is strongly related to a series of underlying genetically-controlled biological events. In an earlier study, based on a hypothesis which stated that CTRF risk was determined by a group of synergistically expressed genes, we successfully identified a cohort of 35 genes which were associated with an increased risk of fatigue in a group of men being treated with radiation therapy for cancers of the prostate (1). We confirmed the predictive validity of the gene cluster in a small, independent cohort of patients with the same diagnosis and treatment.

We reasoned that an analysis of the 35 genes, which constituted the risk prediction cohort, might be informative relative to the relationship of the functionality of the genes to the possible pathobiology underlying CTRF. Furthermore, we reasoned that given the likelihood that the fatigue phenotype shares common biology across multiple etiologies (a biological final common pathway), we would expect some commonality of the detected genes with those described with other fatigue-based pathologies or conditions.

In the current study, we used both directed and undirected approaches to analyze the genes of interest and to develop functional attributions.

**METHODS:**

A set of 35 genes, which were differentially associated with a risk for clinically significant fatigue (1) among patients being treated with radiation therapy for prostate cancer, were studied **[Figure 1]**.

**Undirected approaches**

Three undirected approaches were used to identify possible phenotypes associated with risk discrimination genes. The set of 35 genes **[Table 1]** was first queried in GeneCardsSuite’s Gene Analytics (5) and analyzed for organ and tissue expression, diseases, phenotype, pathways and biological processes. Positive relationships were defined as those identified by a score of “high.” Next, to assure inclusivity, each gene in the set was individually searched in GeneCardSuite GeneCards (5), where summaries, functions, phenotypes and entirety of the publications were reviewed. Lastly, genes not identified by the GeneCardSuite database were queried in the NCBI NLM Gene database (6) and summary, phenotype and general gene information were reviewed.

**Directed approaches**

Two directed search strategies were used. With PUBMED, the relationship between each of the 35 genes to a “fatigue” phenotype was first explored. To validate the ‘realism’ of the gene set, we hypothesized that a query of genes known to be associated with malignancy (cancer) and, specifically “prostate cancer” should demonstrate overlap with a number of the differentially expressed genes based on tumor diagnosis. Next we evaluated phenotypes related to RIF by querying expressed genes using GeneCardsSuite’s phenotyper, VarElect (7) using search terms of “fatigue,” “narcolepsy/sleep,” “chronic fatigue syndrome,” and “depression.” Lastly, more broad phenotypes noted to have cited possible biological or functional linkages to the fatigue phenotype were queried using the same method. This group included “mitochondria,” “inflammation,” “muscle,” “diabetes/glucose/insulin,” “metabolic syndrome,” “neuron,” “sleep,” “calcium” and “fat/adipose” **[Table 2]**. Only those genes directly related to fatigue as reported by VarElect were considered.

**RESULTS:**

**Genes Identified Through Secondary Means**

Of the 35 genes reported in the previous study (1), four were not identified by GeneAnalytics (*FLJ32790*, *LOC100505812*, *OTTHUMG00000183952 /// RP11-727A23.11*, and *PHF17*), and were queried in NCBI NLM gene database.

*FLJ32790* is largely uncharacterized. *LOC100505812* is slightly more studied, but did not relate with any fatigue-relevant phenotypes. *OTTHUMG00000183952 /// RP11-727A23.11* was present in neither GeneAnalytics nor the NCBI NLM gene database, and other sources (e.g. GeneProf (8) ) showed no functional annotation for the gene. However, *PHF17*, or more preferably named Jade-1, is known as a negative regulator of cell growth and G1/S transition of mitotic cells. It is a renal tumor suppressor (9) involved in pathogenesis of renal cell carcinoma and von Hippel-Lindau disease (10).

**Validation: Prostate Cancer-Related Gene Expression**

Of the 31 genes identified by GeneAnalytics, six genes (all six of which were downregulated in highly fatigues patients (HF) compared to mildly or low fatigued patient (LF) ) were associated with prostate cancer pathogenesis. This finding provided confirmation of the validity of the genomic data obtained based on their tumor diagnosis of men studied by Saligan. They include: *TUBB3*, *ZEB1*, *SP3*, *RICTOR*, *GNRHR2*, and *HIPK3 (11-23)*.

**Relevant Phenotypes From Large Scale Genetic Studies:**

Using GeneAnalytics’ archives based on large-scale, nonspecific genomic studies, several phenotypes were identified.

Radiation Resistance

Of the genes studied, 6 were associated with radiation responsiveness/resistance. Increased ionizing radiation sensitivity is associated with *DR1* (24) and *FAM63B* (24). Increased gamma-*H2AX* phosphorylation, which is a marker of double strand DNA breaks (25), was also reported to be a phenotype of *DOCK11* (26), *EIF1AX* (26), *GNRHR2* (26). Whereas *FAM63B* could be associated with either a decrease or increase in homologous recombination repair frequency (27), *ZMYM2* included the phenotype of decreased homologous recombination repair frequency (27).

Cell Viability

A number of genes (*DENND4C*, *DOCK11*, *DR1*, *EIF1AX*, *FAM63B*, *FMR1*, *HIPK3*, *HLA-DQA1*, *HLA-DQB1*, *MRGB*, *PREPL*, *RICTOR*, *SP3*, *TDP2*, *TRMT13*, *TUBB2A*, *TUBB3*, *ZEB1*, and *ZFPL1*) were associated with decreased cell viability (28).

Cell Cycle Regulation

Several genes also had archived phenotypes that included cell cycle regulation. Several genes (*HIPK3*, *HLA-DQA1* and *ZEB1*) were associated with increased G1 DNA content (29). *HLA-DQA1* also had the phenotypes of G0/1 arrest (29) and increased number of mitotic cells (29).

**Directed and undirected searches using phenotypes:**

“Fatigue,” “Chronic Fatigue Syndrome,” and “Narcolepsy/sleep”

*HLA-DQA1* is the second most discriminative gene of the 35 genes associated with RIF phenotype in this clinical population. A specific allele of this gene, *HLA-DQA1\*01*, is a known risk factor for Chronic Fatigue Syndrome (30). A different *HLA-DQA1* allele, *DQA1-0102*, is also strongly associated with narcolepsy (31). Similarly, a specific *HLA-DQB1* allele, *DQB1-0602*, was found to be carried by 90-100% of narcoleptic patients (32). *DQB1-0602* is also associated with poor sleep and hypersomnia (33). Lastly, deletion of a different gene, *SMCR8*, causes a congenital disease that includes sleep abnormalities (along with mental retardation and behavioral abnormalities) (34). This gene was downregulated in HF participants.

“Mitochondria”

Only one of the 35 genes was associated with mitochondrial function. *IMMP1L* codes for a protease that processes Diablo/Smac, allowing the mitochondrial protein to be released into cytosol and induce apoptosis (35). Interestingly, mitochondrial pathways may be implicated in a complex (mTORC2) formed by a different gene, RICTOR (36).

“Inflammation” and “immunity”

Several genes were associated with inflammation and immunity. *SP3* codes for a transcription factor that is an inhibitor of *FOXP3* gene, which in turn codes for a transcriptional regulator that is involved in the development of T-regulatory cells (37). *SP3* gene product also allows basal level expression of extracellular superoxide dismutase (38), which has inflammatory roles. Furthermore, *ZEB1* codes for a zinc finger transcription factor that is a suppressor of the cytokine IL2 gene activation (39) (40), a strong recruiter of T cells. *TDP2* also seems to have significant immune system roles as it codes for a protein that associates with components of CD40, TNF, TGF-b, TRAF, and NFkB (41-44). TDP2 expression seems to inhibit NFkB (36, 44). Interestingly, all of these genes were downregulated in HF men.

Lastly, specific alleles of *HLA-DQA1/DQB1* genes are associated with numerous inflammatory diseases, such as celiac disease (45).

“Neuron”

A notable number of associations were made among the gene set and the query phenotype of “neuron.”

Firstly, the *SP3*-encoded transcription factor promotes neuronal survival in response to oxidative stress (46-48). Similarly gene products of *ZEB1* promote a protective response in neurons undergoing ischemia (49). Both *SP3* and *ZEB1* were downregulated in HF men.

*SP3* expression may also modulate neuronal signaling in several other ways, such as modulation of the expression of neuronal nicotinic Ach receptor (46), expression of Mu opioid receptor (50), and activation of dopamine receptors (51, 52). Product of *RICTOR*, another downregulated gene in HF men, is a subunit of a complex that is involved in myelin gene expression and oligodendrocyte differentiation (53). *SP3* expression is also required for the expression of the main *DMD* gene product in the brain, Dp71 (54), the dysregulation of which may be implicated in cognitive impairment seen in *DMD (55)*.

Activity of a *RICTOR* has been associated with consolidation of long-term memory (56). However, patients with Chronic Fatigue Syndrome seem to have more difficulty with short-term memory than long-term memory. Of note, RICTOR is required to Ubiquitinate SGK1 (57), which is involved in neurogenesis and psychological wellbeing (58).

As for other genes, *TUBB3* is reported to be enriched in neuritis, increasing in expression in response to increasing duration of nerve growth factor stimulation (59). Interestingly, ZEB1, which is downregulated when comparing HF to LF patients, is reported to increase TUBB3 expression in the context of breast cancer (60).

The HLA genes are also associated with neurological disorders: specific alleles of *HLA-DQA1* have been associated with multiple sclerosis (61) and myasthenia gravis (62, 63), while specific *HLA-DQB1* alleles are associated with Parkinson’s Disease (64) and myasthenia gravis (62, 63).

Lastly, while differential expression of *TUBB2A*, is seen in frontotemporal lobar dementia (65), *TUBB3* dysregulation is more highly associated with congenital and developmental neurological diseases such as Down syndrome (66) and cortical development/migration defects (67). *TUBB3* is also involved in neurogenesis and axonal guidance (67), however, this was reported in the context of congenital development. A different gene, *FAM126A*, is also associated with hypomyelinating leukodystrophies (68), including a specific neurological congenital condition called hypomyelination and congenital cataract (69). While nucleotide expansion in the *FMR1* gene (and thus dysfunction) is the cause of the neurological disorder, Fragile X Syndrome, that too only is relevant in a congenital context (70, 71).

“Muscle” and “calcium”

*SP3* expression is linked to muscle metabolism is multiple ways. *SP3*’s gene product is known to repress *GLUT1* expression in both muscle and non-muscle cells (72). It also downregulates myosin chain expression during muscle inactivity (73), and upregulates calcium sensing receptor expression in response to IL6 signaling (74). RICTOR expression is also increased after strength training (75).

Furthermore, the HLA allele, *HLA-DQB1\*0401* may contribute to dermatomyositis and polymyositis (76). As previously mentioned, alleles of both *HLA-DQA1* and *DQB1* are associated with myasthenia gravis. Lastly, deletion of *PREPL* may cause hypotonia-cystinuria syndrome, a congenital disorder where, among other characteristics, patients exhibit hypotonia at birth and show growth hormone deficiency (77).

“Metabolic syndrome,” “diabetes,” “glucose,” “insulin,” and “fat/adipose”

While no specific link was found with the genes involved and the query, “metabolic syndrome,” several genes related with the sub-phenotypes of metabolic syndrome.

For instance, *DENND4C* knock down reduces *GLUT4* translocation in adipocytes, which would otherwise be a part of a normal response to insulin (78). Furthermore, as previously mentioned, *SP3* is a repressor of *GLUT1* expression (72). *SP3* expression also enhances *SOCS3* expression (79), a hepatic compound that seems to be implicated in insulin resistance (80). Both *DENND4C* and *SP3* were downregulated in HF men.

On a more hereditary basis, certain alleles of *HLA-DQA1* confer protection against diabetes, while others confer susceptibility (81). A similar phenomena is seen with regards to *HLA-DQB1* alleles and diabetes. For example, *DQB1\*0301* has negative association with diabetes risk, while *DQB1\*0302* is positively associated with the condition (81).

In regards to “adipose” and “fat” regulations, two genes show relevance. *SP3* regulation is involved in activation of human lipoprotein expression (82), and inhibition of adipocyte specific apM-1 (adipose most abundant gene transcript-1) (83), which may be implicated to obesity-related insulin resistance. Lastly, *ZEB1* represses adipose tissue accumulation in female mice (84).

**DISCUSSION:**

In an earlier study we identified 35 genes which were associated with increased risk of radiation-induced fatigue in a cohort of patients being treated for prostate cancer. In the current analysis, we set out to evaluate the functional significance of those genes and their similarities to known genomics associated with other fatigue-related conditions. Using specific phenotypes that have previously been linked to either radiation induced-chronic fatigue or chronic fatigue, we reviewed each gene in detail using both a directed and a more broad, undirected approach to evaluate potential commonalities between the genes of interest and a fatigue phenotype. Furthermore, we reasoned that shared pathways might be informative relative to the pathobiology of Cancer Treatment Related Fatigue.

Firstly, we validated our gene set by looking for genes associated with prostate cancer. We reasoned that prostate cancer patients should show differential expression of genes associated with prostate cancer. We found six genes among the 35 that have direct correlations with prostate cancer pathology. TUBB3 is associated with treatment resistance prostate cancer (11, 12) while ZEB1 was discovered to promote epithelial to mesenchymal transition (13-15) and migration (16) of prostate cancer cells. When used with Gleason scoring, a study (17) demonstrated that SP3 expression predicts prostate cancer recurrence. In fact, SP3 has been associated with increased PSA expression (18). RICTOR, a subunit of MTORC2, is also implicated in androgen dependent prostate cancer proliferation and survival (19). HIPK3 overexpression also enhanced androgen receptor-dependent transcription in several cell lines, including a rat prostate cancer cell line (20). While a different study reported that HIPK3 may be a part of a protein kinase complex that modulates the apoptotic FAS signaling pathway, cDNA data were isolated from mouse testis and not prostate tissue (21). In contrast to the tumor promoting pathways, GNRHR2 codes for a gonadotropin receptor (22), which is involved in a pathway that has an anti-proliferative effect on prostate cancer cells (23).

Interestingly, all six of the prostate cancer-correlated genes were downregulated in HF patients relative to the LF patients. This pattern raises the question of whether the fatigue phenotype is in part a complication of the primary prostate cancer (and its resolve and/or other characteristics), or whether it is purely due to systematic effects of radiotherapy. This may be investigated by genetic analysis of prostate cancer patients at their initial diagnosis, and those undergoing non-radiotherapy treatments.

To avoid bias in our directed approach of using premeditated search phenotypes, we performed a completely undirected review of the entire literature referencing the 35 genes. This led to introduction of additional search phenotypes, and an ensuing repetition of the directed phenotype search. The directed and the undirected searches together led to a highly sensitive and inclusive, but not very specific analysis. Therefore, certain associations were linked to fatigue in a very broad manner. For example, *SP3* can modulate expression of neuronal nicotinic Ach receptors and activation of dopamine receptors, which may or may not be involved in the pathology of central fatigue (Central Nervous System Fatigue). Relevantly, methylphenidate has been successfully used in a small sample of prostate cancer patients to treat cancer-related fatigue (85).

While supported only by nonspecific large-scale studies, phenotypes related to radiation resistance are noteworthy. *DR1*, *FAM63B*, *DOCK11*, *EIF1AX*, and *GNRHR2* are associated with phenotypes such as increased ionizing radiation sensitivity, increased gamma-H2AX phosphorylation (a marker of double strand breaks, as often caused by ionizing radiation (25), and change in frequency of homologous recombination repair. This suggests that decreased sensitivity to ionization radiation (i.e. treatment response), but also decreased repair of radiation-induced DNA damage (i.e. recovery from treatment), may be implicated in the pathophysiology to developing fatigue post-radiation. However, this warrants further investigation as the supporting evidence is not in the context of cancer.

Analyzing more specific evidence is just as complicated. Although many genes pose the possibility of being candidate culprits of cancer-related fatigue, no one gene strongly stands out as a clear determinant of the phenotype. This finding supports our initial hypothesis that, rather than a ‘magic bullet’ fatigue-inducing gene, the symptom more likely results from a simultaneous and complex interactions reflecting the dysregulation of multiple genes.

In fact, the literature review suggests that several of our genes may theoretically be involved in multiple plausible fatigue-causing pathways. *HLA-DQA1* / *HLA-DQB1*, *SP3*, *ZEB1*, and *TUBB3* are some examples, and each gene can theoretically be implicated in fatigue through neurological pathways, inflammatory pathways, and glucose/metabolic pathways.

Considering the associated genes and pathways, some plausible grounds of RIF may be suggested. For instance, it can be hypothesized from literature that down-regulation of *SP3* and *ZEB1 may* cause upregulation of *IL2* and *FOXP3* (implicated in T-regulatory cell development), while downregulation of *TDP2* may impact the activities of CD40, TNF, TGF-b, TRAF and NFkB. Downregulation of the *SP3*, *ZEB1* and *RICTOR*, *may* also implicate decreased neuronal survival in certain contexts (e.g. oxidative stress or ischemia), and affect myelin expression. A different group of genes (*SP3*, *DENND4C* and *ZEB1*) suggests metabolic dysregulation, as their observed downregulation may possibly cause increased *GLUT1* expression in both muscle/non-muscle cells, insulin-induced *GLUT4* translocation in adipocytes, decreased *SOCS3* expression (implicated in insulin resistance), and possibly altered adipocyte metabolism. Clearly these concepts remain speculative until definitive data can be obtained.

These effects are supported not only by the differential expression of the above mentioned genes, but also the specific directional change in their regulation. However, these implications are highly hypothetical until further investigations are completed (e.g. further prospective patient outcome studies or animal knock down trials). Regardless, we aimed to provide a direction from a possible candidate gene pool for further trials.

Interestingly, the overwhelming downregulation of the genes when comparing the HF patients to LF patients may or may not be reflective of the homeostatic and/or metabolic status of HF patients in response to radiotherapy. Among the 35 genes, all but 4 were downregulated. Of the four genes that were upregulated in HF patients, only *HLA-DQA1* has been significantly characterized. However, since the HLA genes have numerous alleles, and we are not aware of the exact alleles the patients had, effectively, we were not able to analyze any of the four upregulated genes. Regardless, it is noteworthy that most of the genes distinguishing LF and HF patients were downregulated.

The lack of characterization of many of the genes in our gene set is a major weakness of this study. Of the entire 35 gene set, 10 of the genes (*BTNL3*, *EPS15P1*, *FAM63B*, *FLJ32790*, *IMMP1L*, *LOC100505812*, *PHF17*, *POLR2J4*, *RP11-727A23.11*, *TRMT13*) have been referenced in only 10 or less publications globally. Furthermore, GeneAnalytics could not provide *phenotype* information on 10 of the genes (*BTNL3*, *EPS15P1*, *FAM126A*, *LYSMD3*, *POLR2J4*, *PREPL*, *SMCR8*, *TRMT13*, *ZFPL1*, and *ZMYM2*) **[Figure 2]**. However, given their discriminative power of predicting radiotherapy associated chronic fatigue, these uncharacterized genes may be suitable grounds for further investigation.

There were also other limitations in our study. For instance, many of the associations may be rooted to only one or two references. However, this is to be expected when the gene list as a whole is not well characterized. Another limitation of our study is its assumptions in biological relevance. For example, while we used Chronic Fatigue Syndrome (CFS) as a search phenotype and found several associations with our gene set and CFS, one study (86) found that in practice, CFS shares few genes with prostate cancer treatment-related fatigue.

Lastly, some of the search phenotypes we used returned gene matches that are different from those found by other reports. For example, we used “Mitochondria” as a search phenotype based on a study by Hsiao et al. that associated differential mitochondrial gene expression with radiation-induced non-metastatic prostate cancer fatigue (87). However, of the genes from our set that associated with mitochondrial function, none matched the 11 genes reported by this study (Although, *IMMP1L* from our gene list is a paralog of *IMMP2L*, a gene differentially expressed in the study by Hsiao et al.). Such differences prompt whether and how non-genetic factors, such as nutrition, comorbidities, and concurrent pharmacological interventions, or epigenetic factors may also be implicated in prostate cancer patients developing fatigue post-radiation. Future investigations will likely benefit from integrating these aspects.

While these various pathophysiologic mechanisms of cancer treatment-related fatigue may be explored to understand this debilitating complication, experiment design should also focus on other steps in the central dogma of biology (e.g. transcriptomics and proteomics) that may be implicated in RIF. Already, a recent proteomic study reported three proteins (ApoE, ApoA1, transthyretin) to be associated with different fatigue levels at baseline and midpoint of radiation therapy (88). Given our current preliminary evidence that many genes may be involved in this complex phenotype, establishing implicated proteomics and building interactomes will emphasize the hubs and bottlenecks (89), where which fatigue treatment may be focused.

Studying factors outside of the central dogma, e.g. non-transcribed genetic markers and etc., is also imperative. The genes and pathways we report here help provide grounds for more specific future investigations by limiting possible mechanisms of the inciting trauma leading to the phenotype of radiation-induced fatigue. However, given the likely paradigm of this phenotype arising from both radio-oncological modulation of cellular metabolism as well as genetic susceptibility **[Figure 3]**, other genetic markers of susceptibility, such as single nucleotide polymorphisms (SNPs) and etc., should also be investigated. Aside from marking individual susceptibility, exploring inter-genic and intra-genic SNP’s may also allow for discovery of implicated genes that are otherwise more difficult to unveil (90). This approach where a disease phenotype first directs discovery of implicated genes to allow ensuing transcriptomic and proteomic discovery of underlying the pathways (i.e. forward genetics), and then seemingly non-dogmatic markers are used to further establish individual susceptibility and other implicated pathways, may apply to study of other complex diseases or phenotypes.

**CONCLUSION:**

Given the analysis of the 35 genes that discriminated the fatigue phenotype in men receiving radiation therapy for prostate cancer, it is only more evident that biological mechanisms underlying this phenomenon are complex. It is reasonable to expect that the development of fatigue post radiation therapy for cancer is mediated by both a genetic predisposition to the phenotype, and the effects of the radiation therapy itself. This analysis provides subtle grounds for further studies to focus on the uncharacterized genes differentially expressed in HF patients as compared to LF patients, and to consider the possible underlying etiologies based on the characterized gene attributions.

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**AUTHOR CONTRIBUTIONS**

Conceived and conducted the experiments that provided the RIF-associated gene-set analyzed in this manuscript: SS, LS, JLFM

Analyzed the data: SH, SS

Wrote the first draft of the manuscript: SH, SS

Contributed to the writing of the manuscript: SH, JLFM, LS, SS

Agree with manuscript results and conclusions: SH, JLFM, LS, SS

Jointly developed the structure and arguments for the paper: SH, SS

Made critical revisions and approved final version: SH, JLFM, LS, SS

All authors reviewed and approved the final manuscript.

**DISCLOSURE AND ETHICS**

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

**TABLES:**

**Table 1**: The 35 Genes ranked according to their prediction of development of HF vs. LF in patients.

|  |  |  |
| --- | --- | --- |
| Predictive Rank | Gene | Change in regulation |
| 1 | TUBB2A |  |
| 2 | HLA-DQA1 |  |
| 3 | BTNL3 |  |
| 4 | TUBB3 |  |
| 5 | HLA-DQB1 |  |
| 6 | IMMP1L |  |
| 7 | ZFPL1 |  |
| 8 | GNRHR2 |  |
| 9 | DR1 |  |
| 10 | DOCK11 |  |
| 12 | FMR1 |  |
| 13 | ACAP2 |  |
| 14 | ZEB1 |  |
| 15 | FLJ32790 |  |
| 16 | LOC100505812 |  |
| 17 | DENND4C |  |
| 18 | PREPL |  |
| 19 | FAM63B |  |
| 20 | LYSMD3 |  |
| 21 | OTTHUMG00000183952 /// RP11-727A23.11 |  |
| 22 | HIPK3 |  |
| 23 | POLR2J4 |  |
| 24 | PHF17 |  |
| 25 | SP3 |  |
| 26 | MRGBP |  |
| 27 | NAP1L1 |  |
| 28 | FAM126A |  |
| 29 | EPS15P1 |  |
| 30 | SMCR8 |  |
| 31 | ZMYM2 |  |
| 32 | EIF1AX |  |
| 33 | TRMT13 |  |
| 34 | TDP2 |  |
| 35 | RICTOR |  |

**Table 2**: Gene Attributions and their evidence.

| Association | Gene | Change in Regulation [[1]](#footnote-1) |  | Gene Significance Supporting Evidence/PMID |
| --- | --- | --- | --- | --- |
| CALCIUM METABOLISM | |  |  |  |  | | --- | --- | --- | --- | | SP3 |  | Involved in Calcium-Sensing Receptor expression | [IL6 upregulates Calcium-Sensing Receptor expression via SP3 and other constructs (PMID: 18348986)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=18348986&dopt=b) | | | | |
| [OTHER] ENDOCRINE | |  |  |  |  | | --- | --- | --- | --- | | GNRHR2 |  | May modulate GnRHR-1 receptor (main Gonadotropin Releasing Hormone receptor) | [PMID: 15761034](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=15761034&dopt=b) (22) | | HLA-DQA1 |  | HLA-DQA1\*0501 as a marker for Grave’s Disease | [PMID: 11272094](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=11272094&dopt=b) (91) | | HLA-DQB1 |  | HLA-DQB1\*0602 offers protection against Grave’s Disease | [PMID: 11272094](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=11272094&dopt=b) (91) | | | | |
| FATIGUE / SLEEP | |  |  |  |  | | --- | --- | --- | --- | | HLA-DQA1 |  | 1. DQA1\*01 is a risk factor for Chronic Fatigue Syndrome 2. DQA1-0102 allele is strongly associated with narcolepsy | 1. [PMID: 16049290](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=16049290&dopt=b)  2. [PMID: 25277311](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=25277311&dopt=b) | | HLA-DQB1 |  | 1. DQB1\*0602 associated with poor sleep 2. HLA-DQB1\*0602 is present in patients with hypersomniac, and is strongly associated with narcolepsy | 1. [Patients with DQB1\*0602 were more fatigued at baseline, and had poorer sleep quality and cognitive performance (PMID: 20975052)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=20975052&dopt=b)  2. [90-100% of narcoleptic patients carry HLA-DQB1\*0602 (PMID: 14769912)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=14769912&dopt=b) | | | | |
| GLUCOSE METABOLISM | |  |  |  |  | | --- | --- | --- | --- | | DENND4C |  | Initiates GLUT4 Transport to plasma in response to insulin | [DENND4C knock-down inhibits GLUT4 translocation (PMID: 21454697)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=21454697&dopt=b) | | HLA-DQA1 |  | Susceptibility/resistance to insulin dependent diabetes mellitus | [Certain alleles confer protection while others confer susceptibility (PMID: 8929711)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=8929711&dopt=b) | | HLA-DQB1 |  | Allele specific associations with diabetes | [DQB1\*0301 has negative association, while DQB1\*0302 is positively associated (PMID: 8929711)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=8929711&dopt=b) | | SP3 |  | 1. Represses GLUT1 expression 2. Sp3 enhances SOCS3 expression (which prevents insulin resistance) | 1. [PMID: 10556032](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=10556032&dopt=b) 2. [Sp3 and SOCS3 (PMID: 15554904)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=15554904&dopt=b) ; [SOCS3 and insulin resistance (PMID: 17295835)](http://www.ncbi.nlm.nih.gov/pubmed/17295835) | | | | |
| INFLAMATION / IMMUNITY | |  |  |  |  | | --- | --- | --- | --- | |  | | | | | RICTOR |  | 1. Regulation of PDGFRbeta signaling 2. Negatively regulates Mast Cell degranulation 3. Required for Neutrophil chemotaxis | 1. [PMID: 17599906](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=17599906&dopt=b) (92)  2. [PMID: 25378594](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=25378594&dopt=b) (93)  3. [RICTOR depletion impairs actin polymerization and PMN directional migration (PMID: 24006489)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=24006489&dopt=b) (94) | | SP3 |  | 1. Inhibits FOXP3 (FOXP3 is involved in T-Regulatory cell development) 2. Allows basal SOD level expression | 1. [PMID: 20462637](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=20462637&dopt=b) 2. [PMID: 15451065](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=15451065&dopt=b) | | TDP2 (aka TTRAP) |  | Inhibits NFkB | [PMID: 10764746](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=10764746&dopt=b) and [PMID: 19757154](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&cmd=search&Dopt=b&term=19757154) | | ZEB1 |  | May repress IL2 production (T cell recruitment) | [PMID: 19181930](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=19181930&dopt=b) , [PMID: 1840704](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=1840704&dopt=b) | | | | |
| LIPID HOMEOSTASIS | |  |  |  |  | | --- | --- | --- | --- | | SP3 |  | 1. Involved in sphingolipid homeostasis 2. May be involved in Human LipoProtein expression | 1. [SP3 promotes Glycolipid Transfer Protein expression (PMID: 20974858)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=20974858&dopt=b) (95) 2. [PMID: 9788252](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=9788252&dopt=b) | | ZEB1 |  | Represses adipose tissue accumulation | [PMID: 20041147](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=20041147&dopt=b) | |  | | | | | | | |
| MITOCHONDRIAL FUNCTION | |  |  |  |  | | --- | --- | --- | --- | | IMMP1L |  | Encodes mitochondrial membrane peptidase | [Processes the mitochondrial protein Diablo/Smac, which induces apoptosis (PMID: 15814844)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=15814844&dopt=b) | | | | |
| MUSCLE HOMEOSTASIS | |  |  |  |  | | --- | --- | --- | --- | | HLA-DQB1 |  | HLA-DQB1\*0401 may contribute to Dermatomyositis / Polymyositis risk | [PMID: 12170471](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=12170471&dopt=b) | | PREPL |  | Deletion is implicated in hypotonia-cystinuria syndrome | [PMID: 16385448](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=16385448&dopt=b) | | RICTOR |  | 1. Mitochondria is implicated in the RICTOR response 2. RICTOR expression increases after strength training | 1. [PMID: 21170086](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=21170086&dopt=b)  2. [PMID: 19422645](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=19422645&dopt=b) | | SP3 |  | 1. Downregulates myosin chain expression during muscle inactivity 2. Required for Dystrophin (Dp71) expression 3. Represses GLUT1 expression in muscle (and non-muscle) cells | 1. [PMID: 15572681](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=15572681&dopt=b) 2. [PMID: 15550398](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=15550398&dopt=b) 3. [PMID: 10556032](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=10556032&dopt=b) | | | | |
| NEURONAL HEALTH | |  |  |  |  | | --- | --- | --- | --- | | FAM126A |  | Possible role with CNS/PNS myelination/leukodystrophy | [Mutation causes hypomyelination and congenital cataract disease (PMID: 23998934)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=23998934&dopt=b) , also [PMID: 24417797](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=24417797&dopt=b) | | HLA-DQA1 |  | Specific alleles associated with Multiple Sclerosis, and Myasthenia Gravis | [Multiple Sclerosis (PMID: 17489940)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=17489940&dopt=b), and [Myasthenia Gravis (PMID: 21917268)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=21917268&dopt=b) | | HLA-DQB1 |  | Specific alleles associated with Parkinson’s disease | [Parkinson’s Disease (PMID: 12944708)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=12944708&dopt=b) | | RICTOR |  | 1. Required to Ubiquitinate SGK1 (SGK1 is involved in neurogenesis and psychological wellbeing) 2. RICTOR (mTORC2) activates Akt to protect cell from oxidative stress and toxic agents (but in the context of Parkinson’s Disease) | 1. [Loss of RICTOR/Cullin leads to increase in SGK1 (PMID: 20832730)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=20832730&dopt=b)  and [On SGK1 and neurogenesis and depression/stress (PMID: 23650397)](http://www.ncbi.nlm.nih.gov/pubmed/23650397)  2. [RICTOR and Akt in context of Parkinson’s disease (PMID: 21177249)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=21177249&dopt=b) (96) | | SP3 |  | 1. Promotes neuronal survival in response to oxidative stress 2. Regulates expression of a neuronal nicotinic Ach receptor 3. May decrease expression of Mu Opioid Receptor 4. Modulate DA receptor activation 5. Required for Dystrophin (Dp71) expression | 1. [PMID: 12736330](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=12736330&dopt=b) and [PMID: 17012241](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&cmd=search&Dopt=b&term=17012241) 2. [PMID: 9325332](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=9325332&dopt=b) 3. [SP3 works synergistically with NRSF to repress Mu Opioid Receptor (MOR) expression (PMID: 17130167)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=17130167&dopt=b) 4. [(PMID: 15816870)](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&cmd=search&Dopt=b&term=15816870) and [(PMID: 10984499)](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&cmd=search&Dopt=b&term=10984499) 5. [PMID: 15550398](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=15550398&dopt=b) | | TUBB2A |  | Differentially expressed in FrontoTemporal Lobar Degeneration | [Differentially expressed in FrontoTemporal Lobar Degeneration compared to control (PMID: 22360420)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=22360420&dopt=b) | | TUBB3 |  | A tubulin involved in neurogenesis/axonal guidance | * [Phosphorylated beta III tubulin is enriched in neuritis, and increases with increasing duration of Nerve Growth Factor (PMID: 8951104)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=8951104&dopt=b) * [Reduced in Down Syndrome, and dys-regulated in other neurological disorders (PMID: 15068247)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=15068247&dopt=b) * [TUBB3 mutations results in cortical development and migration defects (PMID: 20829227)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=20829227&dopt=b) * [Review of brain tumors and TUBB3](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=14736079&dopt=b) (97) | | ZEB1 |  | 1. Protective response in neurons undergoing ischemia 2. ZEB1 Upregulation increases TUBB3 / TUBB1 expression | 1. [PMID: 19194497](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=19194497&dopt=b) 2. [ZEB1 and TUBB 3 in breast cancer (PMID: 23869586)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=23869586&dopt=b) | | | | |
| PROSTATE CANCER | |  |  |  |  | | --- | --- | --- | --- | | GNRHR2 |  | GNRHR2 activation reduces prostate cancer cell growth | [GNRHR2 activated GNRHR1, thereby causing an antiproliferative effect on prostate cancer cells (PMID: 19190109)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=19190109&dopt=b) | | HIPK3 |  | 1. Increases androgen receptor mediated transcription  2. Possible anti-apoptotic role | 1. [ANPK activates Androgen Receptor (PMID: 9725910)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=9725910&dopt=b) 2. [While cell death is not affected, HIPK3 overexpression inhibits FAS mediated Jun kinase activation (PMID: 11034606)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=11034606&dopt=b) | | RICTOR |  | A part of mTORC2, which promotes Androgen Dependent prostate cancer cell survival | [PMID: 18776922](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=18776922&dopt=b) | | SP3 |  | 1. Possible predictor of prostate cancer 2. Increase PSA expression | 1. [SP3 when used in conjunction with Gleason scoring predicted prostate cancer recurrence (PMID: 23028678)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=23028678&dopt=b)  2. [(PMID: 15708372)](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed&cmd=search&Dopt=b&term=15708372) | | TUBB3 |  | Associated with treatment resistant prostate cancer | * [Elevated BIII-Tubulin expression is associated with prostate tumor aggressiveness, but was not associated with lower patient survival (PMID: 21045157)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=21045157&dopt=b)   [TUBBIII expression associated with castration-resistant cancer, elevated TUBBIII associated with Chemotherapy Resistance in prostate cancer (PMID: 9473684)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=9473684&dopt=b) | | ZEB1 |  | Promotes Epithelial to Mesenchymal Transition (EMT) and migration in prostate cancer model | * On EMT: [PMID: 22249256](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=22249256&dopt=b) , [PMID: 19225155](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=19225155&dopt=b) and [PMID: 21747944](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=21747944&dopt=b) * [On migration (PMID: 20729552)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=20729552&dopt=b) | | ZMYM2 |  | May be implicated in prostate cancer | [SUMOylation of Splicesome factors in prostate cancer (PMID: 25027693)](http://www.ncbi.nlm.nih.gov/pubmed?cmd=search&term=25027693&dopt=b) (98) | | | | |

**FIGURE LEGENDS:**

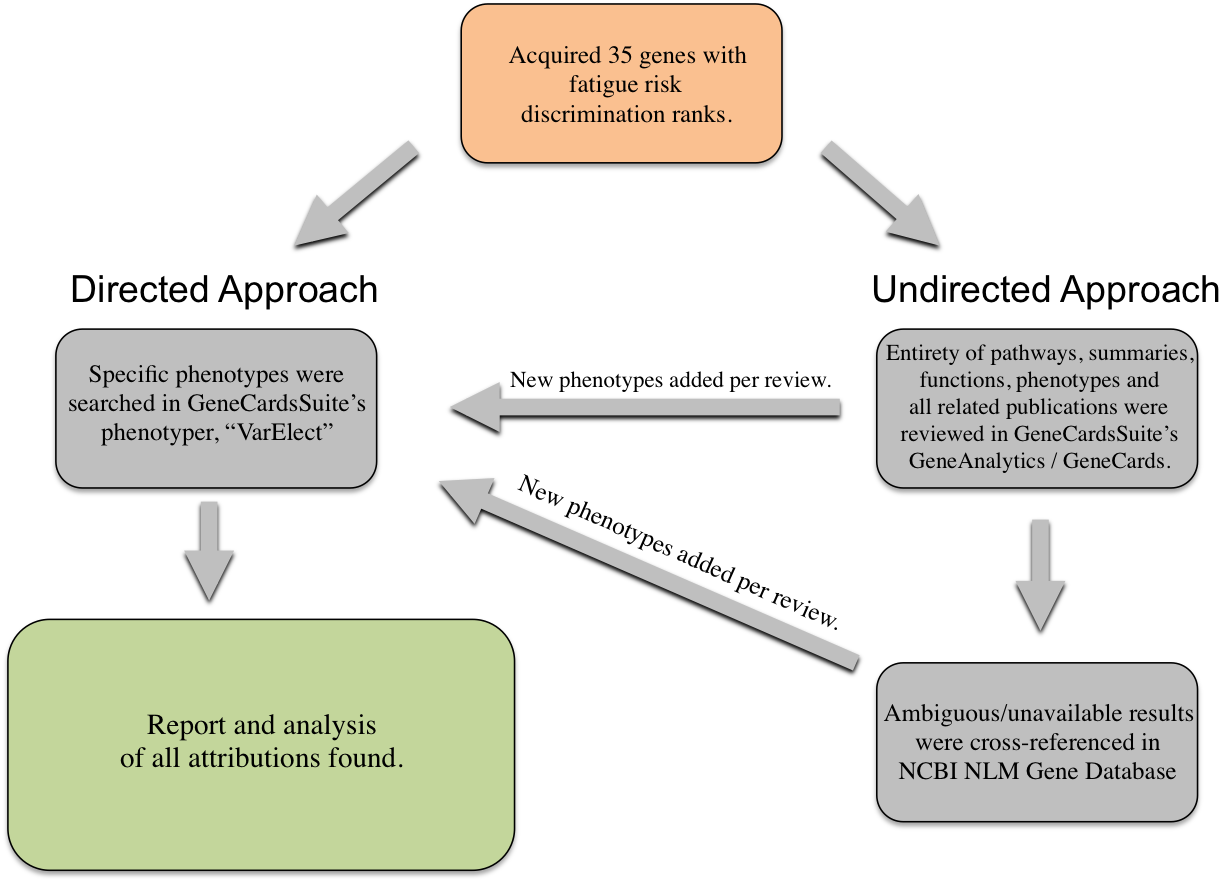
**Figure 1**: The process of studying the RIF-associated genes to discover possible attributions.

**Figure 2:** Venn Diagram of poorly studied genes (studied in 10 or less publications) and unphenotyped genes (reported as “no phenotype” or “inconclusive phenotype” by GeneAnalytics).

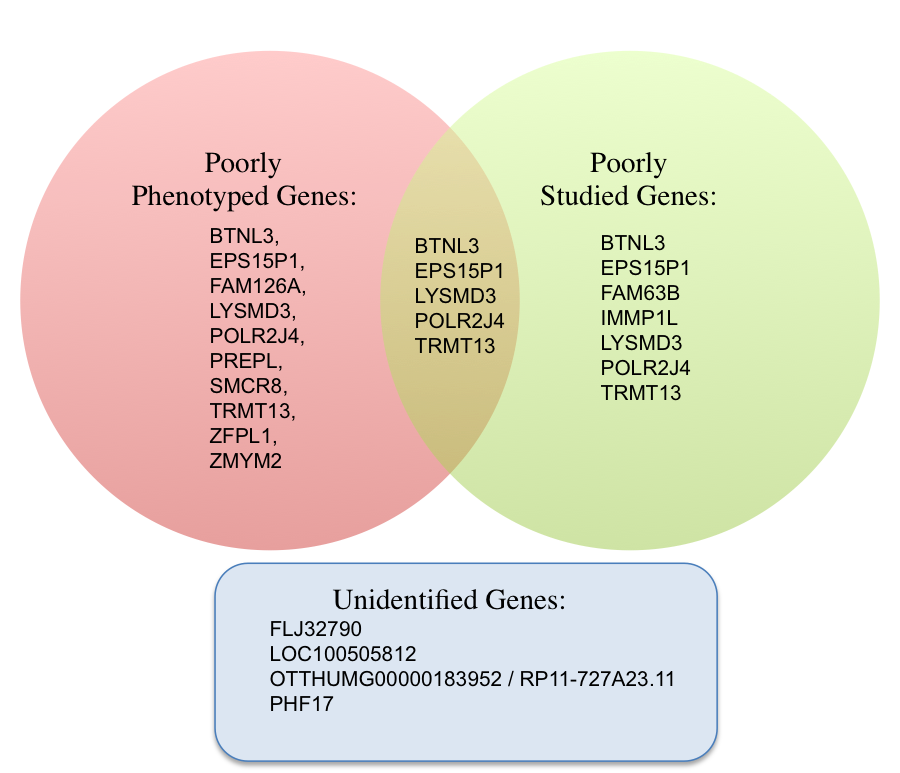
**Figure 3:** Venn Diagram of genetic predisposition for and activated fatigue genes due to radiation therapy.

**FIGURES:**

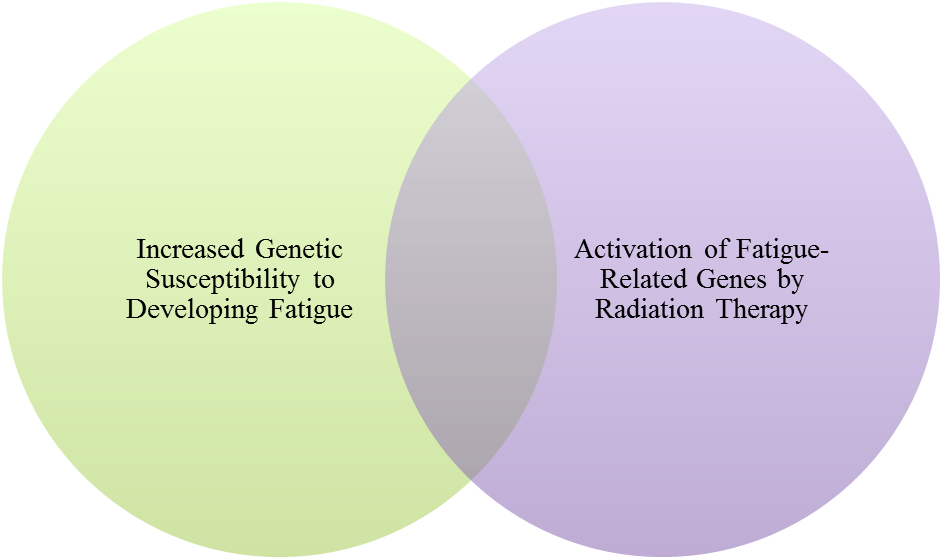
**Figure 1**:



**Figure 2:**

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**Figure 3:**



Radiation

Induced

Fatigue in

Prostate

Cancer

Patients

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1. Comparison of Low Fatigue (LF) vs. High Fatigue (HF) patients: Green signifies that gene is up-regulated in HF patients; red signifies that gene is down-regulated in HF patients. [↑](#footnote-ref-1)