Utilization of Whole-Genome Sequencing as an Advanced Detection Tool for Cutaneous T-Cell Lymphoma By Kathya Sareddy

Abstract

Cutaneous T-cell lymphoma (CTCL) is a slow-developing cancer that starts in T-cells and invades the skin. It is an extremely challenging cancer to detect or diagnose, as cancer cells do not appear in lymph nodes until Stage 4, and lymph nodes do not enlarge until Stage 3 or 4, allowing the disease to potentially progress beyond the point of effective treatment. Current diagnostic techniques have traditionally relied on biopsies and protein tests. Advances in genetic testing technology have the potential to precisely diagnose CTCL. Previous research on CTCL has linked mutations in many genes, particularly those associated with the immune system pathways, JAK-STAT and NF-kB. I hypothesize that those pathways get affected, leading to a dysregulated cell cycle, which in turn causes cancer. We will explore how whole genome and single locus sequencing can serve as a diagnostic tool for CTCL. Applying genetic testing to diagnose CTCL could lead to earlier detection, increased treatment success rates, and serve to identify targets for precision medicine.

Summary

We explore how whole genome and single locus sequencing can serve as a diagnostic tool for CTCL, a cancer that is hard to detect until later stages.

Introduction

Cutaneous T-cell lymphoma (CTCL) is a type of non-Hodgkin's lymphoma that affects T-cells, which subsequently infiltrate the skin (Bagherani et. al, 2016). This is important, as this is a different mechanism than other skin cancers like melanoma. There are two main forms of CTCL, mycosis fungoides, which is the most common at 60% of cases, and Sézary syndrome, which comprises <5% of cases (Hague et. al, 2022). The main symptoms of mycosis fungoides are dry, red, scaly patches of skin. In later stages, tumors develop, metastasize, and cancer cells are found in the skin. In Sézary syndrome, a large rash covers most of the body and a low amount of cancerous Sézary cells develop in the blood. In the last stages, the Sézary cell count is high and the lymph nodes become enlarged. The cancer is also more likely to spread to organs like the liver or spleen (Markman, 2022; Healy, 2024).

In both cases, the cancer originally presents as common dermatological conditions such as eczema or psoriasis. Even in later stages, the cells themselves do not look too abnormal (Healy, 2024). Because of this, early testing for CTCL is difficult and inaccurate. Our current diagnostic is a skin biopsy, which can delay the discovery of the cancer until later stages (Markman, 2022). Due to the relative rarity of CTCL (accounting for only 4% of non-Hodgkin's lymphoma cases), there has been limited development in treatment options for this cancer (Wiese et al., 2023). However, the survival rates and median overall survival from earlier stages (70-88% and 21.5-35.5 years, respectively) are much higher compared to later stages (15-18%

and 1.4-3.8 years) (Hristov et al., 2023). Diagnosing this cancer earlier would lead to better treatment success rates, a crucial need for the 12.4 million patients diagnosed in the United States annually (Wiese et al., 2023).

Some risk factors of CTCL are immune system weakening through AIDS/HIV or drug suppressants, exposure to other chemicals, and bacterial or viral infections (Markman, 2022). In a study published on multiple pairs of twins to explore the heredity of CTCL, it was found that the female to male ratio is equal to 1:1.8 and CTCL commonly developed around the average age of 53 (Odum et. al, 2017). African Americans are also twice more at risk than other racial groups (Histrov et al., 2023). Treatment for CTCL can include chemotherapy, radiation therapy, photodynamic therapy, immune therapy, targeted therapy, and other medicines. Current diagnostic and staging procedures are a complete physical exam, multiple biopsies, blood tests, and looking through medical history (Markman, 2022). Most commonly, a complete blood count is performed. CTCL patients are more likely to have elevated white blood counts (Brown et al., 2024). Sézary blood cells can be specifically tested for with flow cytometry, as their shape is abnormal due to the cell's nucleus and they are larger than a regular blood cell (**Fig. 1**) (Naiem et al., 2013).

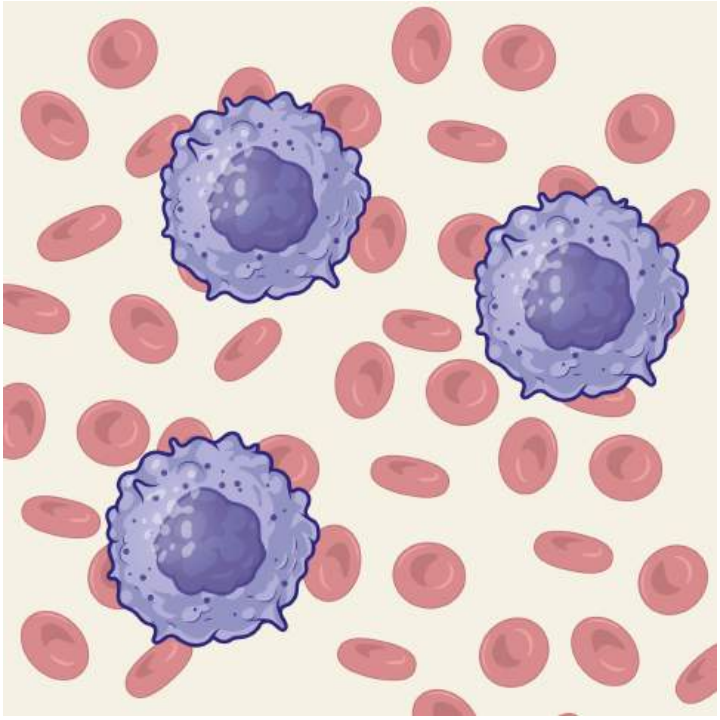

Figure 1. Sézary cells in the bloodstream
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Serum protein electrophoresis is performed to test for abnormal protein levels, which are common in lymphomas. If protein levels are abnormal, a bone marrow biopsy is recommended (Shinohara, 2024). Skin biopsies are done to test for cancerous T-lymphocyte cells. Lymph node biopsies are done to confirm the diagnosis and spread of the cancer (Horwitz et al., 2019). These

are not as effective, because these biopsies usually don't show cancer cells (Ludmann et al., 2023). To find the cancer in the early stages, we need better diagnostic tests.

Genetic testing is a great diagnostic tool that is being used in the detection of many diseases and conditions such as Down syndrome, trisomy 18, trisomy 13, neural tube defects, cystic fibrosis, sickle cell anemia, Fragile X syndrome, and Tay-Sachs (Griffin et al., 2023). New research has shown that genetic testing can help detect certain cancers, such as breast and colon cancers (Winstead, 2023). The development of new genetic testing technologies and recent discoveries in the nature of the disease could make CTCL a candidate for genetic diagnostics.

Genetic Testing Methodologies

A classic method of genetic testing that has been used since the 1840s is cytogenetics. Cytogenetics is the study of chromosomes, their behavior during cell reproduction (mitosis and meiosis), their influence on phenotypes, and their structural changes. Some early discoveries in cytogenetics are the chromosome theory of inheritance, the identification of 46 chromosomes in humans, the discovery of the X and Y chromosomes, and karyotypes. The idea of clinical cytogenetics was made in the 20th century when Jerome Lejeune proved that chromosome abnormalities affect the phenotype (Mathew et al., 2024). Cytogenetic testing originally started with banding techniques, such as quinacrine banding (Q-banding), constitutive heterochromatin banding (C-banding), reverse banding (R-banding), nucleolar organizing regions banding (NOR-banding), and Giemsa-banding (G-banding). The Q-banding technique treats the chromosome with quinacrine to create a banding pattern of alternating dull and bright regions. The highly fluorescent areas are filled with adenine and thymine (Burnett et al., 2006). A big milestone for cytogenetics was fluorescent in-situ hybridization (FISH), which is a technique of mixing fluorescent probes to detect certain nucleic acid sequences, and it is still commonly used today. Another common technique we progressed to is molecular array comparative genomic hybridization or CGH, which compares DNA strands and detects chromosomal changes like deletions, duplications, and amplifications (Kannan et al., 2009; Moore et al., 2021). Some diseases discovered through cytogenetics are Down syndrome (trisomy 21) and Edwards syndrome (trisomy 18) (Ataman et al., 2012; Balasundaram et. al, 2023). Due to the progression of genetics in the past decades, there are currently many different methods for the diagnosis of genetic diseases, but the main categories are biochemical and genetic testing.

Rather than identifying DNA mutations, biochemical testing is used to identify defects in proteins and other molecules. Some examples of biochemical tests are antibody-antigen testing, total protein level tests, high-performance liquid chromatography (HPLC), and mass spectrometry. Antigens are anything that triggers an immune response, and looking for those through tests can help see if the immune system is stimulated and if an antigen is active. Antibody tests look for past times the immune system has been stimulated, and those tests are most commonly used for detecting past infections or diseases. These types of tests are used to diagnose respiratory infections such as influenza, respiratory syncytial virus (RSV), and coronavirus disease (COVID-19), among many other diseases. Fluid samples are typically used

and mixed with a reagent to get the results in 15-30 minutes (Zimlich et al., 2024). In total protein tests, blood samples are collected and the serum is isolated from the red and white blood cells. Then, protein electrophoresis is performed on the serum to separate the proteins by size. Total protein tests can detect many things, such as kidney damage, liver disease, malnutrition, edema, autoimmune disease, cirrhosis, and some cancers like multiple myeloma (Martel et al., 2018). High-performance liquid chromatography (HPLC) is a way of separating liquid samples. The sample is pushed by a high-pressure pump through a column. The different solubilities of each component of the sample lead to different velocities at which they move through the column, leading to separation. The results are measured by a detector connected to the column and the data is input to make a chromatogram (Bower, 2024). HPLC is primarily used for testing concentrations in medicine and can detect abnormal hemoglobin variants like sickle cell or thalassemia (George et al., 2001). Mass spectrometry converts molecules into ions and those ions are then sorted by their mass-to-charge ratio by magnetic and electric field manipulation. Those ratios are measured with a detector and the results are on a mass spectrum chart. Mass spectrometry is commonly used to diagnose diseases through biomarkers, which are molecules found to be associated with certain pathways, cellular processes, etc. (Garg et al., 2023). Overall, these and other biochemical tests are very fundamental for diagnosis and are used for clinical applications. The higher level ones such as HPLC and mass spectrometry are less commonly used and more expensive but are still essential in pharmaceutical uses and drug testing.

The main kinds of genetic testing are Sanger sequencing and next-generation sequencing (NGS). These types of tests are based on polymerase-chain reactions (PCR) and how it can target sections of DNA, even though the whole genome is large. PCR has three main steps: denaturing, annealing, and elongation. First, the DNA's double helix structure denatures due to heat. Then, designed DNA primers attach to a complementary section of the parent strand DNA through hybridization (annealing). Lastly, the targeted DNA sequence is duplicated repeatedly with the help of the primers, nucleotides, and DNA polymerase (which works from the 5' end to the 3' end), to create an elongated version of the targeted DNA (Smith, 2024).

The idea of targeting certain genes, which is evident in PCR, is used in single-gene sequencing, specifically Sanger sequencing. To determine the position of specific nucleotides in a sequence, Sanger sequencing employs dideoxynucleotide triphosphates (ddNTPs).The difference between ddNTPs and regular DNA nucleotides is the missing oxygen on the 3' end, preventing the phosphodiester bond from forming. This stops the strand of DNA from building any further. There are four separate ddNTPs, one for each of the four different nitrogenous bases (nucleotides), and they are marked with fluorescent proteins. The first part of the process of Sanger sequencing is a PCR, denaturing the double helix, and then cooling it back down, and adding nucleotides with primers and DNA polymerase. The fluorescent ddNTPs are also incorporated with the primers and added by the DNA polymerase with their complementary bases, which then prevents elongation by DNA polymerase. This creates DNA fragments of different lengths, which all have a fluorescent ddNTP at the end. Then, the fragments can be separated by gel electrophoresis, and a laser excites the fluorophores in the ddNTPs. The

smallest fragment is simply the 5’ end of the original DNA strand. The DNA sequence is determined by organizing the fragments from the smallest fragment (5’ end) to the longest fragment (3’ end) (**Figure 2**) (Heather et al., 2016). Sanger sequencing is considered the most accurate type of DNA sequencing to date, with a high success rate of 99.99% (Shendure et al., 2008).

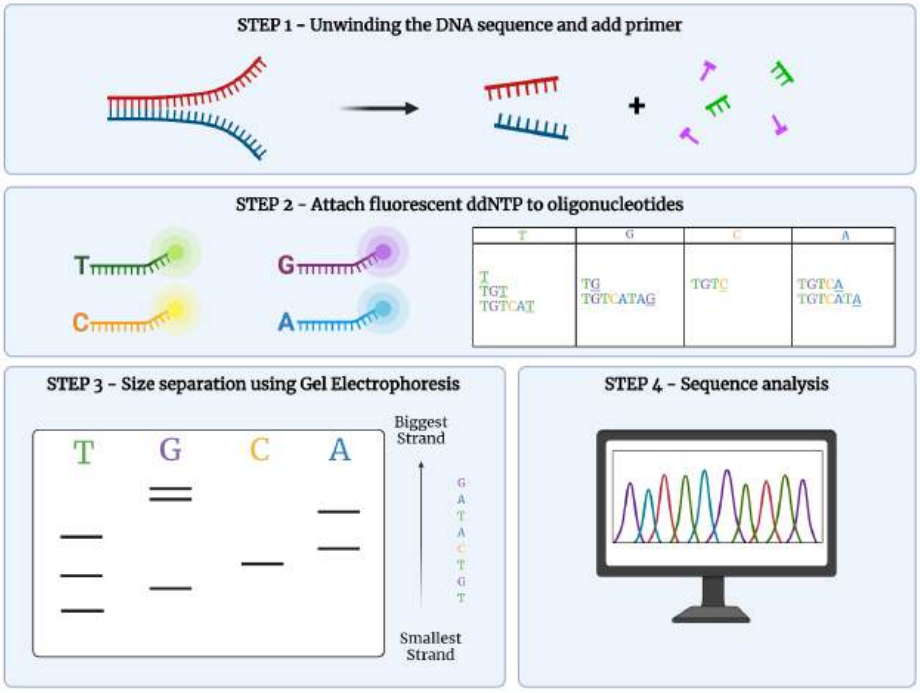

Figure 2. Sanger sequencing process
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Sanger sequencing is mainly used for figuring out a single gene, or single locus sequencing, but is also used for diagnosing diseases. It can test for hereditary conditions, specifically autosomal recessive conditions (i.e. cystic fibrosis). It can also act as a foresight for testing for specific genes, for example, breast cancer and the *BRCA1* gene variant. Currently, some machines conduct Sanger sequencing and read the bands from the gel electrophoresis, making the process faster. The main limitation of Sanger sequencing is sequencing multiple genes or many samples. It is not cost-efficient and it has a limited input of DNA. To solve these limitations, researchers developed new technologies collectively labeled next-generation sequencing (Frost et al., 2022).

Next-generation sequencing (NGS) is a technique that enables the simultaneous analysis of millions of base pairs and DNA strands. NGS has many variations that use different methods for library prep, PCR amplification, and base reading. However, the main method for NGS is fragmenting the DNA, then marking those fragments with some sort of indicator (library prep), putting those fragments through an NGS sequencer (sequencing), and then analyzing and comparing the given data to a reference genome (Qin, 2019). There are two main kinds of NGS that are typically used in clinical testing: whole genome sequencing (WGS) and exon

sequencing. WGS analyzes all of the patient's DNA to determine the entire genome sequence. This means that WGS can detect any mutations in the DNA, which is why it is currently used to diagnose genetic disorders and developmental delays. It's also used for newborn screenings and cancer detections and is a breakthrough for personalized medicine (Brlek et al., 2024). Exon sequencing analyzes just the coding regions (exons), specific sections of DNA that are transcribed to RNA, and then translated to proteins. Only 1% of the human genome is exons, and exon sequencing is a much more efficient way to identify disease-causing mutations, as exons are the only pieces of DNA that produce primary proteins (Brlek et al., 2024). Exon sequencing has been used in the detection of diseases such as autism, epilepsy, brain malformations, congenital heart disease, and neurodevelopmental disabilities, and has identified new disease pathways (Retterer et al., 2016). Overall, NGS can pinpoint specific mutations that can lead to the discovery of a disease-causing mutation.

Analogously, NGS could be used for CTCL, as much research points towards multiple gene mutations being linked to causing CTCL. Numerous studies show that CTCL could be a cancer that is caused by genetic mutations, which can be identified easily with NGS. Biochemical tests can also be applied to test for certain proteins in patients and see if it is linked to the genes mutated in NGS. NGS is a good alternative for current diagnostics and could solve the problem we face when testing for CTCL.

Current Understanding of the Genetic Causes of CTCL (Results)

Genetic diseases are currently identified through sequencing because there is typically one gene that leads to a direct association with the disease.An example of this is cystic fibrosis, where a mutation in the CFTR gene leads to the dysfunctional transport of salt and water across epithelial cells. This creates the mucus around the lungs, which then leads to cystic fibrosis (Csanády et. al, 2018). There are direct-to-consumer (DTC) tests for diseases that have clear markers. However, using genetic testing or DTC tests for cancers to pinpoint the specific gene(s) with cancerous mutations is a challenge. For CTCL, this remains an issue as studies have found a varied number of mutations linked with this cancer. Using NGS to identify a panel of genetic mutations is the best way to figure out each of these mutations and compare them to multiple patients, leading to an effective diagnosis of CTCL.

The majority of these genes are associated with T-cell activation and apoptosis, chromatin remodeling, DNA damage response, and NFκB and JAK/STAT signaling pathways (Choi et al., 2015; Litvinov et al., 2017; Argyropoulos et al., 2020; Lai et al., 2021; Zhang et al., 2021; Park et al., 2021; Motamedi et al., 2021; Song et al., 2022; Tensen et al., 2022; Ren et al., 2023). One study found seventeen genes linked with the cancer through whole exon sequencing (WES), whole genome sequencing (WGS), and RNA sequencing on forty CTCL patients, all of them in late stages (IVA1 - IVB). Scientists have hypothesized that cancer targets the immune system pathways NF-κB and JAK-STAT along with multiple tumor-suppressing mechanisms (Choi et al., 2015). A different study found eighty-six putative genes by incorporating SSNVs (somatic single nucleotide variations), SCNVs (somatic copy number variation), and structural variant

data (Park et al., 2021). Another study found a hundred and fifty recurrent genes and identified fifteen genes associated with the progression of mycosis fungoides by using data from other publications. Those genes are correlated with cell proliferation, immune checkpoints, apoptosis, and immune response (Motamedi et al., 2021). In Sézary syndrome, it is hypothesized that five major processes are affected: cell cycle regulation, MAP-kinase signaling, T-cell receptor/NF-κB signaling, JAK-STAT signaling, and chromatin modification. The data is from multiple studies and research that took pools of patients–one study had as many as 220 participants– and used NGS to identify common mutations. Most mutations, including novel ones, support the idea that those five processes are the ones being affected (Tensen et. al, 2022). Here are the common genes mutated in CTCL (**Table 1**).

Gene Function Groups/Association	Gene Names	Sources
Oncogenes	*TOX, BLK, DEPDC, MYC, PLK1, GTSE1*	Choi et al., 2015; Litvinov et al., 2017; Lai et al., 2021; Motamedi et al., 2021; Park et al., 2021; Tensen et al., 2022; Song et al., 2022; Ren et al., 2023
Tumor Suppressors	*RMB5, TSC1, TP53,*	Choi et al., 2015; Litvinov et al., 2017; Argyropoulos et al., 2020; Motamedi et al., 2021; Park et al., 2021; Tensen et al., 2022; Song et al., 2022; Ren et al., 2023
Chromosome Instability/Remodeling	*BCOR, KDM6A, SMARCB1, TRRAP, DNMT3A, ATM*	Choi et al., 2015; Litvinov et al., 2017; Argyropoulos et al., 2020; Lai et al., 2021; Zhang et al., 2021; Park et al., 2021; Tensen et al., 2022; Song et al., 2022; Ren et al., 2023
Apoptosis	*BIRC5, TRAF1, IFI6, TNFSF11, MELK, BMP2K, HN1, TGFB1/TGFBR1, IL15, STAT1, NPHP3, FAS, PLCG1, TNFAIP3*	Choi et al., 2015; Litvinov et al., 2017; Argyropoulos et al., 2020; Lai et al., 2021; Zhang et al., 2021; Motamedi et al., 2021; Park et al., 2021; Tensen et al., 2022; Song et al., 2022; Ren et al, 2023
NF-κB/JAK-STAT/MAP-kinase signaling	*STAT5B, NFKB2, STAT1, MAP4K3-FIGLA, MAP2K1, NF1, PRKCB, CSNKA1, JAK1, JAK3, STAT3*	Choi et al., 2015; Litvinov et al., 2017; Argyropoulos et al., 2020; Lai et al., 2021; Zhang et al., 2021; Motamedi et al., 2021; Park et al., 2021; Tensen et al., 2022; Song et al., 2022; Ren et al., 2023
Activation Markers	*SELL, CCR6, ITGB1, BRD2, TNFRSF25, RELN, TSPAN2, TNFRSF4, NR4A2*	Litvinov et al., 2017; Argyropoulos et al., 2020; Lai et al., 2021; Zhang et al., 2021; Motamedi et al., 2021; Ren et al., 2023
Immune Markers	*TOX, TIGIT, CTLA-4, PDCD1, LAG3*	Choi et al., 2015; Litvinov et al., 2017; Lai et al., 2021; Motamedi et al., 2021; Park et al., 2021; Tensen et al., 2022; Song et al., 2022; Ren et al., 2023

Table 1. Potential gene mutations in CTCL

However, scientists do not know exactly how everything is connected, especially because there are so many different results, leading to confusion and gaps. There is no clear genetic marker or indication for CTCL and the direct mechanisms of the cancer yet. However, there are many ideas based on the current data given.

Hypothesis: Mutations in critical immune pathways trigger dysregulation of the cell cycle

The typical formation of cancer is when a cell's DNA gets mutated such that the cells go through mitosis much faster. This cell with the mutated DNA then gets selected for in the body, as rapid duplication leads to more chances of survival, invasion, and metastasis. This would eventually build a tumor, and the longer the tumor remains in the body, the more malignant it could become, leading to cancer (Cooper et al., 2020). This suggests that in the formation of cancer, the cell cycle checkpoints is a vital aspect, because the cancer cells bypass them to grow.

My hypothesis states that damage to immune system pathways subsequently affects cell cycle checkpoints, ultimately leading to the development of CTCL. The data suggests that JAK-STAT, NF-κB, and MAP-kinase signaling are affected. JAK-STAT and NF-κB are innate immune systems or the first thing that defend against pathogens, and MAP-kinase signaling determines cell proliferation, differentiation, and death (Alberts et al., 2002; Morrison, 2012). So if these three particular pathways become damaged, antigens might not be fought against and cells could die quickly. Cancer cells as such can also grow rapidly, due to the lack of cell differentiation. This affects the cell cycles and their checkpoints. During the restriction point, apoptosis won't be done to damaged cells, which is why genes like *FAS, PLCG1, TNFAIP3*, and many more are also affected (Manso, 2014; Yenamandra et al., 2022). The data also supports the possibility that affected S-phase genes could result in DNA damage and improper chromatin remodeling. For example, the data suggests that there are mutations in the *DNMT3A* and *ATM* genes. *DNMT3A* plays an integral role in DNA methylation, which determines which gene segments are carried out or silenced (Brunetti et al., 2017). If there is a mutation in this gene, it could result in extra proteins and a lack of necessary proteins, indicating damaged DNA. *ATM* helps with the development of the immune system, damaged DNA detection, and DNA break and repair (Lee et al., 2021). *ATM* mutations could cause damaged DNA to pass through cell checkpoints and inhibit the immune system pathways. Moreover, our body cannot tell apart cells with damaged DNA due to the damaged MAP-kinase signaling pathway.

However, this is simply a hypothesis. We currently don't have clear genes associated with CTCL or indications of the mechanism of the cancer, which leads to a gap. One way to advance the understanding is to use NGS to identify or pinpoint common mutations among a diverse pool of participants. This could lead to a list of common mutations, which leads to a clear diagnosis and genetic markers for the disease. We would also get a better understanding of the cellular processes involved which can inform future scientists and experiments, leading to advanced treatment.

Future Applications of Genetic Testing for CTCL (Discussion)

Due to the complicated amount of gene mutations in CTCL, WGS is the best type of genetic diagnostic tool we can use. Some of these mutations might not be in the exons, which means that exon sequencing isn't specific enough. WGS technology is also getting more and more affordable and common, so this experiment can be performed in a few years. First, we would have to get a decently diverse and large pool of participants who do not have CTCL and compare groups that are more at risk for CTCL than others. Most studies picked out genomes at random, therefore not giving an insight as to why certain groups are more at risk. Picking out specific groups of people who are less and more at risk helps narrow down the many mutations that have been linked with the disease. Given that African American males are at the highest risk for developing CTCL (Markman, 2022), we could compare potential genetic links to CTCL across different genetic ancestries. We would also get different CTCL patients at different stages of the cancer to participate, so that we could see the progression of the cancer, what genes get affected in different stages, and how they show. Most studies take CTCL patients in similar stages, but taking a variety of stages can help show how the cancer cells can accumulate mutations (similar number of people in different stages). We would then compare the genomes to patients at-risk for CTCL and of control patients to identify characteristics or mutations associated with CTCL. This could be accomplished through an analysis like a genome-wide association study (GWAS). We would take samples of the skin, lymph nodes, bone marrow, and the blood, as these are the areas that are most affected by the cancer and are typically biopsied on. Each group would have about fifty people, so that you would see common mutations. This would ensure that other mutations evident in one specific person do not influence the overall data. By comparing common genes from each group, we would be able to figure out which exact genes are being affected in the cancer. This would then lead to clear genetic markers of the cancer, which becomes an effective diagnosis. Clear genetic markers also lead to a better understanding of the mechanisms of the cancer, which then leads to more advanced treatment for earlier stages.

Conclusion

CTCL is an extremely hard cancer to diagnose due to the fact that it presents itself like other skin conditions and cancer cells do not show in the biopsies until late stages, if at all. This creates a huge problem which could be solved with genetic testing. Out of all genetic testing methods, NGS would be a great tool to diagnose CTCL as it can detect exact mutations and it is cost efficient compared to other methods. However, CTCL has multiple genes associated with it, not just one, so it would be hard to find a clear genetic marker. So far, the data suggests that the cell cycle, innate immune systems (JAK-STAT and NFκB), chromatin remodeling, and tumor suppressants are targeted in the cancer. My hypothesis suggested immune system damage and improper cell signaling (MAP-kinase pathway) leads to cell cycle dysregulation. This then leads to cells being unable to perform apoptosis, leading to damaged DNA and cells staying alive in the body, which would ultimately form cancer cells. However, this is just a hypothesis and there is no elucidated mechanism that is associated directly with the cancer. To find a direct correlation

between specific genes and the cancer, I designed an experiment that involved comparing genomes of CTCL patients at different stages of the cancer, “normal” genomes, and genomes that were from more at-risk groups for the cancer. This would show the clear progression of the cancer and lead to a better understanding of CTCL mechanisms.

There are a few limitations to this experiment. The first is the magnitude of this experiment. This is due to the fact that there are 8 specific stages for this cancer (IA - IVB), and then considering the more at-risk and less at-risk groups would lead to around needing at least 600 participants alone for the experiment. Then we would need a big group of scientists to analyze the data, collect samples, etc. Not only is it hard to make an experiment this huge, but it is also hard to get enough people that meet the specific criteria of each group. Another limitation is the cost due to the size of the experiment. WGS technology is typically used for 5-10 genomes. It would be extremely expensive to run 600 genomes through WGS technology. Even though WGS technology costs have decreased dramatically in recent years, it would still cost about $1,000 per test, leading to $600,000 in costs for tests alone (Wetterstrand, 2021). You would also have to get scientists who are willing to work on huge experiments like this, which then again, would become costly very quickly. This would require funding from a government agency, private company, or a research foundation. This designed experiment would be different than what’s currently available for genetic testing, meaning that the patient could be ineligible for insurance coverage for the tests if not for the experiment. Instead, they would be enrolled in this study. If we do find clear indications of the disease through this experiment, then there could be potential FDA-approved DTC tests on the market. Because DTC tests have become very popular in the last decade, having them on the market increases the accessibility of the diagnosis.

CTCL has a survival rate as low as 15% when it has advanced to later stages, but as high as 88% when detected during early stages (Hristov et al., 2023). Developing the process to identify genetic testing markers for CTCL has the power to elucidate new oncogenes, which could impact more than just CTCL patients. Cancer is one of the most elusive, but common diseases in the world. We need to take dramatic, direct steps to understand the development, rapidly diagnose, and improve the treatment of cancer. By using CTCL as a model disease that has been difficult to diagnose, we can apply what we learn to other cancers. Most importantly, developing early detection methods could dramatically improve the lives of the millions of people diagnosed with CTCL each year.

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