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Executing and Teaching Science--the Breast Cancer Genetics and Technology-Rich Curriculum Professional Development Studies of a Science Educator

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EXECUTING AND TEACHING SCIENCE—THE BREAST CANCER GENETICS AND TECHNOLOGY-RICH CURRICULUM PROFESSIONAL DEVELOPMENT STUDIES OF A SCIENCE EDUCATOR

by

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DEDICATION

This manuscript is dedicated to the Creator, my ancestors, my angels, my teachers, my biological and spiritual parents and family, and my friends. There is no part of this experience which has culminated into this document that would have been possible without your presence in my life and prayers on my behalf. At times, the inner me (enemy) lost faith, sight of the vision, and purpose. Still you never let me give up or give in to defeat. So to you and for you, I am eternally and unequivocally grateful!

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ABSTRACT

This dissertation presents my explorations in both molecular biology and science education research. In study one, we determined the *ADIPOQ* and *ADIPORI* genotypes of 364 White and 148 Black breast cancer (BrCa) patients and used dominant model univariate logistic regression analyses to determine individual single nucleotide polymorphism (SNP) and haplotype associations with tumor or patient characteristics in a case-case comparison. We found twelve associations between individual SNPs and patient or tumor characteristics that impact BrCa prognosis. For example, the *ADIPOQ* rs1501299 C allele was associated with estrogen receptor positive (ER+) tumors (OR=4.73, p=0.001) among White women >50 years of age at their time of diagnosis. Also, the A allele was more frequent in the Black patient population among whom more aggressive subtypes are common. Similarly, the *ADIPORI* rs12733285 T allele was associated with both PR+ and ER+ tumors. (OR=2.18 p=0.001; OR=1.88 p=0.019, respectively). Our data suggest that several polymorphisms individually or as specific *ADIPOQ* and *ADIPOR1* haplotypes are associated with tumor characteristics that impact prognosis in BrCa patients. Thus, genotyping additional groups of patients for these SNPs could offer insight into the involvement of adiponectin signaling allele variance in BrCa outcomes.

In our second study, we examined 1) how teachers' beliefs about themselves and their students influence the fidelity of implementation of their enactment of a technology-

rich curriculum, and 2) how professional development support during the enactment leads to changes in teacher beliefs. From the analysis of two teachers' experiences through interviews, surveys, journal entries, and video recordings of their enactments, several different themes were identified. For example, teachers' beliefs regarding students' ability to learn using the curriculum influenced the fidelity of implementation and student learning. These observations led to the development of a model of professional development that would promote faithful implementation. This model included teaching of content knowledge, practice with the technology, modeling of classroom management skills, and reflective feedback of enactments in formal and informal environments. The implications of these findings are discussed in relation to professional development programs and curriculum designs seeking to institutionalize the practices of scientists in schools with a high level of fidelity of implementation.

PREFACE

> *Each one, reach one. Each one, teach one. What you do not know, you must learn. Once you have learned, you must teach.*
>
> *– Mantra of the University of South Carolina Association of African American Students*

When I entered my first teaching position as a chemistry teacher on August 7, 2003, I was inexperienced when it came to the culture of science. I had spent five years earning a Bachelor of Science degree in chemistry and Master of Teaching degree in secondary science education. During my four undergraduate years, I attended all of my classes and recitations, studied notes and homework sets, read my text books, went to my professors or teaching assistants for help as needed, and graduated magna cum laude. However, outside of a sixth-month internship in the lab of a local electric company, I had no real bench science expertise. My graduate degree program of study included intensive science teaching methods and practicum courses and had no requirements for content area science or research.

Within five years of teaching three levels of chemistry and two levels of physical science in two public schools, I accepted that something was missing from my practice. I engaged students in hands-on, inquiry activities, and I experienced few disciplinary problems because I respected the students and they respected me in return. Though I

could model for them the best practices of being a good student, I could not, with my lack of bench scientific experiences, provide my students with a true understanding of the nature of science.

While coming to terms with the fact that my undergraduate degree did not prepare me to be a scientist, I was taking an advanced level of biochemistry as a requirement for the Science Education doctoral program. In divine timing with my acceptance about my lack of experience, the professor, Dr. Robert Lawther, informed me that he was impressed by my test scores and class participation and thought I was a good student. He said that I should meet his colleague, Dr. Bert Ely, who had a grant for teachers to complete bench research during the summer, and he arranged a meeting for the next day.

During the meeting with Dr. Ely, I learned about his projects in breast cancer, bacteria, and fish population genetics. We also discussed his research interests in science education and what, at that point in time, was his consideration of becoming the Director for the USC Center for Science Education. I shared with Dr. Ely my desire to challenge myself and further my experience in bench science research. By the end of the meeting, Dr. Ely agreed to allow me to work in his lab over the summer and the course of my professional and personal life changed.

I chose to work with the breast cancer genetics project because of my personal experience with loved ones and the disease. My first project over the summer involved genotyping patients from the Cancer Research Repository for mutations in the IL-6 gene promoter region. The project challenged me to not only learn and master techniques that were new to me, but I also stretched my content knowledge by having to review and

apply recent literature. By the end of the summer, I knew that I wanted to pursue my studies further. In January 2008, I quit my job as a full-time classroom teacher, applied for and enrolled in the Integrative Biology doctoral program, and became a full-time research assistant.

Through the Integrative Biology doctoral degree flexible program of study, I was able to develop a coursework plan and research program that allowed me to gain bench experience while still pursuing my science education research career. I took classes in molecular biology, cancer biology, and cancer epidemiology to narrow my interests in breast cancer health disparities research. I decided to pursue a study with genetic polymorphisms of the adiponectin signaling pathway to gain more understanding regarding how obesity influences breast cancer incidence and progression.

Dr. Ely eventually accepted the director position for the Center for Science Education, and by working with him and Dr. Christine Lotter, I was able to develop the Taste Receptor Analysis curriculum unit kit and the professional development program to implement its use throughout the State of South Carolina. The Taste Receptor Analysis curriculum was designed to engage students in the technical practices of molecular biologists. Biology teachers often have students test their ability to taste the bitter compound phenylthiocarbamide (PTC) when teaching Mendelian genetics. The curriculum kit allows teachers to partner with our laboratory to allow students to genotype themselves for a mutation related to their inability to taste PTC. Through my experiences working with teachers to enact the Taste Receptor Unit, I gained an interest in barriers to technology integration research. My dissertation study pursues understanding how teachers' beliefs influence their enactment of technology-rich

curriculum and how to support teachers' beliefs that encourage successful technology-rich curriculum integration.

This dissertation presents my research projects in both breast cancer genetics and science teacher professional development that were made possible through the Integrative Biology doctoral program. Background information on both projects is included in the introduction chapter. Chapter two fully presents *Genetic Variation in Adiponectin Signaling Pathways May Influence Breast Cancer Prognosis* while chapter three details *Teachers' Beliefs of Technology Use to Teach Genetics*. This dissertation concludes with a fourth chapter that broadly contextualizes the results of both studies.

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List of Abbreviations

ADIPQ ..... Adiponectin Protein

ADIPOR1 ..... Adiponectin Receptor I Protein

ADIPOR2 ..... Adiponectin Receptor II Protein

BAG1 .....BCL2-Associated Athanogene

BMI ..... Body Mass Index

BrCa .....Breast Cancer

CRR.....South Carolina Cancer Research Repository

DCIS .....Ductal Carcinoma In Situ

DHEA .....Dehydroepiandrosterone

ER .....Estrogen Receptor

FOI ..... Fidelity of Implementation

Her2..... Human Epidermal Growth Factor Receptor 2

HWE .....Hardy-Weinberg Equilibrium

IBC.....Inflammatory Breast Cancer

IGF-1.....Insulin-Like Growth Factor-1

IDC.....Invasive Ductal Carcinoma

ILC .....Invasive Lobular Carcinoma

LCIS.....Lobular Carcinoma In Situ

NGSS .....Next Generation Science Standards

PCR.....Polymerase Chain Reaction

PR..... Progesterone Receptor

PTC .....Phenylthiocarbamide

RFLP .....Restriction Fragment Length Polymorphism

SHBG..... Sex-Hormone Binding Globulin

SNP ..... Single Nucleotide Polymorphism

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND OF STUDY 1—*GENETIC VARIATION IN ADIPONECTIN SIGNALYING PATHWAYS MAY INFLUENCE BREAST CANCER PROGNOSIS*

1.1.1 *The heterogeneity of breast cancer*

Breast cancer (BrCa) is the uncontrolled growth and spread of abnormal cells that initiates in mammary tissue. BrCa most often begins in the ducts, the tubes that drain milk from the breast, or in the lobules, the glands in the breast that make milk (Argani and Cimino-Mathews 2012). There is no single known cause of BrCa, and only five to ten-percent of BrCa diagnoses are attributed to genetic mutations inherited from a parent. Of these cases, *BRCA1* and *BRCA2* mutations are associated with an eighty-percent and sixty-five percent lifetime risk of BrCa diagnosis, respectively. Outside of genetics, several risk factors for the disease have been established— increased age, family history of breast cancer, early-age menarche, late-age menopause, late-age first live birth, extended use of hormone replacement therapy, alcohol consumption, and living a sedentary lifestyle (Hankinson et al. 2008).

Men can develop BrCa, but the disease is one-hundred times more common in women and is the most common cancer diagnosed among women (ACS 2013). Like all cancers, breast tumors are categorized with a high degree of diversity of clinical characteristics, disease pathologies and therapeutic responses. "Carcinoma in situ" means that the cancer is still restricted to its tissue of origin. There are two types of

breast carcinoma in situ—lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS). In situ breast cancers are treated with resection surgery and radiation therapy. However, women with LCIS are at higher risk of having a future occurrence of invasive cancer in either breast, and untreated DCIS will likely grow into an invasive cancer (Argani and Cimino-Mathews 2012).

Invasive cancers are those that have spread from the ducts and lobules and into other breast tissue, fatty tissue, or surrounding lymph nodes. Invasive ductal carcinomas (IDC) and invasive lobular carcinomas (ILCs) are the most frequent diagnoses of invasive breast cancer diagnosed with an eighty-percent and fifteen-percent frequency, respectively (ACS 2011). There are four subtypes of IDC—colloidal, medullary, metaplastic, and tubular carcinomas. Among these, both colloidal and tubular carcinomas have a better prognosis because of their lower probability of metastasis. A third, and extremely rare type of invasive breast cancer is inflammatory breast cancer (IBC) and occurs in one to three percent of BrCa diagnoses (Argani and Cimino-Mathews 2012; ACS 2011).

Beyond invasive or in situ, the heterogeneity of the breast cancer can be further classified by stage, grade, and receptor status. The American Joint Committee on Cancer publishes the TNM protocol pathologists use to stage cancers. This protocol calls for the consideration of the size and location of the primary tumor (T), presence of cancer cells in axillary lymph nodes (N), and metastasis of cancer cells to distant organs (M). The grade of a cancer reflects how aggressive it is; high grade, poorly differentiated cancers are more aggressive than low grade, well differentiated cancers. Pathologists can use the Nottingham Histologic Score system to compare the differentiation of the glands, nuclear

features, and mitotic activity of the cancer cells with normal cells to grade tumors (Cancer 2010).

The absence or presence of the estrogen receptor (ER), progesterone receptor (PR) and Human Epidermal Growth Factor Receptor 2 (HER2) along with stage and grade are used as markers of risk of recurrence, risk of mortality, and prediction of therapy response (Cancer 2010). These and other immunohistochemical factors can also be utilized to classify invasive and in situ BrCa tumors into five molecular classifications—luminal A, luminal B, HER2, basal like, and normal breast-like (Table 1.1) that have different incidence frequencies, response to treatment, and disease prognosis (Hankinson et al. 2008; Argani and Cimino-Mathews 2012). Normal breast-like tumors currently have no immunohistochemical distinctions that distinguish them from normal mammary tissue. Luminal A and B tumors generally respond well to hormonal therapy because they express both the estrogen and progesterone receptors. However, luminal A tumors have a better prognosis than luminal B tumors because less than fourteen-percent of these tumor cells generally express Ki-67, a nuclear protein present during cell proliferation and indexed to determine cell growth (Eppenberger-Castori et al. 2002). HER2 tumors are named such because they have amplification and over-expression of the *ERBB2* gene which codes for the HER2 protein. This expression of HER2 protein has an inverse relationship with survival, ER and PR expression, and age. HER2 tumors comprise approximately fifteen-percent of invasive BrCa cases and respond well to anti-HER2 therapies including the monoclonal antibody trastuzumab (McCafferty et al. 2009; O'Brien et al. 2010; Park et al. 2012; Polyak 2011).

1.1.2 *Race and age at diagnosis in regard to BrCa*

BrCa incidence and mortality varies by race. The overall incidence of BrCa is higher in White women in comparison to Black, Asian, Hispanic and Native-American women. Still, BrCa mortality is highest among Black women (CDC 2012). Overall, White women are diagnosed with less aggressive, low grade ER positive cancers in comparison to black women (Cunningham et al. 2010). When diagnosed with BrCa, Black American patients of all ages are more likely to have characteristics of advanced-stage disease, higher risk of recurrence, and poorer overall prognosis which includes malignancy and metastasis (Cross et al. 2002; Jatoi et al. 2003). In comparison to White American patients, Black women have a higher incidence of the more aggressive basal BrCa subtype in comparison to White women (Cunningham et al. 2010; O'Brien et al. 2010), and independent of socioeconomic status, Black American patients are more likely to have poorer overall survival and disease-free survival rates for BrCa in comparison to White American patients (Curtis et al. 2008; Cunningham et al. 2010). Black women have a higher incidence of the more aggressive basal BrCa subtype in comparison to White women (Cunningham et al. 2010; O'Brien et al. 2010) ; however, White women with the basal BrCa subtype have a higher mortality rate in comparison to Black women (O'Brien et al. 2010).

Along with race, BrCa incidence and mortality rates vary with age at diagnosis. In general, BrCa incidence increases with age. American women who are thirty-years-old have a 0.44% risk of developing BrCa in ten years whereas women who are fifty-years-old have a 2.31% chance of developing breast cancer in ten years (Howlader et al. 2013). While there is a direct relationship between incidence of luminal A and luminal

B subtypes and age (Eppenberger-Castori et al. 2002), women younger than fifty have higher survival rates. In considering age and race, young Black and Hispanic women have higher risk for basal subtypes compared to older women within their race and White women (Bauer et al. 2007; Cunningham et al. 2010).

1.1.3 *Obesity as a risk factor for breast cancer in population studies*

Black women are sixty-percent more likely to be obese than White women (C. E. Lewis et al. 1997). Among those who are obese, Black women are fifty-percent more likely to be moderately to severely obese than are White women (Flegal et al. 2002). Though at one point considered a controversial relationship, a number of recent studies have found a negative effect of obesity-- measured as weight gain, body mass index (BMI), waist-hip ratio or percent body fat, on prognosis in woman with breast cancer. The relationship between obesity and breast cancer risk depends on several factors including menopausal status, extent of disease, and receptor status (Majed et al. 2008; Ryu et al. 2001; Carmichael 2006; Dawood et al. 2008; Vitolins et al. 2008; Litton et al. 2007; Kroenke et al. 2005) . Weight before diagnosis also has been found to be directly associated with breast cancer recurrence and death in breast cancer patients who never smoked (Kroenke et al. 2005). In patients who were categorized as obese (BMI >= 30 kg/m^2), overweight (BMI of 25 to < 30 kg/m^2), or normal/underweight (BMI < 25 kg/m^2), high BMI has been associated with postmenopausal breast cancer. Among pre-menopausal women the opposite is true (Carmichael 2006). Being obese also influences more than cancer risk or progression; prognosis based on patient response to treatment is influenced by BMI. High BMI has been shown to have a negative influence on

pathologic complete response to neoadjuvant chemotherapy in women with operable breast cancer (Litton et al. 2007).

To further illuminate the relationship between BMI and cancer development and progression, a Swedish group created a cohort that followed-up hospitalized patients with a discharge diagnosis of obesity. Among cohort participants, there was a thirty-three-percent excess cancer incidence among obese people—twenty-five-percent among men and thirty-seven-percent among women. The study supports a positive association between obesity and elevated risks of several types of cancers including colon, brain, and larynx cancers. In another cohort study of 1,169 breast cancer patients from the Northern Alberta Breast Cancer Registry, data supported an inverse relationship between patient survival and BMI in estrogen receptor negative patients; however BMI and estrogen receptor level independently influenced breast cancer survival (Newman et al. 1997). In a separate cohort of 14,709 patients, obesity was shown to be a negative prognostic factor for metastasis recurrence, disease free interval, overall survival, and second primary cancer outcome even in patients with more advanced tumors at diagnosis time (Majed et al. 2008). In assessing the effect of BMI on prognosis in women with lymph node-positive breast cancer, increased BMI was positively associated with shorter time to recurrence and decreased survival. The negative relationship between BMI and these prognosis factors was stronger for younger women, those with progesterone receptor-negative disease, and those with a greater number of lymph nodes that were positive (Vitolins et al. 2008). Overall, these cohort studies support the hypothesis that obesity has a negative influence on breast cancer prognosis.

1.1.4 *Molecular explanations of obesity as a risk factor for cancer*

The endocrine system is an integrated system of small organs that involve the release of hormones, which are extracellular signaling molecules. The endocrine system is instrumental in the regulation of key body functions such as metabolism, growth, development, and tissue function. The hormones released from the endocrine system also play a part in determining mood. In situations where there is not a consistent availability of food sources, the ability to store excess consumed energy is advantageous for survival. Because of the roles of biological factors that are produced by adipose tissue, it is now considered an organ of the endocrine system. As an endocrine organ, fat cells provide energy stores for gestation and lactation in females and hormones necessary for reproduction, as in the case of leptin for ovulation. Still, excess fat storage can be disadvantageous for long-term survival in that it is linked with orthopedic diseases, endocrine dysfunction, metabolic disease, psychological and psychiatric dysfunction, and increased cancer rates (Jazet et al. 2003; Prins 2002).

Pathologic conditions associated with obesity, such as hyperinsulinemia, metabolic syndrome, and diabetes, seem to increase the risk of breast cancer (Carmichael 2006). One possible mechanism explaining associations between obesity and cancer is insulin resistance, also known as hyperinsulinemia. Insulin enhances the activity of insulin-like growth factor-1 (IGF-1). High levels of circulating IGF-1 are correlated with risk of development of breast cancer (Pollak et al. 2004). Another possible link between breast cancer risk and obesity is the hormone estrogen. Among postmenopausal women, the primary source of estrone is aromatization of plasma dehydroepiandrosterone (DHEA), which is abundant in adipose tissue (Longcope et al. 1982). Obese

postmenopausal women have higher levels of estrone and estradiol in the serum (Wolk et al. 2001; Folsom et al. 1989) and decreased levels of SHBG (sex-hormone binding globulin) which in turn leads to an abundance of bioavailable estrogen (Wolk et al. 2001; Davidson et al. 1981). This bioavailable estrogen may contribute to the risk of breast cancer (Carmichael 2006).

1.1.5 *BrCa risk and adiponectin signaling*

While increased estrogen expression may be one link between obesity and breast cancer risk, adipokines may also affect breast cancer development. Mammary epithelial cells are embedded in adipose tissue. Adipocytes, or fat cells, secrete many adipokines that act as effector molecules or agonists in several cellular processes. One such adipokine is adiponectin (also known as ADIPQ, apMi and Acrp30), a 244 amino acid, 30 kDa protein hormone. A major role of ADIPQ is to enhance hepatic insulin function and reduce hepatic glucose output (Berg et al. 2001); however, intermediate or high ADIPQ signaling has been significantly associated with lower risk for breast cancer (Kaklamani et al. 2008a), and decreased levels of ADIPQ have been shown to be associated with increased breast cancer risk (Duntas et al. 2004).

Because of the physical proximity between breast epithelial and breast adipose cells, ADIPQ secreted by the adipocytes most likely acts on the epithelium in both a paracrine and endocrine manner. ADIPOR1 and ADIPOR2, the transmembrane receptors for ADIPQ, are both expressed in normal and cancerous breast tissue. In comparison to non-cancerous adjacent breast tissue and normal tissue from human females without breast cancer, ADIPOR1 and ADIPOR2 are over-expressed in the cancer

tissue (Korner et al. 2007; Jarde et al. 2009). When ADIPQ binds to its receptors, anti-proliferative action occurs. Growth stimulation with estradiol (the predominant form of estrogen in non-pregnant females) of MCF-7 breast cancer cells is suppressed in the presence of ADIPQ through down-regulation of CYP19A1 and Estrogen Receptor-alpha (ERα) (Dieudonne et al. 2006; Jarde et al. 2009). CYP1A1 is an enzyme that catalyzes estrogen synthesis, and ERα can form homodimers with itself or heterodimers with its isoform Estrogen Receptor-beta (ERβ). Both ERα and ERβ dimerize in the presence of estradiol and bind to target genes or interact with other transcription factors to regulate gene expression. ERα is associated with proliferation, and ERβ's role, though controversial, is thought to interfere with the transcriptional activity of ERα. The ERα to ERβ ratio is higher in tumor versus normal tissue because of loss of ERβ expression during cancer progression. Though ERα is over-expressed in comparison to ERβ in breast cancer cells (Kurebayashi et al. 2000), ERβ mRNA is up-regulated in MCF-7 cells in the presence of ADIPQ (Treeck et al. 2008).

Along with the down-regulation of ERα and CYP1A1 and up-regulation of ERβ, adiponectin may also affect proliferation by down-regulating MAPK3, mitogen-activated protein kinase 3 which is involved in signal transduction for proliferation (Jarde et al. 2009). MAPK is over-expressed in breast cancer cells (Sivaraman et al. 1997), but ADIPQ inhibits MAPK phosphorylation in MCF-7 cells (Dieudonne et al. 2006). In the breast cancer cell line MDA-MB-231, suppression of cell proliferation and induction of apoptosis are caused when the cells are exposed to ADIPQ (Kang et al. 2005). The pro-apoptosis action of ADIPQ may be the down-regulation of BCL2-associated athanogene

(BAG1). BAG1 suppresses apoptosis by binding to mitochondrial membrane protein Bcl-2 and protecting it from antagonistic action (Jarde et al. 2009) (Figure 1.1).

1.1.6 *Genetic association studies*

Genetic polymorphisms in adiponectin and its signaling pathways have been studied for their effect on development and pathology of diseases including breast cancer (Kaklamani et al. 2013; Kaklamani et al. 2008a), prostate cancer (Beebe-Dimmer et al. 2010; Virginia Kaklamani et al. 2011), colon cancer (Kaklamani et al. 2008b), and their co-morbidities including diabetes and cardiovascular coronary artery disease (Soccio et al. 2006; Qi et al. 2006; Bacci et al. 2004). Studies of this kind are defined as genetic association studies and are a method of finding candidate genes that may contribute to disease risk. The most frequent genetic association studies involve single nucleotide polymorphisms (SNPs); however, microsatellite regions, insertions, deletions, variable-number tandem repeats, and copy-number variants are also considered (C. M. Lewis and Knight 2012).

Genetic association studies are either cohort or case-control in design. An example of a cohort study is when individuals are recruited without prior knowledge of their disease status, sorted by the risk factor in question, and observed over a period of time for development of the disease. In a case-control study, individuals who have the disease are recruited as cases and are compared with individuals negative for the disease who are recruited as controls. Both types of studies are able to provide relative risk, normally reported as an odd ratio, of disease incidence (Ziegler and Konig 2010). The assumptions of Hardy Weinberg Equilibrium (HWE) are assumed—a large randomly mating population with no selection, migration, mutation, or population stratification.

When deviation from HWE is observed and violation of the assumptions or genotyping error has been discredited, it may indicate a possible role of the analyzed marker in disease susceptibility (C. M. Lewis and Knight 2012).

A disadvantage of case-control studies involves the problem of selecting true controls. Disease incidence cannot be directly estimated because study participants are selected on the basis of having or not having the disease in question and not on the basis of their exposure to particular risk factors of the disease (Haiman and Hunter 2008). To avoid past exposure and future exposure among controls, a case-only design can be utilized. Though prevalence of disease risk factors and genotype frequencies among the general population may be lost, case-only analyses can be used to determine the absence or presence of interaction between the marker and disease. However, an additional weakness of the case-only study design is the difficulty in assessing the independence between genetic and environmental factors (Blazer et al. 2006).

1.1.7 *Purpose of the study 1*

The genomic DNA of a sample of White and Black BrCa patients were analyzed to determine if genetic factors impacting adiponectin signaling influence patient or tumor characteristics associated with breast cancer prognosis. A "case-case" method that combines the strengths of the case-control and case-only study designs was used in this study. The cases were breast cancer patients who have a patient or breast tumor characteristic and were compared to "control" breast cancer patients who did not have the associated characteristic. Our design provided a better opportunity to identify genetic characteristics associated with obesity and its co-morbidities that may impact the

development of one type of breast cancer more than other types. Genotypes for five single nucleotide polymorphisms (SNPs) in the *ADIPOQ* gene and five SNPs in the *ADIPORI* gene were determined and compared to three tumor characteristics and six patient characteristics to determine if any of these variant alleles influenced breast cancer subtype or prognosis.

1.2 BACKGROUND OF STUDY 2—*TEACHERS' BELIEFS OF TECHNOLOGY USE TO TEACH GENETICS*

1.2.1 *The importance of learning genetics for the 21st century student*

With the technological advances over the past several decades, genetics has become a rapidly advancing field with a tremendous growth of knowledge regarding the mechanisms that govern DNA structure, replication, interactions, and relationship to traits. In the age of the $1000 personal genome, personalized medicine, and genetically modified organisms, it has become more important that science classrooms in the public school system prepare citizens who are literate in the core ideas of modern genetics. This literacy will allow students to be capable of making decisions regarding novel technologies and their application in the public realm (Yilmaz et al. 2011; Venville et al. 2005).

Determining what twenty-first century students need to know about genetics and in what ways they best learn these concepts is driving genetics education course reform in the K-12 and collegiate environment (Redfield 2012; Dawson et al. 2012). Redfield (2012) posits that courses that begin with Mendel's laws and Punnett squares and spend time covering haploid genetics, three-factor crosses, fungal genetics, or tetrad analysis are

outdated. The author suggests that courses begin with personal genomics and human genetic variation and continue with details regarding molecular explanations of genetic inheritance in context of their application to society.

1.2.2 *Genetics standards and curricula in K-12 classrooms*

The recently released Next Generation Science Standards (NGSS) is a framework that prepares science educators to develop coherent curricula. Coherent curriculum organizes the conceptual ideas of a discipline into a coherent framework that builds upon previous concepts that enable learning of future concepts (Schmidt et al. 2002). The performance expectations defined in NGSS integrate the practices of scientists and engineers along with the core and cross-disciplinary concepts of life, physical, earth, and space sciences to increase learning of science from Kindergarten through twelfth grade (NGSS Lead States 2013). The practices of scientists were enumerated by *A Science Framework for K-12 Science Education* and include asking questions, defining problems, developing and using models, planning and carrying out investigations, analyzing and interpreting data, using mathematical and computational thinking, constructing explanations, designing solutions, engaging in argument from evidence, and obtaining, evaluating, and communicating information. By engaging in these practices, students can understand how scientific knowledge develops, be motivated to continue their study, and recognize the role that science and engineering plays in today's society (*A Framework*… 2012).

While the NGSS are not a curriculum and do not explicitly state how students should be instructed so that they can meet the outlined performance expectations, they do

make the practices of engineering and science that students should be able to do, explicit within each content area. The modern genetics performance expectations in the standards include students using models to illustrate cellular division and differentiation; asking questions to clarify relationships between DNA, chromosomes, and traits; making and defending evidence-based claims regarding genetic variation; and applying concepts of statistics and probability to population variation (Table 1.2). The challenge for educators will be in finding ways to integrate these practices while making abstract genetics content accessible for students who often have difficulty learning these concepts (Bahar et al. 1999; Banet and Ayuso 2000; Duncan and Reiser 2007; L. Smith and Williams 2007).

The core concepts of reproduction, biological diversity, mutation, adaption, evolution, cloning, forensic science and other areas of interest of modern genetics are often grouped into three categories—the organism or macro level, the cellular or micro level, and the biochemical or molecular level. Genetic phenomena at the micro and molecular levels present challenging learning experiences for students (Banet and Ayuso 2000; Duncan and Reiser 2007; L. Smith and Williams 2007; Kapteijn 1990; Law and Lee 2004). Students experience better learning outcomes with genetic phenomena at the macroscopic level—those where they can use all of their senses manipulating the whole plant or animal. Kapteijn (1992) proposed one reason for the micro and molecular content challenge is that they require students to understand the chemical nature of biological molecules and their physical interactions. Through their study of ninth-grade genetic novices, twelfth-graders with a declared college biology major, and pre-service teachers with a biology degree, Marbach-Ad and Stavy (2000) suggest that younger students, because of their cognitive development, should learn genetic concepts in micro

level terms using human beings or similar higher organisms as models. This suggestion is supported by the work of Smith and Williams (2007) who found children's understanding of genetics is tied to knowledge of family inheritance which can create problems with learning abstract micro and molecular content.

Integrating the macro, micro, and molecular concepts of modern genetics into coherent curriculum is essential for increasing the level of science literacy of students. Curricula must be inclusive of not only those concepts that students learned in previous grades or courses but also those that they have formed through experience (Duit and Treagust 2003; Novak 2002). Daily life applications allow students to connect to genetic concepts in meaningful ways and improve learning (Dogru-Atay and Tekkaya 2008; Rotbain et al. 2006). Rotbain, Machbach-Ad, and Stavy (2006) found that teachers were able to improve students' understanding of transcription and translation by using beads as a three-dimensional model. In another example of using everyday materials to improve learning, Dogru-Atay and Tekkaya (2008) were able to quantify gains in knowledge when students used an assortment of beans to model allele and genotype frequencies. The use of computer-based simulations has also been shown to improve student learning of modern genetics topics (Baurhoo and Darwish 2012; Echevarria 2003); however, when compared to experiments in the classroom, computer-based simulations do not lead to the desired understanding of scientific principles (Law and Lee 2004). Therefore, genetics teachers will need access to biotechnology tools in the classroom, like the Taste Receptor Analysis discussed in this dissertation, to plan experiments to maximize students' ability to achieve the "Inheritance and Variation of Traits" performance expectations outlined in NGSS.

1.2.3 *NGSS teacher professional development*

States considering the adoption of NGSS must weigh the substantial time and resources needed to create instructional materials and provide teachers with professional development to enact these materials. Quality teacher professional development is the key to classroom effectiveness of any new curriculum that is to be implemented, and these programs should allow teachers to learn new content, practice teaching the content, have opportunities for reflection, and be equipped with long-term enactment support (Singer et al. 2011; Pinto 2005; Bybee and Loucks-Horsley 2000; Hoekstra and Korthagen 2011). One method of providing quality teacher professional development is through school district and university partnerships. Through these partnerships, teachers could have opportunities to not only learn new content and curriculum but also have access to technology that will allow them to investigate authentic science questions with their students (Desimone et al. 2003; Zimpher and Howey 2005).

1.2.4 *Case study method of analysis*

A qualitative case study is a detailed explanation of a single setting, subject, set of documents, or event (Bogdan and Biklen 1998c). Case studies are framed in the constructivist research paradigm which recognizes truth as relative to individual perspective and knowledge as socially constructed (Baxter and Jack 2008). Case study designs allow researchers to use a variety of data sources to explore phenomena within its context (Glesne 2011c). Examples of when case study designs are used when the study focus is to answer "how" and "why" questions, when the behavior of the study's participants cannot be manipulated, when there is a desire to cover contextual conditions

that may be relevant to the study, or when boundaries are not clear between the phenomena and context of the study (Baxter and Jack 2008).

There are several types of case study designs. Descriptive case studies include the context when describing interventions or phenomena. Causal links in intervention studies are explored through explanatory designs. When data are needed to explain an issue or refine a theory, instrumental case study designs are utilized. Multiple-case studies and comparative case studies both allow researchers to explore differences within and between cases (Baxter and Jack 2008).

Bogdan and Biklen (1998) describe three considerations for researchers attempting case study analysis—data saturation, internal sampling, and generalizability. To prevent data saturation, defined as the point when the amount of time spent on data collection exceeds the amount of new information gained, researchers must clearly define study objectives to focus observations. Internal sampling refers to decisions about participant choice, frequency of observation, and the number and types of observations to collect; researchers must find a balance between the number of data sources and the quality of information from a particular data source. In drawing conclusions, researchers must be careful not to over-generalize typical or exceptional data collected from cases.

1.2.5 *Purpose of study 2*

Previous studies (Pinto 2005; De Ambrosis and Levrini 2010; Chan 2011) have upheld that teachers' effective implementation of technology-rich curriculum increases with support over time. This study focuses on a comparative case analysis of two teachers to describe how their beliefs regarding their own and their students' ability to

use technology in learning influence their enactment of technology-rich genetics curriculum. This study also explores how teachers' beliefs and enactments of the curriculum change as they receive support through quality professional development. As a result, we have been able to make recommendations for the kinds of support needed for teachers to faithfully implement new technology-based lessons in their classrooms.

Table 1.1 Immunohistochemical criteria for defining molecular BrCa subtypes.

Subtypes	Diagnosis Rate	ER	PR	HER2	Ki-67	Prognosis
Luminal A	40%	ER positive and/or	PR positive	Negative	<14%	Best subtype prognosis with longer disease free survival
Luminal B	20%	ER positive and/or	PR positive	Negative or Positive	≥14%	Fairly high survival rates but lower than luminal A
HER2	10-15%	Negative	Negative	Positive	Any	Lower survival and higher recurrence than luminal subtypes
Basal	15-20%	Negative	Negative	Negative	Any	Worst disease free survival of the subtypes
Normal breast-like	6-10%	n/a	n/a	n/a	n/a	Overall high disease free survival

*Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2(HER2), Ki-67 proliferation index (Ki-67. Sources of information: (McCafferty et al. 2009; O'Brien et al. 2010; Park et al. 2012; Polyak 2011)

Table 1.2 Next Generation Science Standards— Performance expectations of "Inheritance and Variation of Traits."

Students who demonstrate understanding can	
HS-LS1-4.	Use a model to illustrate the role of cellular division (mitosis) and differentiation in producing and maintaining complex organisms. [*Assessment Boundary: Assessment does not include specific gene control mechanisms or rote memorization of the steps of mitosis.]*
HS-LS3-1.	Ask questions to clarify relationships about the role of DNA and chromosomes in coding the instructions for characteristic traits passed from parents to offspring. [*Assessment Boundary: Assessment does not include the phases of meiosis or the biochemical mechanism of specific steps in the process.*]
HS-LS3-2.	Make and defend a claim based on evidence that inheritable genetic variations may result from: (1) new genetic combinations through meiosis, (2) viable errors occurring during replication, and/or (3) mutations caused by environmental factors. [Clarification Statement: Emphasis is on using data to support arguments for the way variation occurs.] [Assessment Boundary: Assessment does not include the phases of meiosis or the biochemical mechanism of specific steps in the process.]
HS-LS3-3	Apply concepts of statistics and probability to explain the variation and distribution of expressed traits in a population. [Clarification Statement: Emphasis is on the use of mathematics to describe the probability of traits as it relates to genetic and environmental factors in the expression of traits.] [*Assessment Boundary: Assessment does not include Hardy-Weinberg calculations.*]

Source of information: (NGSS Lead States 2013)

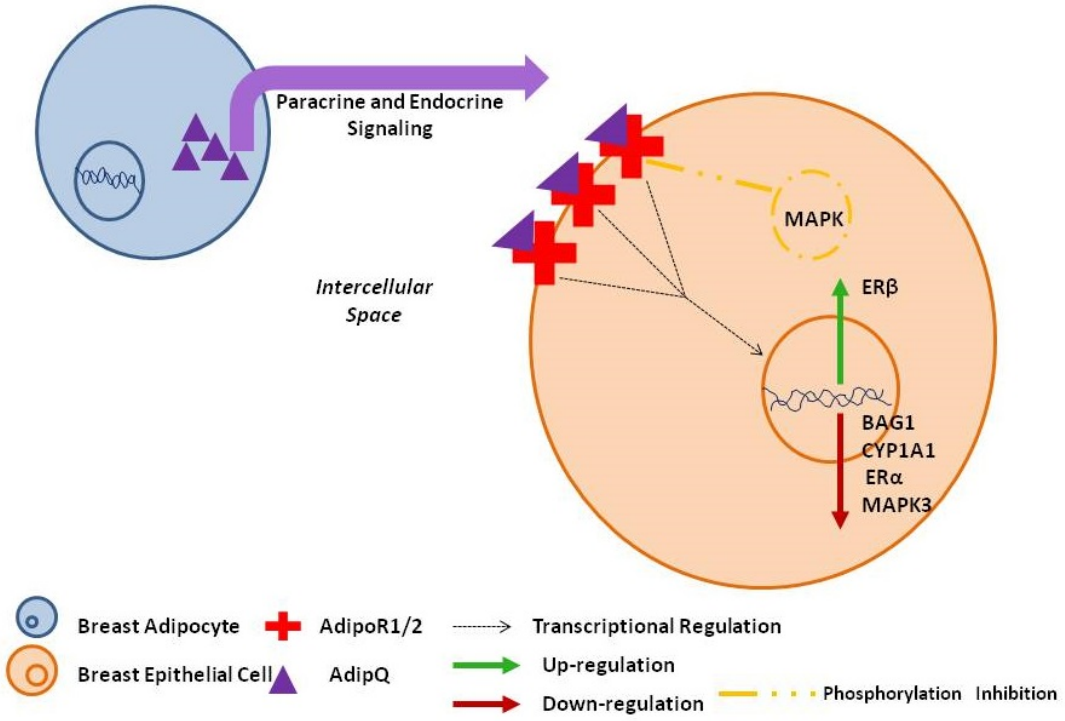

Figure 1.1 Illustration of ADIPQ mechanism of pro-apoptosis and anti-proliferation effect. ADIPQ is secreted by breast adipocyte cells and binds with ADIPOR1 and ADIPOR2 receptors in the membrane of the breast cancer cell. Upon binding, ADIPQ induces apoptosis by down-regulating BAG1. ADIPQ suppresses cancer cell proliferation by down-regulating CYP1A1, MAPK3, and ERα, up-regulating ERβ, and inhibiting the phosphorylation of MAPK.

CHAPTER 2

GENETIC VARIATION IN ADIPONECTIN SIGNALYING PATHWAYS MAY INFLUENCE BREAST CANCER PROGNOSIS

2.1 INTRODUCTION

Breast cancer (BrCa) is a heterogeneous disease with different tumor subtypes that have been associated with diverse genetic and environmental risk factors. Racial disparity in the presentation of BrCa and in the outcome of its treatment is well established. Incidence and mortality rates vary among different populations of Black American, Hispanic, Asian and Native American women, but all have a lower incidence and higher mortality rate compared to those of non-Hispanic White women. When diagnosed with BrCa, Black American patients of all ages are more likely to have characteristics of advanced-stage disease, higher risk of recurrence, and poorer overall prognosis which includes malignancy and metastasis (Cross et al. 2002; Jatoi et al. 2003). In comparison to White American patients, Black American patients have been found to be at higher risk for positive axillary nodes, hormone receptor-negative tumors and positive axillary nodes associated with smaller tumors. Independent of socioeconomic status, Black American patients are more likely to have poorer overall survival and disease-free survival rates for BrCa in comparison to White American patients (Curtis et al. 2008; Cunningham et al. 2010).

Epidemiological studies indicate that differences seen in disease incidence and mortality rates among different populations may be attributable in part to population

variation in obesity and body fat distribution. Black American women are 60% more likely to be obese than White American women (C. E. Lewis et al. 1997). Among those who are obese, Black American women are 50% more likely to be moderately to severely obese than are White American women (Flegal et al. 2002). Though at one point considered a controversial relationship, a number of recent studies have found a negative effect of obesity-- measured as weight gain, body mass index (BMI), waist-hip ratio or percent body fat; on prognosis in postmenopausal woman with BrCa (Carmichael 2006; Dawood et al. 2008; Majed et al. 2008). Weight before diagnosis also has been found to be directly associated with BrCa recurrence and death in BrCa patients who never smoked (Kroenke et al. 2005). Among pre-menopausal women the opposite is true (Carmichael 2006), which is an example of how the relationship between obesity and BrCa is confounded by several non-weight related factors including menopausal status, extent of disease, and tumor receptor status (Carmichael 2006; Kroenke et al. 2005; Majed et al. 2008; Vitolins et al. 2008).

As an endocrine tissue, fat cells provide energy stores for gestation and lactation and hormones necessary for biological processes including reproduction. Still, excess fat storage can be disadvantageous for long-term survival and is associated with orthopedic diseases, endocrine dysfunction, metabolic disease, psychological and psychiatric dysfunction, and increased cancer rates (Jazet et al. 2003; Prins 2002). Obesity results in elevated estrogen and androgen bioactivity, hyperinsulinemia, and lack of homeostasis of adipokines. Adipocytes, or fat cells, secrete adipokines that act as effector molecules or agonists in several cellular processes. One such adipokine is adiponectin (also known as ADIPQ, apMi and Acrp30), a 244 amino acid, 30 kDa protein hormone that is encoded

by the *ADIPOQ* gene. A major role of ADIPQ is to enhance hepatic insulin function and reduce hepatic glucose output (Berg et al. 2001). The adiponectin receptor I (ADIPOR1) protein is a 375 amino acid transmembrane protein that is encoded by the *ADIPOR1* gene and is expressed in sites critical for glucose metabolism, including skeletal muscle, liver, and pancreatic cells, and in other human tissues, including the breasts (Yamauchi et al. 2003; Civitarese et al. 2004; Kharroubi et al. 2003).

Intermediate or high ADIPQ signaling has been significantly associated with lower risk for BrCa (Kaklamani et al. 2008a), and decreased levels of ADIPQ have been shown to be associated with increased BrCa risk (Kang et al. 2007). Like serum protein levels, several studies support the idea that single nucleotide polymorphisms (SNPs) in genes that code for products involved in ADIPQ signaling may predict risk for cancer (Virginia Kaklamani et al. 2011; Kaklamani et al. 2008a; Beebe-Dimmer et al. 2010; Zhou et al. 2013; Kaklamani et al. 2013) and its co-morbidities including coronary artery disease, metabolic syndrome, and Type 2 diabetes (Qi et al. 2006; Soccio et al. 2006; Bacci et al. 2004; Filippi et al. 2005; Han et al. 2013). These previous studies associated SNPs in the adiponectin and its receptors' genes with disease risk in case-control studies. However, in seeking to understand how these polymorphisms may influence risk for BrCa disease subtypes, we determined the genotypes of selected SNPs in the *ADIPOQ* and *ADIPORI* genes in a population of BrCa patients. We then used dominant model logistic regression analysis to identify associations of individual SNP and combined *ADIPOQ* or *ADIPORI* haplotypes with tumor and patient characteristics that are linked to BrCa prognosis.

2.2 METHODS

2.2.1 *Study participants*

Researchers at the University of South Carolina partnered with physicians at South Carolina Oncology Associates to form the South Carolina Cancer Research Repository. The purpose of the repository was to generate a collection of buccal cell DNA samples from individuals with cancer. DNA samples obtained from the repository could then be used in studies of genetic factors involved in cancer risk. In addition to a submission of saliva samples, patients authorized researchers to access their medical records. Pathology reports from these medical records were used to add clinical information to the coded database so that researchers could look for correlations between coded data and genetic information. Patients' personal information was protected by assigning them an accession number and not including sensitive information in the database utilized for analysis. Our initial study was performed with DNA provided by the repository from 364 White American BrCa patients to evaluate potential associations between SNPs and haplotypes of *ADIPOQ* and *ADIPOR1* and factors utilized to determine BrCa subtype associated with disease prognosis. A second study was performed with DNA from 148 Black American BrCa patients in an attempt to replicate the findings from the first study. Table 1 describes the patient and tumor characteristics of these study populations. There was no significant difference in the frequencies of patient and tumor characteristics between populations.

2.2.2 *Patient and tumor characteristics* BrCa

Patient characteristics that were used in our study were the patient's age at first BrCa diagnosis, body mass index at the time of diagnosis, and immediate family history

of BrCa. Tumor characteristics included expression or lack of expression of the estrogen (ER), progesterone (PR) or human epidermal growth factor (Her2) receptors, presence of BrCa cells in axillary lymph nodes, grade of the primary cancer, and size of the primary tumor (Table 2 (Carmichael 2006; Mathew et al. 2004; Chia et al. 2004; Dawood et al. 2008; Majed et al. 2008; Ryu et al. 2001; Hartman et al. 2007; Dunnwald et al. 2007; Fisher et al. 1998; Winstanley et al. 1991; Gusterson et al. 1992; Saez et al. 1989; Nemoto et al. 1983; Fisher et al. 1983; Carter et al. 1989; Koscielny et al. 1984)).

2.2.3 *Selection of SNPs for genetic analysis*

The SNPs analyzed in this study were chosen based on previous studies that suggested 1) an association with serum adiponectin levels; 2) association with BrCa, another cancer, or a co-morbidity of BrCa including obesity, diabetes, and cardiovascular disease; or 3) functional relevance of the location of the mutation (Table 3 (Kaklamani et al. 2008b; Qi et al. 2006; Beebe-Dimmer et al. 2010; Mtiraoui et al. 2012; Moschos and Mantzoros 2002; Pollak et al. 2004; Soccio et al. 2006; Filippi et al. 2005; Kaklamani et al. 2008a; Heid et al. 2007; Menzaghi 2010; He et al. 2011; Mather et al. 2012; Virginia Kaklamani et al. 2011; Gui et al. 2009; Yuan et al. 2012; Siitonen et al. 2006; V. Kaklamani et al. 2011)). Only SNPs that have minor allele frequencies greater than 10% in European or Caucasian populations were chosen for our analyses (Ss#105435426, 1669820, 18097808, 20480656, 23288850, 23914895, 24254263, 24254429, 44472128, 71642409 2010).

2.2.4 *Genotype determination*

One of three methods of genotyping were utilized—PCR-RFLP (rs266729, rs1501299, and rs7539542), Sanger Sequencing (rs822395, rs822396, and rs2241766),

and Allele-Discrimination PCR (rs2232853, rs12733285, rs1342387, and rs10920531) based on the characteristics of each locus. Primers (Table 4) for PCR amplification of each DNA sequence were designed utilizing PrimerQuest software (Integrated DNA Technologies, Coralville, IA, USA), and restriction enzymes for RFLP analysis were identified via the NEBcutter V2.0 software (New England Biolabs, Ipswich, MA, USA). Sanger sequencing was performed by the High-Throughput Genomics Center (Seattle, WA, USA). Genotypes of the remaining SNPs were determined by Allele-Discrimination PCR via the TaqMan® SNP Genotyping Assay utilizing an ABI 7900HT, and results were automatically called using the TaqMan® Genotyper Software (Life Technologies, Carlsbad, CA, USA). Ten-percent of samples for each locus that was genotyped using either PCR-RFLP or Allele-Discrimination PCR were checked for accuracy through Sanger Sequencing. Control population samples were genotyped using Sanger Sequencing as well.

2.2.5 *Innovation*

We utilized a "case-case" method in which individuals who have a patient or breast tumor characteristic were compared to breast cancer patients who did not have the associated characteristic. Most current research paradigms in population genetics that analyze molecular marker-associated risk with a particular disease utilize a case-control method in which the cases belong to the disease group and the controls are selected from individuals in the same population who have not been diagnosed with the disease being studied. Therefore, the control group may include individuals who will be diagnosed with the disease at a later date. In addition, with respect to breast cancer, the risk factors analyzed in the study may have affected some types of breast cancer and not others. As a

result, genetic variation that could be associated with characteristics of breast cancer subtype, such as receptor positivity or tumor size, may not be detected due to the inclusion of other breast cancer subtypes among the case sample. In contrast, a case-case comparison provides a better opportunity to identify genetic characteristics that impact the development of one type of breast cancer more than other types. Hence, comparing cases to cases may capture significant associations between genotypes and tumor characteristics that cannot be detected in case-control studies.

2.2.6 *Statistical analysis*

Allele frequencies were checked for variance from Hardy-Weinberg equilibrium via Pearson's χ^2 calculations. When the observed minor allele frequencies differed more than 5% from the allele frequencies reported in dbSNP (National Center for Biotechnology Information, Bethesda MD), local population sample allele frequencies were determined for comparison. Local population samples consisted of fifty Black and fifty White Americans from the same study area who have never had a BrCa diagnosis. Associations between individual alleles and tumor or patient characteristics were determined by calculating odds ratios and 95% confidence intervals using univariate logistic regression analysis in STATA 11.0 (StataCorp LP, College Station, TX). We also used the patient's age and BMI at diagnosis along with family history of breast cancer in covariate analysis to determine if these factors contributed to significant results. In cases where statistical cells contained fewer than 15 individuals, Fisher's Exact test was used to determine odds ratios and significance levels. A p-value less than 0.05 was considered to be significant.

2.2.7 *Haplotype analysis*

Haplotypes were determined by combining the results of single-SNP analyses within the same gene. Odds ratios of SNPs that were found to be individually associated with a patient or tumor characteristic were compared to the odds ratios of multiple SNP combinations. If the haplotype logistic regression analysis resulted in a decreased probability and an increased odds ratio compared to those of the single SNP analysis, we report it as a significant combination suggesting that the combined haplotype has a greater impact than the single SNP used in the comparison.

2.3 RESULTS

2.3.1 *Sample genotypes*

For all of the *ADIPOQ* and *ADIPOR1* loci, the distribution of genotypes in both the White and Black American BrCa patient samples (Table 5) was consistent with Hardy-Weinberg equilibrium expectations with the exception of the *ADIPOQ* rs1501299 SNP in the Black BrCa population (χ^2=7.43, p=0.024) and the *ADIPOR1* rs7539542 SNP in the White BrCa population (χ^2=8.94, p=0.011). Furthermore, the allele frequencies of rs1501299 differed from the local Black control population with the variant A allele being more frequent than expected in the patient population ($p=7.29x10^{-4}$). For rs7539542, the variant C allele frequency in the White BrCa sample was significantly lower than that of the local White population sample ($p=1.70x10^{-5}$) and from the frequencies found in dbSNP ($p=8.21x10^{-8}$). Though there was no allele frequency data available for Black Americans or Africans in dbSNP, we also found that the variant C allele for rs7539542 was less frequent in the Black BrCa population in comparison to the

local Black control population ($p=3.46x10^{-4}$). These data suggest that the C allele at this locus may reduce the chances of getting breast cancer in both Black and White women.

2.3.2 *Association of ADIPOQ alleles with BrCa tumor characteristics*

Four of the five *ADIPOQ* SNPs analyzed in this study were found to be associated with one or two tumor characteristics known to affect prognosis in White women (Figure 1a and Table 6). For example, the *ADIPOQ* rs1501299 C-allele was associated with estrogen receptor positive tumors (OR=1.71, p=0.027) among White women. When age at diagnosis was considered, the OR increased to 4.73 (p=0.001) for White women over 50 at the time of diagnosis (Table 7) suggesting that the *ADIPOQ* rs1501299 C allele is a risk factor for ER+ tumors in older women. In a second example, we found that the C-allele of the *ADIPOQ* rs822395 SNP nearly doubled the risk for primary tumors larger than two-centimeters among White women (OR=1.87, p=0.010) and among Black women over the age of 50 (OR=2.79, p=0.039) as well. Conversely, the A-allele of *ADIPOQ* rs1501299 was found to triple the risk for primary tumors less than or equal to two-centimeters (OR 3.36, p=0.006) in white women under fifty years of age at the time of diagnosis (Table 7).

2.3.3 *Association of ADIPORI alleles with BrCa tumor characteristics*

Three of the five *ADIPORI* SNPs analyzed in this study were associated with BrCa tumor characteristics known to affect prognosis in White women (Figure 1b and Table 6). For example, the *ADIPORI* rs12733285 T allele was associated with both PR+ and ER+ tumors (OR=2.18 p=0.001; OR=1.88 p=0.019, respectively). Furthermore, we found that White women over the age of 50 were more likely to be diagnosed with an estrogen-receptor positive cancer when carrying the T allele (OR=2.52, p=0.008, Table

7). When the study was replicated with Black BrCa patient genotypes, we found no significant associations similar to those found in our White patient sample. However, the black breast cancer patient sample was less than half the size of the white breast cancer patient sample so it is possible that corroborating associations with the White BrCa population could be obtained with a much larger black patient sample. A unique result that was found with the Black BrCa patient sample was an increased risk for diagnosis with BrCa after age fifty among women with the *ADIPORI* rs7539542 C allele (OR=2.80 p=0.005).

2.3.4 *The impact of ADIPOQ haplotypes and ADIPORI haplotypes on BrCa tumor characteristics*

Since multiple SNPs were analyzed in both the *ADIPOQ* and the *ADIPORI* genes, we generated haplotype information by combining the genetic analyses in each gene to determine if particular haplotypes had a stronger association with a particular patient or tumor characteristic than that of the corresponding single alleles and five cases of increased significance were observed (Table 8).

Poorly differentiated cancers were associated with the combined *ADIPOQ* rs1501299 A and rs266729 C haplotype (OR=1.63, p=0.029) and with the combined *ADIPOQ* rs2241766 G and rs822396A haplotype (OR=2.02, p=0.011). Also, White women with the *ADIPOQ* rs1501299 A and rs2241766 T haplotype were almost twice as likely to have primary tumors that were less than or equal to two-centimeters (OR=1.71, p=0.027) as White women without this haplotype. Similarly, White women homo- or heterozygous for the C-C- allele combination for the *ADIPORI* rs1342387 and rs12733285 loci were nearly three times as likely to have an estrogen receptor negative cancer as White women without the C-C- haplotype (OR=2.62, p=0.017), and estrogen

receptor positivity was associated with the combined T allele of *ADIPORI* rs12733285 and C allele of rs2232853 haplotype (OR=1.99, p-value=0.010). When frequencies of these haplotypes were examined, we found significant differences between frequencies in the White and Black patient samples for both the *ADIPOQ* rs2241766 G/ rs822396 A and the *ADIPORI* rs12733285 T/ rs2232853 C haplotypes (Table 9) suggesting that haplotype frequency differences could contribute to racial differences in tumor characteristics.

2.4 DISCUSSION

The anti-proliferative and pro-apoptotic effect of ADIPQ has been linked to its ability to upregulate genes with known growth inhibitory or apoptotic functions in mammary epithelial cells (Treeck et al. 2008). For example, treatment of the BrCa cell line MDA-MB-231 with ADIPQ caused suppression of cell proliferation, cell growth arrest and apoptosis (Kang et al. 2005). Also, growth stimulation with estradiol of MCF-7 BrCa cells was suppressed in the presence of ADIPQ (Dieudonne et al. 2006). Similarly, an inverse relationship has been seen between serum adiponectin levels and breast cancer risk among post-menopausal women (Mantzoros et al. 2004). In a study of endometrial cancer, another type of hormone-dependent cancer, lower serum levels of ADIPQ were observed in patients with higher grade cancers (Rzepka-Gorska et al. 2008). Therefore, SNPs in genes that code for products involved in ADIPQ signaling have been examined in previous studies to determine if they impact BrCa risk (Kaklamani et al. 2013; Kaklamani et al. 2008a; Treeck et al. 2008). In this study, we found significant associations between both individual SNPs and haplotype combinations of *ADIPOQ* and *ADIPOR1* and BrCa patient or tumor characteristics associated with disease prognosis.

Kaklamani et al. found that the AC and CC genotypes of *ADIPOQ* SNP rs1501299 were associated with a 59% or 80% increased risk for BrCa, respectively, in White women (Kaklamani et al. 2008a). In a more recent study (Kaklamani et al. 2013), Kaklamani et al. found that these genotypes increase the risk of BrCa among Black American women as well. Consistent with these results, we found that the C-allele is associated with a two-fold increase in risk for estrogen receptor positive tumors. This association between the C-allele and estrogen receptor positive tumors increases to nearly five to one among White women who were older than fifty years of age at their time of diagnosis. Also, the combined T-A- haplotype of *ADIPOQ* rs1501299 and rs224166 was associated with primary tumors that were less than or equal to two-centimeters at the time of diagnosis in White women (Table 8). Consistent with these results, we reported in a previous study that the less aggressive BrCa tumors that were both estrogen receptor positive and well or moderately differentiated, increased in frequency and were substantially more common among older White Americans than among Black Americans in both Ohio and South Carolina (Cunningham et al. 2010). Conversely, the more aggressive estrogen receptor negative and poorly differentiated subtype was more common among younger Black American BrCa patients than among White American BrCa patients. In this study, we found the allele frequencies of rs1501299 were not consistent with Hardy Weinberg equilibrium expectations in the Black patient population sample which suggests a possible role of this SNP in BrCa susceptibility. A similar trend was found in the White patient sample as well, but the difference was not significant ($p=0.138$). Also, the A-allele was associated with poorly differentiated cancers in White women older than fifty years at the time of diagnosis. These data imply that though the

C-allele of rs1501299 may be associated with increased risk for BrCa, it is associated with increased risk for the more common, less aggressive estrogen-receptor subtypes; conversely, when the A allele is present, it may increase the risk for characteristics associated with poor BrCa prognosis. This conclusion was reinforced by the finding that the rs1501299 A and rs266729 C *ADIPOQ* haplotype, appeared to increase the risk for poorly differentiated grade BrCa subtypes within our sample of White patients (Table 8).

The GG genotype of *ADIPOR1* SNP rs7539542 has been associated with a 30-40% lower ADIPOR1 mRNA levels and with increased risk for coronary artery disease and Type 2 diabetes (Qi et al. 2006; Soccio et al. 2006). Conversely, the CC and CG genotypes of rs7539542 have been shown to increase ADIPOR1 mRNA levels and have been associated with 43% lower BrCa risk (Kaklamani et al. 2008a). In our study, the C-allele was associated with age of diagnosis greater or equal to fifty years in Black women. In addition, the C-allele frequency was decreased in both the Black and White BrCa samples compared to the local population, and the genotypic frequencies were not consistent with Hardy-Weinberg equilibrium in the White BrCa patient sample. These data suggest that this association between the C-allele and age at diagnosis may indicate that the C allele protects against early onset BrCa which tends to be more aggressive (Mathew et al. 2004; Chia et al. 2004).

We found several correlations between patient or tumor characteristics associated with disease prognosis and *ADIPOQ* and *ADIPOR1* SNPs that have not been previously associated with risk for BrCa. For example, we found that the rs224166 G and rs822396A *ADIPOQ* haplotype appeared to increase the risk for poorly differentiated grade BrCa subtypes within our sample of White patients (Table 8). Also, the C allele of

the *ADIPOR1* SNP rs10920531 was associated with primary tumors that were less than or equal to two-centimeters at the time of diagnosis in White women. Since cancer grade is correlated with relative risk of recurrence within five years (Saez et al. 1989; Nemoto et al. 1983) and distant recurrence rates and median time to the development of metastatic disease increase with tumor size (Carter et al. 1989; Koscielny et al. 1984), these results suggest that these additional *ADIPOQ* and *ADIPOR1* alleles may impact BrCa prognosis and warrant further study to determine if the correlations are reproducible or if they represent false positive associations.

The expression of both the estrogen and the progesterone receptors is associated with prognosis because of the relationship between loss of receptor expression and mortality and disease treatment options (Dunnwald et al. 2007; Fisher et al. 1998). The C allele of *ADIPOQ* rs1501299, and the C-T- haplotype of *ADIPOR1* rs12733285 and rs2232853 may be associated with better disease prognosis in White women because they increased the odds of having a receptor positive cancer. In contrast, the C-C- haplotype of *ADIPOR1* rs1342387 and rs12733285 more than doubled the risk for estrogen receptor negative cancers in this patient sample. Similarly, the CC and CT genotypes of *ADIPOR1* rs2232853 tripled the risk for axillary node positive cancers in White women in our study. Since there is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence (Saez et al. 1989; Nemoto et al. 1983) and five-year survival (Fisher et al. 1983), this haplotype may contribute to the formation of more aggressive tumors.

One limitation of our study is the inability to exclude potentially false positive associations with a second patient sample because of low sample sizes. Similarly, we

were unable to analyze haplotypes with respect to age at diagnosis because of our small population numbers, and therefore we may have missed significant associations. However, a strong point of our study is the ability to use BrCa case-case analyses to identify genetic characteristics that impact the development of one type of breast cancer more than other types.

In conclusion, our study suggests that several polymorphisms separately, or as part of *ADIPOQ* and *ADIPOR1* haplotypes, are associated with tumor characteristics that impact BrCa subtypes with different prognoses. These associations can be further affected by the patient's age at diagnosis. If these associations can be replicated, patient genotypes for these SNPs could offer insight in determining treatment options and distinguishing the involvement of adiponectin signaling allele variance in BrCa race disparity outcomes.

Table 2.1 Frequency of patient and tumor characteristics by race.

	White American n=364 (%)	Black American n=148 (%)	X^2 p-value
Age at Diagnosis (Dx_age):	364 (100)	148 (100)	
<50 years	112 (30.8)	44 (29.7)	0.817
≥50 years	252 (69.2)	104 (70.3)	
Body Mass Index:	354 (97.2)	142 (95.9)	
BMI≥25 kg/m^2	201 (55.2)	85 (57.4)	0.530
BMI≤24.9 kg/m^2	153 (42.0)	57 (38.5)	
Family history of BrCa:	361 (99.2)	145 (98.0)	
Yes	278 (77.0)	104 (71.7)	0.211
No	83 (23.0)	41 (28.3)	
Estrogen Receptor Status (ER)	336 (92.3)	129 (87.1)	
ER-	79 (21.7)	38 (29.5)	0.186
ER+	257 (70.6)	91 (70.5)	
Progesterone Receptor Status (PR)	336 (92.3)	128 (86.5)	
PR-	107 (23.5)	53 (41.4)	0.053
PR+	229 (76.5)	75 (58.6)	
Human Epidermal Growth Factor Receptor Status (Her2)	287 (78.8)	109 (73.6)	
HER2-	233 (81.2)	83 (76.1)	0.265
HER2+	54 (18.8)	26 (23.9)	
Axillary Node Status (node)	332 (91.2)	132 (89.1)	
negative	215 (64.8)	87 (65.9)	0.815
positive	117 (35.2)	45 (34.1)	
Grade of Primary Cancer (PD)	344 (94.5)	133 (89.9)	
Moderately or Well Differentiated	207 (60.2)	78 (58.6)	0.760
Poorly Differentiated	137 (39.8)	55 (41.4)	
Size of Primary Tumor	339 (93.1)	135 (91.2)	
≤2cm	236 (69.6)	88 (65.2)	0.349
>2cm	103 (30.4)	47 (34.8)	

Table 2.2 List of characteristics of BrCa subtype and their association with disease prognosis.

Characteristic (Abbreviation)	Characteristic Description	Characteristic Significance	Data Source
Age at Diagnosis (Dx_age)	Patient's age at first BrCa diagnosis in two categories: greater than or equal to 50 years and less than 50 years	Five-year survival rates are higher for women diagnosed at age >50; survival rates for younger women are lower because pre-menopausal cancers tend to be more aggressive (Chia et al. 2004; Mathew et al. 2004)	pathology report
Body Mass Index (BMI_OO)	Patient's BMI at time of diagnosis categorized into two categories-- overweight or obese (BMI$\geq$25 kg/m^2) and normal or underweight (BMI$\leq$24.9 kg/m^2)	Studies have found a negative effect of obesity-- on prognosis in woman with BrCa. Patients who were categorized as obese, overweight, or normal, high BMI has been associated with postmenopausal BrCa (Carmichael 2006; Dawood et al. 2008; Majed et al. 2008; Ryu et al. 2001).	Calculated from pathology report
Family history of BrCa	Prevalence or absence of BrCa in immediate family (mother, sister, or daughter)	The five-year breast cancer specific prognosis can be impacted by the outcome of breast cancer among affected first-degree relatives (Hartman et al. 2007)	patient self-report
Estrogen Receptor Status (ER)	Expression or lack of expression of estrogen receptors with primary tumor	Receptor negativity was associated with higher risk for mortality and need for the use of chemotherapeutic agents, in contrast to hormone therapy use when cancers are determined to be receptor positive (Dunnwald et al. 2007)	pathology report

Table 2.2 continued

Progesterone Receptor Status (PR)	Expression or lack of expression of progesterone receptors with primary tumor	Used along with ER status to predict mortality and benefit of adjuvant therapy (Fisher et al. 1998; Dunnwald et al. 2007)	pathology report
Human Epidermal Growth Factor Receptor Status (Her2)	Expression or lack of expression of human epidermal growth factor receptors with primary tumor	Over-expression of the receptor is associated with increased tumor aggressiveness, increased rates of recurrence, and increased mortality in node-positive patients and is used to predict response to endocrine therapy and chemotherapy (Winstanley et al. 1991; Gusterson et al. 1992)	pathology report
Axillary Node Status	Presence of breast cancer in axillary lymph nodes	there is a direct relationship between the number of involved axillary nodes and the risk for distant recurrence(Saez et al. 1989; Nemoto et al. 1983) and five-year survival (Fisher et al. 1983)	pathology report
Grade of Primary Cancer	Grade of Primary Cancer with moderately and well differentiated grades combined versus poorly differentiated	Directly correlated with relative risk of recurrence within five years (Saez et al. 1989; Nemoto et al. 1983)	pathology report
Size of Primary Tumor	The size of the primary tumor in two categories: greater than 2cm; less than or equal to 2cm	Distant recurrence rates and median time to the development of metastatic disease increase with tumor size (Carter et al. 1989; Koscielny et al. 1984)	pathology report

Table 2.3 Location and significance of selected SNPs.

***ADIPOQ* SNPs**	
rs266729	Located in the 5'flanking region; this area was associated with adiponectin levels and has been considered to be a disease causing region of *ADIPOQ*. The G allele was associated with decreased colorectal cancer risk (Kaklamani et al. 2008b), and the GG genotype was associated with decreased adiponectin levels (Qi et al. 2006).
rs822395	Located in intron 1; the CC genotype was associated with decreased risk for obesity(Beebe-Dimmer et al. 2010)
rs822396	Located in intron 1; the G-allele was associated with type 2 diabetes (Mtiraoui et al. 2012)
rs2241766	Synonymous (GGG→GGT; Gly→Gly) mutation found in exon 2; TT genotypes were associated with decreased plasma adiponectin levels (Moschos and Mantzoros 2002; Pollak et al. 2004). This locus has been found to be associated with altering ADIPQ levels, obesity, and risk of insulin resistance, cardiovascular disease, and hypertension (Soccio et al. 2006; Qi et al. 2006; Filippi et al. 2005). The G allele was associated with decreased BrCA risk (Kaklamani et al. 2008a), and the GG genotype was correlated with increased ADIPQ levels (Heid et al. 2007)
rs1501299	Located in intron 2; this SNP has been found to be associated with altered ADIPQ levels, obesity, and risk of insulin resistance, cardiovascular disease, and hypertension (Soccio et al. 2006; Qi et al. 2006; Menzaghi 2010; Beebe-Dimmer et al. 2010; Gui et al. 2009; Yuan et al. 2012). The C allele was associated with increased BrCA risk and the CC genotype associated with decreased levels of circulating adiponectin (Kaklamani et al. 2008a)

Table 2.3 continued.

***ADIPOR1* SNPs**	
rs2232853	Located in the 5' flanking region; the heterozygous genotype was associated with breast cancer risk (Kaklamani et al. 2008a).
rs12733285	Located in intron 1; heterozygous genotypes were associated with decreased colorectal cancer risk (Virginia Kaklamani et al. 2011; He et al. 2011); the T allele is associated with increased diabetes risk (Mather et al. 2012).
rs1342387	Located in intron 4; the T allele was associated with increased diabetes risk and decreased colorectal cancer risk (Mather et al. 2012; He et al. 2011). The C-allele was associated with higher body measures including weight, waist and hip circumference, and body mass index (Siitonen et al. 2006).
rs7539542	Located in exon 8; the C allele was associated with decreased BrCA risk (Kaklamani et al. 2008a) increased mRNA levels of adiponectin (Soccio et al. 2006).
rs10920531	Located in the 3' flanking region; this marker has been studied for its association with breast cancer and colon cancer (Virginia Kaklamani et al. 2011; V. Kaklamani et al. 2011; Kaklamani et al. 2008a; Kaklamani et al. 2008b) and has been associated with prostate cancer risk (Virginia Kaklamani et al. 2011)

Table 2.4 Single nucleotide polymorphisms, primers, and genotyping method for *ADIPOQ* and *ADIPOR1*.

	PCR Primers	Polymorphism (Ancestral/ Variant)	Primary Genotyping Method
***ADIPOQ* SNPs**			
rs266729	F 5'-CTTCTCTTGAAATATTTGGACATTAG-3' R 5' –GCAACATTCAACACCTTGGACTTTC-3'	C/G	PCR-RFLP
rs822395	F 5'- GGCACGTTTGCACTGACCTTCAAT-3' R 5'-TGCTTGTCACCTCCACCCTTTCTT-3'	C/A	Sanger Sequencing
rs822396	F 5'-GGCACGTTTGCACTGACCTTCAAT-3' R 5'-TGCTTGTCACCTCCACCCTTTCTT-3'	A/G	Sanger Sequencing
rs2241766	F 5'-GCAATCACTGAATTCATAATCT-3' R 5'-TGCCATCTCTGCCATCACGG-3'	T/G	Sanger Sequencing
rs1501299	F 5'-TCCCCAAAGGCAGGACTGA-3' R 5'-CAGGTAAGAATGTTTCTGGC-3'	C/A	PCR-RFLP

Table 2.4 continued

***ADIPOR1* SNPs**			
rs2232853	F 5'-TCAAGTGGTAGCAGCAGCTGGGAAT-3' R 5'-GGTATACTCAGCCTGCCTCAAGCTG-3'	C/T	Allele Discrimination [1]
rs12733285	F 5'-TCATGCTATGCTCAACCCACAAGCA-3' R 5'-AGTTGAAAGCAACCGGCAATCTAGT-3'	C/T	Allele Discrimination[2]
rs1342387	F 5'-AAAAAAGGGAATGTGTACACTTTGA-3' R 5'-GGTTGATGTTTTTGAATCAGAGAGC-3'	C/T	Allele Discrimination[3]
rs7539542	F 5'-ACTACTATAGCATACTGATTTCTCTA-3' R 5'-ATCATTGCTATGTATCTTGATGC-3'	G/C	PCR-RFLP
rs10920531	F 5'-AAACTTGACTCTTGACATGAACCCA-3' R 5'-CTTTAACTCAAAAAGACTGCCCTTA-3'	A/C	Allele Discrimination[4]

[1] Applied Biosystems TaqMan® SNP Genotyping Assay ID C____198957_10; [2]Applied Biosystems TaqMan® SNP Genotyping Assay ID C__26186730_10; [3] Applied Biosystems TaqMan® SNP Genotyping Assay ID C_____37350_10; [4]Applied Biosystems TaqMan® SNP Genotyping Assay ID C__26186735_10

Table 2.5 Genotype and allele frequencies for *ADIPOQ* polymorphisms with Hardy-Weinberg Equilibrium p-values.

ADIPOQ						
	White American (n=364)			Black American (n=148)		
SNP	**Genotype frequencies**	**Allele freq.**	**p-value**	**Genotype frequencies**	**Allele freq.**	**p-value**
rs266729	CC 0.530 CG 0.396 GG 0.074	C 0.728 G 0.272	0.718	CC 0.795 CG 0.193 GG 0.012	C 0.882 G 0.108	0.824
rs822395	CC 0.090 CA 0.419 AA 0.491	C 0.299 A 0.701	0.987	CC 0.193 CA 0.493 AA 0.314	C 0.439 A 0.561	0.191
rs822396	AA 0.661 AG 0.304 GG 0.035	A 0.813 G 0.187	0.442	AA 0.657 AG 0.307 GG 0.036	A 0.811 G 0.189	0.932
rs2241766	TT 0.810 TG 0.180 GG 0.010	T 0.900 G 0.100	0.981	TT 0.901 TG 0.096 GG 0.003	T 0.949 G 0.051	0.810
rs1501299	CC 0.530 CA 0.396 AA 0.074	C 0.728 A 0.272	0.108	CC 0.523 CA 0.400 AA 0.077	C 0.723 A 0.277	0.024*
ADIPOR1						
	White American (n=356)			Black American (n=147)		
SNP	**Genotype frequencies**	**Allele freq.**	**p-value**	**Genotype frequencies**	**Allele freq.**	**p-value**
rs2232853	CC 0.501 CT 0.414 TT 0.085	C 0.708 T 0.292	0.939	CC 0.672 CT 0.296 TT 0.032	C 0.820 T 0.180	0.301
rs12733285	CC 0.439 CT 0.447 TT 0.114	C 0.663 T 0.337	0.716	CC 0.570 CT 0.370 TT 0.060	C 0.755 T 0.245	0.175
rs1342387	CC 0.288 CT 0.497 TT 0.215	C 0.536 T 0.464	0.952	CC 0.311 CT 0.493 TT 0.196	C 0.558 T 0.442	0.915
rs7539542	GG 0.161 GC 0.481 CC 0.358	G 0.402 C 0.598	0.011*	GG 0.383 GC 0.472 CC 0.145	G 0.619 C 0.381	0.844
rs10920531	AA 0.133 AC 0.464 CC 0.403	A 0.365 C 0.635	0.846	AA 0.311 AC 0.493 CC 0.196	A 0.558 C 0.442	0.999

* denotes significance with α=0.05.

Table 2.6 Significant associations of *ADIPOQ* and *ADIPOR1*alleles with BrCa patient and tumor characteristics in the White BrCa sample.

Gene	SNP-Dominant Allele	Characteristic of BrCA Subtype	P-Value	O.R.	95% C.I. Lower	95% C.I. Upper
ADIPOQ	rs266729-C	Age at Diagnosis <50 years	0.039	3.11	1.06	9.12
ADIPOQ	rs266729-G	Well or Moderately Differentiated Grade	0.026	1.64	1.06	2.55
ADIPOQ	rs822395-C	Primary Tumor > 2cm	0.010	1.87	1.16	2.99
ADIPOQ	rs2241766-G	Poorly Differentiated Grade	0.016	1.95	1.13	3.35
ADIPOQ	rs1501299-C	Estrogen Receptor Positive	0.027	2.33	1.10	4.94
ADIPOQ	rs1501299-A	Poorly Differentiated Grade	0.036	1.59	1.03	2.46
		Primary Tumor ≤ 2cm	0.027	1.71	1.06	2.75
ADIPOR1	rs2232853-C	Axillary Lymph Node Positive	0.042	2.82	1.04	7.70
ADIPOR1	rs12733285-T	Estrogen Receptor Positive	0.019	1.88	1.11	3.18
		Progesterone Receptor Positive	0.001	2.19	1.35	3.54
ADIPOR1	rs1342387-C	Estrogen Receptor Negative	0.019	2.57	1.16	5.65
ADIPOR1	rs10920531-C	Primary Tumor ≤ 2cm	0.036	1.96	1.05	3.69

Associations between individual alleles and tumor or patient characteristics were determined by calculating odds ratios and 95% confidence intervals using univariate logistic regression analysis in STATA 11.0 (StataCorp LP, College Station, TX). A p-value less than 0.05 was considered to be significant.

Table 2.7 Significant associations of *ADIPOQ* and *ADIPOR1*alleles with BrCa patient and tumor characteristics in the White BrCa sample stratified by age at diagnosis.

Women ≤ 50 years of age						
Gene	**SNP-Dominant Allele**	**Characteristic of BrCA Subtype**	**P-Value**	**O.R.**	**95% C.I. Lower**	**Upper**
ADIPOQ	rs1501299-A	Primary Tumor ≤ 2cm, age<=50	0.006	3.36	1.42	7.94
Women > 50 years of age						
Gene	**SNP-Dominant Allele**	**Characteristic of BrCA Subtype**	**P-Value**	**O.R.**	**95% C.I. Lower**	**Upper**
ADIPOQ	rs1501299-A	Poorly Differentiated Grade, age >50	0.032	1.79	1.05	3.04
ADIPOQ	rs1501299-C	Estrogen Receptor Positive, age >50	0.001	4.73	1.97	11.3
ADIPOR1	rs12733285-T	Estrogen Receptor Positive, age >50	0.008	2.52	1.27	5.01

Associations between individual alleles and tumor or patient characteristics were determined by calculating odds ratios and 95% confidence intervals using univariate logistic regression analysis with stratified age at diagnosis as a cofactor in STATA 11.0 (StataCorp LP, College Station, TX). A p-value less than 0.05 was considered to be significant.

Table 2.8 Haplotypes of the adiponectin gene (*ADIPOQ*) and adiponectin receptor 1 gene (*ADIPOR1*) associated with tumor characteristics in the White BrCa sample.

ADIPOQ										
Characteristic of BrCa Subtype	**rs266729**	**rs822395**	**rs822396**	**rs224166**	**rs1501299**	**v**	**P-VALUE**	**O.R.**	**95% C.I. Lower**	**Upper**
Poorly Differentiated Grade	**C**	**-**	**-**	**-**	**A**	**0.442**	**0.029**	**1.63**	**1.05**	**2.51**
Poorly Differentiated Grade	**-**	**-**	**A**	**G**	**-**	**0.187**	**0.011**	**2.02**	**1.18**	**3.47**
Primary Tumor ≤ 2cm	**-**	**-**	**-**	**T**	**A**	**0.429**	**0.027**	**1.71**	**1.06**	**2.75**

Table 2.8 continued

ADIPOR1										
Characteristic of BrCa Subtype	**rs2232853**	**rs12733285**	**rs1342387**	**rs7539542**	**rs10920531**	**v**	**P-VALUE**	**O.R.**	**95% C.I. Lower**	**Upper**
Estrogen Receptor Negative	**-**	**C**	**C**	**-**	**-**	**0.769**	**0.017**	**2.62**	**1.19**	**5.77**
Estrogen Receptor Positive	**C**	**T**	**-**	**-**	**-**	**0.541**	**0.010**	**1.99**	**1.18**	**3.19**

Associations between haplotypes and tumor or patient characteristics were determined by calculating odds ratios and 95% confidence intervals using univariate logistic regression analysis in STATA 11.0 (StataCorp LP, College Station, TX). A p-value less than 0.05 was considered to be significant.

Table 2.9 Frequencies of the haplotypes of Adiponectin gene (*ADIPOQ*) and Adiponectin Receptor 1 gene (*ADIPOR1*) in the White and Black BrCa samples.

***ADIPOQ* Haplotypes**							
rs266729	**rs822395**	**rs822396**	**rs224166**	**rs1501299**	**White American n=364 (%)**	**Black American n=148(%)**	**X^2 p-value**
C	**-**	**-**	**-**	**A**	**161 (44.2)**	**63 (42.6)**	**0.731**
-	**-**	**A**	**G**	**-**	**68 (18.7)**	**15 (10.1)**	**0.017***
-	**-**	**-**	**T**	**A**	**163 (44.8)**	**64 (43.2)**	**0.751**
***ADIPOR1* Haplotypes**							
rs2232853	**rs12733285**	**rs1342387**	**rs7539542**	**rs10920531**	**White American**	**Black American**	**X^2 p-value**
-	**C**	**C**	**-**	**-**	**280 (76.9)**	**109 (73.6)**	**0.273**
C	**T**	**-**	**-**	**-**	**197 (54.1)**	**59 (39.9)**	**0.002***

* denotes significance with α=0.05

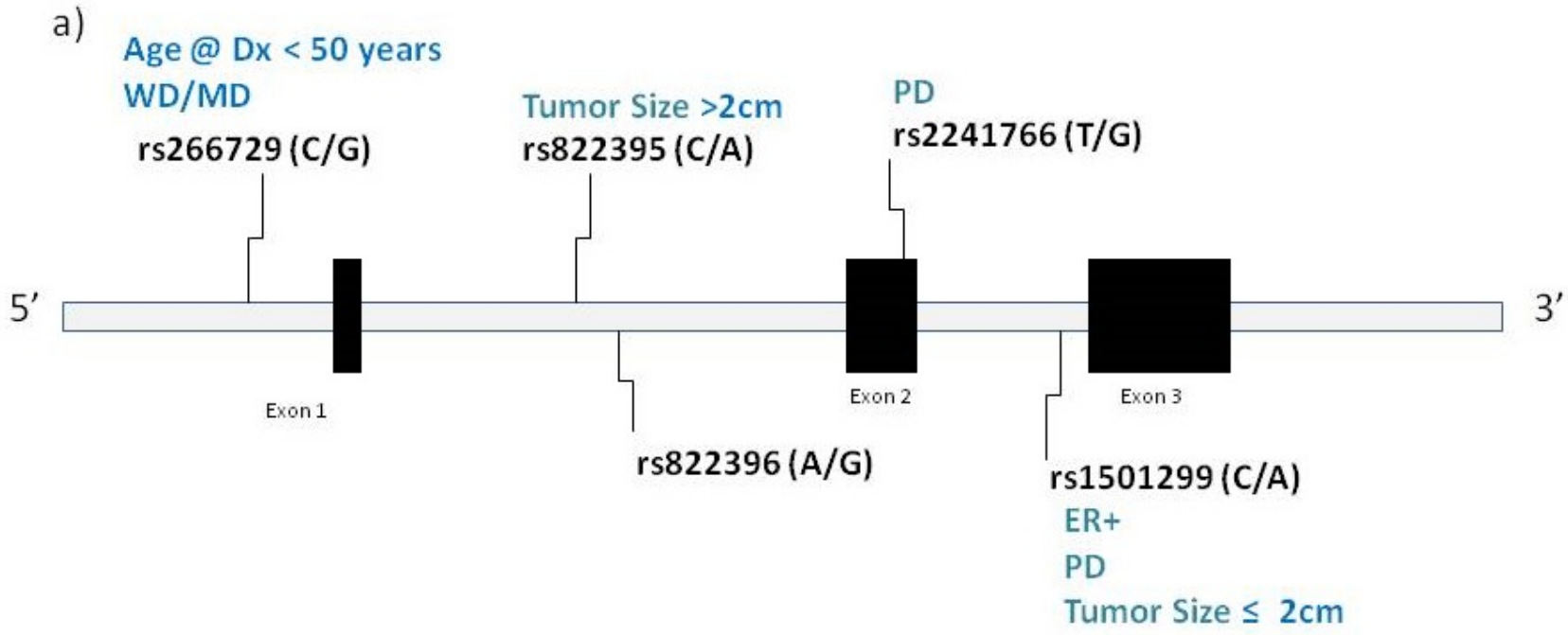

Figure 2.1 a) BrCa patient and tumor characteristics associated with SNPs in the adiponectin gene (*ADIPOQ*) as detailed in Table 2.6.

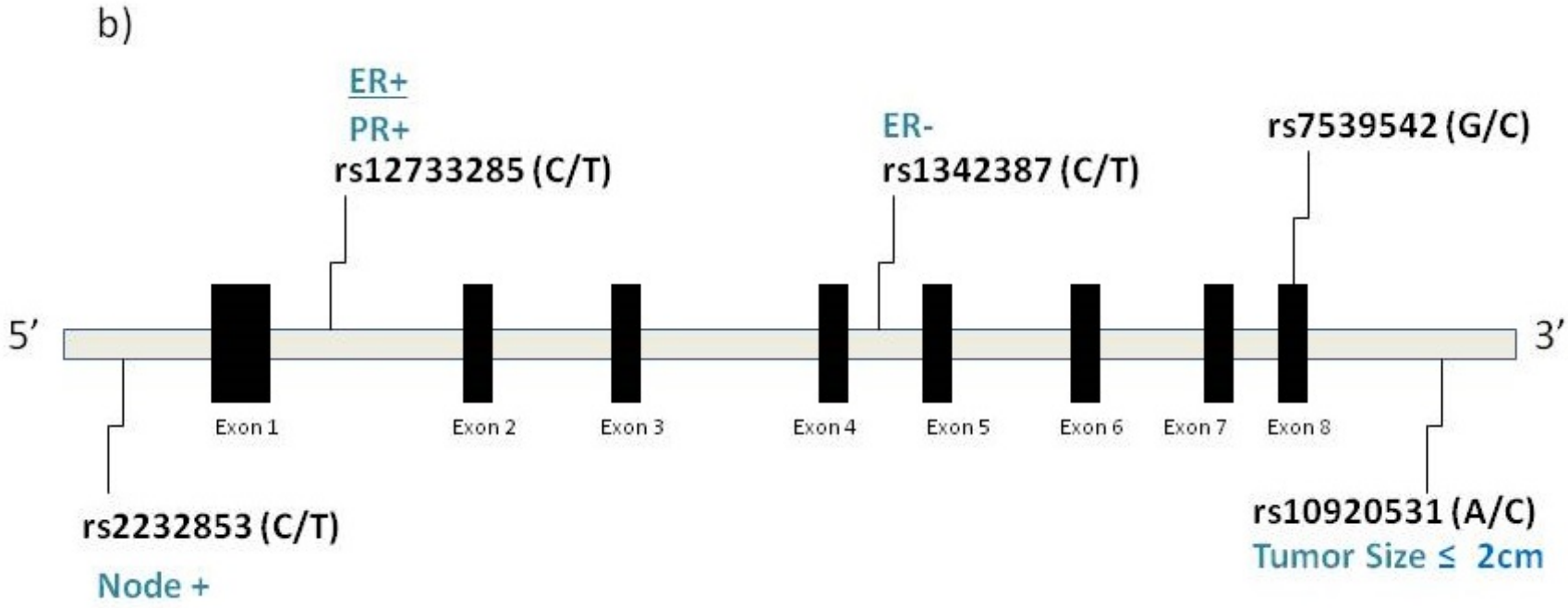

Figure 2.1 b) BrCa patient and tumor characteristics associated with SNPs in the adiponectin receptor 1 gene (*ADIPOR1*) as detailed in Table 2.6. Plain-text characteristics denote significant association is within the White BrCa sample only; the underlined characteristic (ER+) denotes a significant association with the *ADIPOR1*allele in the Black BrCa sample.

CHAPTER 3

TEACHERS' BELIEFS OF TECHNOLOGY USE TO TEACH GENETICS

3.1 INTRODUCTION

Teaching science beyond the accumulation of theory and facts and more as an interdisciplinary practice and way of knowing is at the core of the Next Generation Science Standards (NGSS Lead States, 2013). The Next Generation Science Standards, which set performance expectations rooted in science and engineering practices, core disciplinary ideas, and crosscutting concepts outlined in the *Framework for K-12 Science Education* (2012), will require teachers to instruct in new, more challenging ways. As professional development program and curriculum designers begin the work of preparing teachers to implement the new standards, they will need to prepare teachers to engage students in the use of technological tools during scientific inquiry. The findings from this study inform professional development program and curriculum designers on how to best support teachers' beliefs that enable high fidelity of implementation of technology-rich curriculum.

3.2 THEORETICAL FRAMEWORK

3.2.1 *Technology-rich curriculum*

Recommendations for science education reform from agencies and researchers include an increase in the use of scientific practices within K-12 classrooms (*A*

Framework… 2012; Wang et al. 2012; Hayden et al. 2011). The Next Generation Science Standards (NGSS Lead States, 2013) emphasize the connection between science, engineering, and technology in the development and use of scientific knowledge. While experts involved in science education reform uphold how the integration of technology into classrooms can also enhance the learning environment, teachers also find value in technology use. Burton and Frazier (2012) described how expert teachers believe using technology in the classroom engages students in meaningful learning experiences, builds student ownership of scientific knowledge, increases trust between teachers and students, and helps teachers set high expectations for learning. These expert teachers also believe that classroom management is enhanced through meaningful, activity-based experiences with technology because the experiences help motivate student learning, support learning communities, and reduce the need to discipline students for misbehavior. Students have also described technology-integration as positively influencing their learning (Goldenberg 2011). Many researchers support these students' conceptions by describing how lab equipment integration (Craney et al. 1996; Liddicoat and Sebranek 2005) and computer and internet-based technology integration (Lee et al. 2010; Keengwe et al. 2012) positively correlate with student knowledge gains.

3.2.2 *Teachers' beliefs regarding technology-rich curriculum implementation*

Even though technology is a relevant tool of scientists, the failure of technology use in classrooms has been attributed to teacher buy-in, issues related to access, technical difficulties, organization, and time (Waight and Abd-El-Khalick 2007). Windschitl (2002) found that the best predictor of pre-service teachers' use of inquiry in the classroom was their engagement in long-term research experiences. Teachers' beliefs

about the value of the use of technology to teach students influences if and how they decided to implement technology-rich curriculum into their own practice (Blumenfeld et al. 2000; Pajares 1992; Briscoe 1991). Teachers' use of technology is not just a matter of their subject or technological knowledge which influences their self-perceived ability to effectively implement the lessons, but use is also dependent upon teachers' perceptions regarding how technology will add to or enable student learning (Blumenfeld et al. 2000; Pajares 1992; Briscoe 1991). These perceptions are formed from the expectations and resources of their current institution (Tobin and McRobbie 1996; Geddis 1991) and from past and present learning environments-- how teachers themselves were taught and how they learn (Brickhouse and Bodner 1992; Huibregtse et al. 1994).

3.2.3 *Supporting teachers with new curriculum implementation*

Teachers' decisions to enact innovative, technology-integrated curriculum are predicated upon what they believe and on how well they are supported in the classroom during implementation (Pinto 2005). Hoekstra and Korthagen (2011) found that when teachers were supported in implementing new curriculum, they became more aware of their beliefs and practices that inhibit change toward enacting the new curriculum. These authors explain how this awareness can bring the reward of the development of new beliefs and teaching behaviors which enhance student learning.

Pinto (2005) described how the first time teachers enact an inquiry oriented curriculum, they may become frustrated with the materials. However, teachers' attitudes change throughout the implementation of new, technology integrated curriculum. Initially, teachers may exhibit hesitation and mistrust of all or parts of the new

curriculum. Then as teachers practice, discuss, and reflect on the enactment of different aspects of the program, which may conflict with their current pedagogical practices, with colleagues and professional development program facilitators, they begin to value the new curriculum and may eventually accept it as part of their own practice (Pinto 2005; De Ambrosis and Levrini 2010; Chan 2011).

However, it takes time for teachers to effectively use innovative, technology-integrated curriculum. Teachers need extended scaffolding experiences to support them as they attempt to enact inquiry (Schneider et al. 2005). Each time teachers enacted a lesson utilizing innovative technologically-involved curriculum, Fogleman, et al. (2011) found that there was an increase in their understanding regarding how to use the innovation with their students as well an increase in student knowledge gains. Studies have shown that professional development models that support teachers for extended periods of time have gains in teachers' perceptions about their teaching skills, their use of the curriculum, and the influence of the curriculum on their students and the school (Spektor-Levy et al. 2008). By relating to teachers how instructional effectiveness and student learning increase with curriculum usage over time, teachers may be encouraged to try using the curriculum more than once (Fogleman et al. 2011; Gerard et al. 2010; Sandoval and Reiser 2004).

To support teachers in the successful implementation of technology in their classrooms, they should be provided with scaffolded modeling experiences along with opportunities for peer feedback, meaningful reflection, and time to try new materials together with colleagues and designers (Bickel and Hattrup 1995; Darling-Hammond 1994; Darling-Hammond and Richardson 2009; Singer et al. 2011). By having

scaffolded practice-teaching experiences, participants are able to learn from those with more experience and expertise, how the curriculum and changes to it can benefit student learning (Chan 2011; Viennot et al. 2005). Therefore, by providing a supportive environment to address the needs of teachers and students, curriculum designers and researchers can increase teachers' effective implementation of technology-rich curriculum (Pinto 2005).

Krajcik, McNeill, and Resier (2008) address yet another way professional development teams and curriculum designers can support teachers in the implementation of innovative, technologically-rich curriculum. They suggest including a discussion about what aspects of the curriculum make it effective in the classroom during professional learning opportunities for teachers. Effective curriculum must have content primarily focused on a coherent set of age appropriate learning goals, an instructional design that supports attainment of these learning goals, and a guide that supports teachers with helping students attain these goals (Kesidou and Roseman 2002; Krajcik et al. 2008). Developers should also adapt the curriculum and training experiences to the outcomes gained from teachers' implementation of the curriculum in their classrooms (Stylianidou et al. 2005; Krajcik et al. 2008). By giving teachers the opportunity to provide feedback and by using this feedback to adjust the curriculum, developers increase the likelihood of its effective implementation (Macdonal & Rudduck 1971; McIntyre & Brown 1979; Pinto 2005).

3.2.4 *Fidelity of implementation*

Curriculum developers and researchers must understand that teachers participating in curriculum implementation are not passive learners but rather they add their own modifications as they implement new ideas (Rogers 2003). Fidelity studies (Mowbray et al. 2003; Dane and Schneider 1998; Dusenbury et al. 2003) define fidelity of implementation as how well an innovation is implemented according to the designer's original program or intent. Dusenbury (2003) further defines five criteria for measuring fidelity of implementation that can be organized into two groups—structure and process. The five criteria are1) adherence (the implementation faithful to the design concepts?), 2) duration (the number, length, and frequency of the implementation), 3) quality of delivery (the manner of implementation), 4) participant responsiveness (the extent to which the participants are engaged by and involved in the activity and content) and 5) program differentiation (critical features of the intervention that differentiate it from control programs absent or present) (O'Donnell 2008). Fogleman, McNeil, and Krajcik (2011) found that the fidelity of implementation, more specifically the quality of delivery determined by the teachers' choice of activity structure, significantly impacted student learning.

3.2.5 *Research questions*

Previous studies (Pinto 2005; De Ambrosis and Levrini 2010; Chan 2011) have supported how teachers' effective implementation of technology-rich curriculum increases with support over time. How well an innovation is implemented according to the designer's original program or intent is also influenced by the teachers' choice of

activities (Fogleman et al. 2011). This study examines how teachers' beliefs regarding their own and their students' ability to use technology influence the fidelity of implementation (O'Donnell 2008) of technology-rich curriculum into their classroom as they receive support through professional development. The following research questions guide this study:

1) How do teachers' confidence in their ability to teach a technology-rich curriculum and their beliefs about their students' ability to learn influence their enactment of technology-rich curriculum?

2) How does professional development support during the enactment lead to changes in teachers' perceptions?

3.3 METHODS

3.3.1 *Taste Receptor Analysis curriculum unit*

The Taste Receptor Analysis curriculum unit was designed to allow students to use biotechnology in conjunction with a common biology class experience—PTC (phenylthiocarbamide) tasting. Many teachers ask students to test their ability to taste the bitter compound PTC to engage students in thinking about concepts of Mendelian genetics. The primary cause of differences in the perception of PTC-like compounds among humans has been traced to genetic variants in the chromosome 7 TAS2R38 gene, which codes for a bitter taste receptor. If someone carries one or two copies of the dominant allele of the TAS2R38 gene, they are likely to be a taster of bitterness. A person has about an 80% chance of being a non-taster of bitterness if they have two copies of the recessive allele of the single nucleotide polymorphism (SNP) tested in this

experiment. It is thought that about 20% of the variation in bitter taste perception of PTC and other bitter compounds is explained by other genetic variation (Wooding et al. 2004; Kim et al. 2003).

We designed the Taste Receptor Curriculum unit so that students could have the opportunity to use DNA technology to analyze their own genotype and be engaged in authentic scientific practice in their secondary science classroom. The unit can be enacted over three fifty-five minute or two ninety-minute class sessions. The unit begins with students being instructed to expel saliva into collection kits and then adding a preservative to their saliva samples. This step is followed by extraction of the DNA contained in the cells in the saliva and then copying the DNA of the TAS2R38 region using the Polymerase Chain Reaction (PCR). After PCR, the copied DNA is subjected to the Restriction Fragment Length Polymorphism (RFLP) reaction during which it is cut by an enzyme that binds to the sequence of only one of the genetic variants. The cut DNA samples are then separated utilizing gel electrophoresis to separate the DNA according to size so that the cut and uncut DNA fragments can be recognized. The final part of the DNA extraction and the Polymerase Chain Reaction are completed in a university laboratory in which two of the co-authors are researchers; however, the teachers and students complete all other experiments and analyses of this unit in their classroom.

The big ideas that are associated with the biotechnology component of the unit include how DNA can be analyzed to determine genotypes and predict phenotypes and that students can understand and perform DNA analyses (including RFLP digestion and gel electrophoresis). To intellectually and technically prepare students to be able to complete the RFLP Reaction, RFLP gel electrophoresis, and PTC allele genotyping, the

unit includes support activities. A Food Color Gel Electrophoresis activity introduces students to the principles of gel electrophoresis by allowing them to practice loading gels with food coloring and observing the separation of the dyes based on their molecular size and charge. Other individual, small-group, and whole-group activities are also used to engage students in the principles of how the *TAS2R38* gene is related to the ability to taste PTC through discussing transcription and translation. Students are also introduced to the concepts of the Polymerase Chain Reaction through an online simulation developed by the Cold Spring Harbor Laboratory for the Dolan DNA Learning Center (Making many copies… n.d.). At the end of the unit, the students should be able to interpret and articulate the big ideas with limited guidance from their teacher.

3.3.2 *Study participants*

The professional development took place over a period of three years with three cohort groups—2009-2010, 2010-2011, and 2011-2012 consisting of eight, four, and two teachers, respectively. Since every teacher responded differently to the professional development, this study focuses on an in-depth comparative case analysis of two cases (Bogdan and Biklen 1998c). A comparative case study explores the aspects of two or more phenomena to discover similarities and differences of patterns across the cases, and cases in these studies may be chosen for several reasons including that they may be representative of other cases, may maximize what is learned, or be more accessible and hospitable toward the study (Stake 1995b). Our cases, whose names have been changed in this account, were Darcy of the first cohort and Nina of the third cohort. Darcy and Nina were chosen from their respective cohorts because they represented extreme examples of support needed to matriculate through the professional development model.

Both Darcy and Nina completed all three phases of the professional development (Figure 1) and both were fully compliant with participating in data collection for the study. In our study the two cases were compared in regard to their beliefs and how their beliefs influenced their fidelity of implementation. A summary of these teachers' professional and school demographics is provided in Table 3.1

3.3.3 *Three phases of professional development*

The development of the extended professional development program for the Taste Receptor Analysis unit was rooted in the situated cognition theory. Situated learning theory suggests that learning happens through immersion in natural contexts. Guided knowledge-gaining experiences, or cognitive apprenticeships, in natural contexts increase conceptual knowledge (Brown et al. 1989). The natural context for teachers is the classroom. Therefore, professional development models that include coaching in the classroom provide teachers with opportunities to learn content and instructional methods through practical teaching experiences (Browne & Ritchie 1991, Dennen & Burner 2007, Lin, Hsu and Cheng 2011).

In order to provide situated support, our professional development design included three phases (see Figure 1): engaging teachers in the curriculum as learners, giving teachers practice experiences with colleagues and students outside of their own classroom, and offering opportunities to enact the unit with support and reflective feedback while using it with their own students. Phase I was implemented in the university classroom setting and all teachers participated as learners and experienced the curriculum as their students would in a K-12 classroom setting. Techniques that could be

used to engage students in the analysis and articulation of the big ideas of the unit were modeled. The teachers were also taught how to prepare reagents and use the equipment, as well as the genetics and biotechnology content that would assist them with enacting the unit on their own. Phase I enactment for the first two cohorts of teachers also allowed for participating teachers to co-teach the unit to summer enrichment camp students with the researcher and other teachers during a two-week summer professional development workshop. Phase I for the third cohort of teachers occurred through a one-week after school graduate school class unit that provided teachers with one day to practice the unit with middle school children visiting the university for academic enrichment programs. Phase II was the teachers' classroom enactments where they received whatever amount of in-class support they desired to achieve successful enactments in their classrooms. Examples of support included co-teaching with the author, reagent and material preparation, and technology scaffolding (assistance with operation and student management). Phase II support ranged in occurrence from one enactment to over three academic semesters of support. Phase III enactments, which consisted of teachers enacting the unit without co-teaching support, were completed by all teachers within two academic years of their Phase I Enactment.

3.3.4 *Measuring fidelity*

The degree of fidelity of implementation (FOI) of the curriculum was grouped into three different levels (Basic, Enhanced, and Full) and was defined by four of Odonnell's (2008) FOI criteria which include: quality of delivery, participant responsiveness, adherence, and program differentiation; duration was omitted due to time limitations of this study (see Figure 2). The quality of delivery assessed how the

curriculum was enacted. To fully align with the design of the big ideas of the curriculum in terms of participant responsiveness and adherence, students should be fully engaged in data analysis and articulating their findings. Program differentiation should include modifications and adaptations that align with or enhance the students' ability to be fully engaged with the technology and interpretation of their data. As depicted in Figure 2, Basic implementation is defined as the enactment meeting at least two (50%) of these criteria, whereas an Enhanced implementation is defined as the enactment meeting three (75%) of these criteria. Enactments that meet all of these criteria (100%) are categorized as Full.

3.3.5 *Data collection and analysis*

The data collection and analysis of this study uses a phenomenological framework which allows researchers to attempt to understand events and interactions by studying people's behavior and their interpretation of their behavior in particular situations (Bogdan and Biklen 1998b). Data collected during Phase I enactments included researchers' field notes, teacher pre and post interviews and journal writings as well as videos of the teachers' reflection on their practice. Phase II and III teaching enactments were recorded, and the author kept a field journal and interviewed the teachers before and after each of the enactments conducted during the phase. Pre-interviews took place within the week before the enactment, and post-interviews took place immediately after or within twenty-four hours of the enactment. Interviews were semi-structured in design (Glesne 2011b) and lasted fifteen to thirty minutes. The pre-interview questions asked teachers to discuss their beliefs about the curriculum, professional development and student learning. In the post-interview, teachers were asked questions similar to

those in the pre-interview with additional questions regarding teachers' beliefs about how they enacted the curriculum as well as teachers' beliefs about how students participated in and learned through their enactment.

The data were analyzed by the author using a constant case comparative structure (Glesne 2011a; Bogdan and Biklen 1998a) through which observations from all of the phases' data sources were transcribed, coded, and segregated into themes which included "teachers' beliefs about student learning," "teachers' beliefs about their practice," " teacher actions", and "student actions." For example, some of the codes that were included in the "teacher actions" theme included "acting as facilitator," "acting as director," "managing student technology use," "directly stating big ideas," "guiding student discussion of big ideas," and "soliciting support." We continued our analysis by exploring how thematic ideas varied from data sources collected between the cases. The thematic variation formed the basis of the discussion section and was used to develop implications and conclusions. Data validity was checked through the triangulation of observations from the themes gleaned from field notes, pre and post enactment interviews, journal writings, and videos of enactments and reflections on enactments (Bodner and Orgill 2007; Stake 1995a).

3.4 FINDINGS

3.4.1 *Case 1 summary-- Darcy*

Darcy was a veteran teacher who had twenty-seven years teaching experience at the beginning of this professional development period. She taught biology, environmental science, and anatomy and physiology courses in the same school for fifteen years. Before

teaching, Darcy worked as a post-baccalaureate researcher in a marine biology laboratory for one year. Through professional development support over two academic years during which she conducted three Phase II and one Phase III enactments, Darcy was able to transition from a Basic Enactment to an Enhanced Enactment of the Taste Receptor Analysis Unit. During this period of support, Darcy's beliefs about her students' ability to learn using the tools of scientists changed along with her own perception regarding her ability to teach using a technology rich curriculum. However before her shift in beliefs, Darcy's lack of fidelity in implementation of the curriculum negatively affected students' opportunity to learn the big ideas of the unit.

3.4.2 *Darcy's Phase I introduction to the unit and initial Phase II enactment.*

Darcy was introduced to the Taste Receptor Analysis curriculum through a two-week professional development program for secondary science teachers. During this Phase I introduction, two co-authors taught the class, and Darcy spent the first week interacting with the curriculum as a student. During the second week of the Phase I enactment, Darcy co-taught the curriculum to summer enrichment middle and high school students with other teachers in the program for four days. Following Phase I, she expressed an eagerness to enact the unit in her own classroom because she believed it to be a unique and engaging activity that would enforce concepts presented in previous grades:

> My plan is to take what we have done about the PTC tasting this week, and apply it when I'm doing those special senses unit in Anatomy and Physiology, and where I'm always trying to come up with something that it is unique and different

> for them to do with that…. And this really ties back in to their genetics information that they got back in the 10th grade; it pulls out something that maybe they never quite got, never quite understood, and it also takes them forward into technology. There's going to be an inherent interest level because it's their own DNA, and it's very doable. So, I'm really excited about incorporating that part into that unit; I think they're going to just love it!

Darcy also expressed that she believed that students of various ability levels could learn using the unit's technology after working with the summer enrichment camp students:

> Doing this with rising 9th and 10th graders and seeing how successful it was gives me some confidence with being able to do it with students who are less…of the scientific mind, you know, not the kids who'll take AP, but the ones that are taking anatomy and physiology and just barely got through biology. So, I feel more confident with what they can do…. This is doable for even the kids that are not higher level.

Darcy reiterated in her first Phase II pre-enactment interview that she wanted to use the Taste Receptor Analysis unit because it would engage her students in a hands-on experience with gel electrophoresis and allow them to work with their own DNA. However unlike her Phase I post-interview, Darcy expressed doubts in her students' ability to learn using the gel electrophoresis equipment before her first Phase II enactment by expressing "my students just don't get this." Her perceptions were influenced by her previous teaching experiences with the students, nd she explained how "they have a hard time with labs" in the interview. She also articulated a lack of

confidence in her own ability to successfully enact the curriculum without assistance. During the interview, she shared, "I hope I don't mess it up." During the first Phase II enactment, she continuously interrupted her dialogue with glances in the direction of the support person and statements of "is that right?" Though Darcy wanted to give her students an authentic hands-on experience using the tools of scientists, she did not believe that her particular students could master the use of technology-rich curriculum and she did not have confidence in her ability to enact the unit without assistance.

Whereas the curriculum is designed for the students to observe and interpret their own results, during her enactment, Darcy's beliefs about student learning and her lack of confidence in her own ability to enact the unit led to poor fidelity of implementation. Darcy omitted the restriction digest activity where students learn to determine the size of DNA fragments after being exposed to restriction enzymes. Without understanding how to differentiate DNA fragments, students were unable to interpret their gel electrophoresis results on their own. Instead, Darcy showed students their fragmented DNA samples and she interpreted the results for them—"Do you see right there? There are two lines. That means you are heterozygous." In the post-interview for this enactment, Darcy stated that she did not include the activity because she was running out of class time and could not explain the nuclease activity of the particular enzyme used in the unit:

> We were getting close to the bell, and I wanted the students to see their results. I figured it would be easier to just show them the DNA pieces on the gel and tell them which one was the uncut non-taster allele. Besides, I'm still a little unclear on the big T (cut DNA), little t (uncut DNA), and [cytosine] versus [guanine]. It's a little confusing to me so I figured it would be confusing to the kids.

Darcy's belief in her own inability to successfully enact the unit without assistance and her limited content understanding compounded with a lack of time and caused her to eliminate the students' opportunity to interpret their own data. Along with interpreting results for the students, Darcy micromanaged students in their use of the equipment and removed key learning activities from the unit. Darcy achieved a Basic degree of implementation during her first Phase II Enactment by attempting to enact the unit but not meeting participant responsiveness, adherence, and program differentiation criteria.

3.4.3 *Darcy's Phase II support and Phase III enactment*

Over the course of two years of professional development support, Darcy was able to achieve an Enhanced degree of implementation during her Phase III Enactment. Part of Darcy's professional development support during her three Phase II enactments included modeling how to identify and train "expert" students who would be entrusted to help other students use the equipment during the unit. By having this classroom management technique modeled, Darcy was able to change her belief of students' ability to use the tools of scientists for learning in her classroom. Before her first Phase II enactment, Darcy believed that her students were not capable of using the electrophoresis equipment without her direct supervision. In her pre-enactment interview for Phase II when she was asked how she planned to manage the students in their use of the equipment she stated, "there is not enough of me to go around…, [and] I don't want them to break anything." Because she believed that she needed to supervise each student group as they worked with the equipment, Darcy was also convinced that she could not successfully enact the lesson with her classes that had more than twelve students. However, during the co-teaching experience in which the researcher modeled how

students could be trained to assist their peers with the equipment freeing the teacher to manage the entire class, Darcy was able to see how students could be trusted to use and learn through their use of the equipment. Darcy adopted this "expert student" concept and expressed how she utilized it successfully during her Phase III enactment post-interview:

> I look for the kids who do really well with the food coloring activity with me and have them help the other kids [with the gel electrophoresis of the digested DNA]. It seems to work, and those kids seem to really like being a leader.

By having the opportunity to see and practice classroom management strategies during professional development support, Darcy's belief changed from one of doubt to faith in students' ability to work with technical equipment and gain experience in the practices of scientists.

Even with this change in beliefs regarding students' ability to learn using the gel electrophoresis, Darcy still did not enact the curriculum with a Full level of fidelity. At the end of the Phase III enactment when students were reading gel results, Darcy interpreted the final results for the students:

> Do you see those two lines? [pauses for student response] Well, those two lines mean that you have both alleles. But look at that other lane where there is only one line. That person is homozygous for the non-tasting allele.

Even though Darcy allowed the students to work with the equipment on their own and did not omit any parts of the unit, she still did not allow students to interpret the gel-electrophoresis results on their own.

Along with co-teaching interactions which supported the change in belief regarding students' ability to learn using technology-rich curriculum, Darcy also received materials management and technological scaffolding during Phase II. This support along with repeated experience with the unit supported a change in Darcy's perception of her own ability to successfully enact the curriculum on her own. Using the Taste Receptor Analysis Unit requires teachers to be able to prepare reagents and materials, utilize a thermocycler and electrophoresis apparatus, and trouble-shoot when problems occur. Phase I of the professional development included instruction and practice in each of these areas. During the pre-interview before her first Phase II enactment, Darcy expressed her need to have assistance with equipment management, specifically preparing gels for electrophoresis. She said, "I know we poured gels over the summer, but I think I need to see it just one more time to be comfortable." Even when preparing materials without support, Darcy admitted in her post-interview for the Phase III enactment that she made mistakes from which she learned and gained confidence. "I forgot to turn the tray one time and lost an entire gel! And another time, I forgot to place the combs and had to re-do the gels. [laughs] I didn't do that again!" By gaining technical knowledge and pedagogical techniques through practice with the unit along with professional development support, Darcy was able to express how her perception in her ability to enact the unit on her own shifted from doubt to confidence. Her Phase III enactment was scored as Enhanced because she was able to enact the lesson without support, utilized "experts" so that all students could be fully engaged with using the technology, and made no adaptations to the unit that maligned the designed intent.

3.4.4 *Case 2 summary-- Nina*

Nina has a Ph.D. in molecular biology with six years of collegiate and three years of high school teaching experience with biology and advanced placement biology courses. Nina completed only one Phase II enactment, and through professional development support, she was able to transition from an Enhanced to Full degree of implementation of the unit between Phase II and Phase III. Before attempting to enact the Taste Receptor Analysis unit during Phase II, Nina was confident in trusting students' abilities to utilize technology in the ways of scientists for learning. However, after her Phase III enactment, Nina expressed how she believed students could continue to learn through repeated exposures to and experiences with the practices of science. She also endorsed the belief that all teachers should be prepared to instruct students using the tools of scientists.

3.4.5 *Nina's Phase I introduction to the unit and initial Phase II enactment*

Nina was introduced to the Taste Receptor Analysis curriculum as a novel way to teach gel electrophoresis and DNA analysis as a student in a professional development course in life sciences for teachers. Through this course, Nina read and discussed recent genetics publications for their theoretical applications and biotechnology techniques. She agreed to observe the enactment of the Taste Receptor unit during Friday SCienceLab at the author's university. During Friday SCienceLab experiences, middle and high school students have the opportunity to engage in science inquiry laboratories using the tools of scientists while working with university professors, research technicians, and graduate students. On the day that Nina attended the Friday Science Lab, the author was the lead

instructor for the Taste Receptor Unit with a class of middle school students. Nina participated as both a learner of the new curriculum and a co-teacher in that she, one of her classmates, and two graduate students assisted students with using the technology.

At the end of the instruction, Nina had the chance to process what she observed during the enactment and how she could implement the unit in her own practice with the author. Nina was impressed with how middle school students were both excited about and capable of using the equipment. She stated, "I thought that they would be nervous or that they would make mistakes, but they did very well. Nobody poked holes in the gel, and they seemed to really like using the pipettes and loading the gels." Nina also drew comparisons regarding the middle school students' ability and what she perceived her high school students were capable of doing:

> I was impressed with how well the kids got the concepts of fragmented DNA and how to tell their genotypes based on how far the DNA fragments traveled through the gel. If middle school kids can get these concepts, I know that the [high school students] can get it and be able to take it further and determine class allele frequencies.

As confident as she was with her students' ability to describe, explain, and interpret evidence when learning through the technology-rich curriculum after Phase I, Nina did express that she felt her only limitations with enacting the unit on her own during Phase II would be preparing the reagents and other materials.

Nina's confidence in her ability to enact the unit was evident in how she planned a professional development workshop for her Phase II enactment. She and her colleague,

who came to the Phase I unit modeling, decided to co-teach the unit to thirty teachers in their district. As a teaching team with Nina as the lead teacher, their initial Phase II enactment displayed an Enhanced degree of implementation— they co-taught the unit, modeled how to use technology, monitored learners with the use of technology, added adaptations that enhanced the big ideas of the unit, but needed assistance with helping learners interpret their own results.

Before the start of the enactment, Nina and her colleague from the Phase I enactment reviewed their roles in the unit enactment; Nina decided to take the lead teacher role. She expressed how she would not have a problem supervising the teachers as learners with using the equipment because she was confident that most would have some level of experience with electrophoresis equipment. Nina supposed that those with the expertise could assist the few who were not familiar with the process. However, as she prompted the group of teachers to form small groups and begin the food coloring activity to practice with the pipettes, she quickly realized through their hesitant or fumbled movements that most of the teachers were not experienced or comfortable with using the equipment. In response, Nina reassembled the small groups of teachers into one large group and demonstrated how to use the equipment. Following the demonstration, Nina, along with her colleague, worked with the teacher-learner groups to monitor them with using the equipment.

Along with modeling and monitoring the use of the equipment with the teacher groups, Nina was able to add changes that enhanced the unit by illustrating unobservable concepts and discussing real-world applications. During whole class discussion, Nina introduced and explained the polymerase chain reaction process, a big idea of the unit

with which the students do not have hands-on experience, through questioning and using a Java based simulation that she found on the web:

> How did we get the DNA that we needed? [learners offering answers] Did you just spit your PTC tasting gene in a cup? [no] No, we had to undergo the PCR process [proceeds to model polymerase chain reaction with the simulation].

Along with finding and implementing simulations to assist in explaining big ideas of the unit, Nina was able to add additional content that enhanced the real-world application of the unit's key concepts. She introduced and discussed research about the importance of and variation in the gene for PTC tasting. While sharing evolutionary data from primates and humans, Nina helped make the information more interesting and relatable to the majority female class by connecting the inherited ability to taste PTC to pregnancy, morning sickness, and cigarette smoking:

> [Shows website and plays sound bite] This is also a hypothesis about morning sickness. Women get [it] to keep them from eating foods that could potentially harm the embryo. I'm not sure about how much data is behind that but it is related to PTC tasting. … Also, people with the tasting allele are less likely to smoke.

Even though Nina was able to enhance the unit with changes that supported the development and understanding of key concepts, she still asked for assistance with guiding learners in the interpretation of their gel electrophoresis results. Nina said she needed a "refresher" on how to distinguish the tasting allele from the non-tasting allele as represented on the gel electrophoresis results. By adding adaptations that enhanced the

big ideas of the unit, co-teaching the material, modeling and monitoring the teacher groups with the use of technology, but needing assistance with helping learners interpret their own results, Nina was able to enact an Enhanced degree of implementation during her first Phase II Enactment.

3.4.6 *Nina's Phase II Support and Phase III Enactment*

Nina did not engage in additional Phase II Enactments after her initial experience. After the professional development workshop that she planned and conducted with her colleague, Nina expressed during the post-enactment interview how she was ready to use the unit with her students, and she did so three months after her sole Phase II enactment. Because of the desire to expose her students to a college campus, Nina decided to enact the unit using one of our standard laboratory classrooms that was furnished with lab tables and chairs. Though she utilized our laboratory space, Nina still prepared her own reagents and materials to enact the curriculum and did not receive any further professional development support during her Phase III Enactment.

Before her Phase III enactment, Nina was confident regarding managing students with equipment-- "I'm completely comfortable with [students using the equipment]. No matter what they do, it can't go so wrong that it leads to tragedy." During Nina's enactment, she allowed students to work with the equipment on their own in groups after showing them how to use the equipment during a whole-class demonstration; she observed student groups and addressed specific questions from students who questioned how to use the equipment. Her belief that students can be trusted to work with technical

equipment and can gain confidence in the practices of scientists was supported through her enactment:

> I feel so strongly that the kids should try even if they don't do it right, it's not the end of the world. So, I just trust that there is going to be something for them to see in the end, and even if they don't do it perfectly, it is better for them to try. If I said, 'Oh no, you're going to mess things up, so I'm going to put it in there' and I did all of the pipetting, that would be the same thing as them watching a video. They just need confidence. It was amazing how hesitant they were when they put in the first dye and by the time they were loading their DNA, there were a lot of kids [who] felt like they really did it well.

When it was time for students to analyze their data using the technology, Nina used questions to guide students in the interpretation of their own results—"That lane has one band but your lane has two. What could that mean in regards to your genotype and how do you know?" Nina's belief in students' ability to describe, explain, and interpret evidence when given the opportunity to work with technology in the ways of scientists allowed her to trust students with the equipment and guide them in interpreting their own results.

Even though Nina believed in students' abilities to use the tools of scientists before her Phase III Enactment, Nina did not express a difference in students' ability to learn through curriculum which simulated laboratory experiences from students' ability to learn from curriculum that allowed them to work with real technology. Before having access to the Taste Receptor Unit and its equipment, Nina described how she typically

taught gel-electrophoresis and restriction fragment length polymorphism reaction analysis through a paper lab where students used scissors to snip paper strands of DNA at restriction sites and then used glue to paste these "fragmented" strands onto a paper gel. However, after her Phase III enactment, through which she was supported by having access to gel electrophoresis and restriction enzyme analysis equipment, Nina expressed the belief that though students can learn through classroom activities that simulate laboratory experiences, students need real experiences with equipment during experiments to fully grasp the complexity of some scientific practices:

> I was really surprised that from what I described to them in class, they didn't have an idea of what a physical gel was or how you would do the process. Having them actually see it and do it I think really helped them to understand it better…. It's as valuable a learning experience as can be for clearing up misconceptions. They had one picture in their minds and now they know what it's really like.

By having access to technical equipment and experiencing how students learned through its use, Nina placed more value on using the tools of scientists in the classroom to increase student learning over using curriculum that simulated laboratory experiences. She stated:

> I want all biology students in my district to complete the Taste Receptor Analysis so that they can really understand gel electrophoresis, PCR-RFLP, and how what they inherit from their parents really is important. I don't think they get a good understanding from the [paper digest] lab we have been using. I want to do a

professional development workshop with all biology teachers at the beginning of next semester and make it mandatory for all teachers to use the gel electrophoresis equipment.

Prior to the professional development, Nina's beliefs included high confidence in her students' ability to learn through the use of technology and her own ability to manage students' technology use. However, through her experience with the professional development unit, Nina now valued students' engagement in repeated authentic experiences with tools and practices of scientists.

3.5 DISCUSSION

In looking at the case narratives developed from these two teachers' interviews, surveys, journal entries, and video recordings of their enactments, several different themes were identified. This study adds to the literature in describing in-depth the situated support needed for two teachers to enact technology rich science curriculum with a high level of fidelity of implementation. Teachers' beliefs regarding their own ability to enact technology rich curriculum were influenced by their educational experiences before and throughout the professional development. These beliefs influenced the teachers' fidelity of implementation of the curriculum and their perceptions of their students' abilities to learn from the technology rich curriculum experiences. However, the fidelity of implementation of the curriculum and the teachers' perception of their ability to successfully enact the unit were increased with an extended professional development model. This situated model provided opportunities for teachers to engage in reflective

feedback, learn technical content, use the technology, and experience modeled classroom management of students with the technology in informal and formal environments.

3.5.1 *Teachers' beliefs and educational experiences*

Teachers' classroom practices can be influenced by their previous experiences with science; having constructivist practices that engage students in the practices of scientists is related to teachers' out-of-school science experiences (L. K. Smith 2005; Lotter et al. 2007). Teacher self-efficacy, which Bandura (1993) defined as the perceived ability to effectively implement lessons, is a strong predictor of new curriculum implementation in that teachers who believe they are able to achieve specific teaching goals are more willing to try new curricula in their classrooms (Tschannen-Moran et al. 1998). Darcy, who did not perceive that she could effectively implement the curriculum during Phase II without co-teaching support, chose not to teach critical activities of the unit which resulted in missed opportunities for student learning of content and scientific practices. However, Nina, who exhibited high perceived self-efficacy, achieved the teaching goals of the unit resulting in Phase II and Phase III enactments aligning with or enhancing curriculum goals. Both teachers held undergraduate degrees in biology, which is part of the qualifications to become certified to teach the subject area in secondary settings in most teacher preparation programs (Biology teacher, secondary 2013). What differentiated these two teachers' background educational experiences was the extent to which they were engaged in scientific research experiences. However, our situated professional development model supported both cases. By having diverse mentored teaching experiences in separate classroom environments and with different students,

teachers had opportunities to perform and then change their perceptions regarding their capability to teach and students' ability to learn with technology.

3.5.2 *Professional development and teachers' beliefs*

Teachers' perceptions of their ability to effectively implement the technology-rich curriculum and their beliefs regarding how students learn in science were influenced by supported experiences during the professional development program. Our findings support those of Pinto (2005) and Fogleman et al. (2011) who emphasized the importance of immediate teacher reflection on curriculum adaptations. Through reflective experiences, Darcy was able to see how omitting activities limited students' opportunities to engage in analyzing and articulating big ideas on their own. These results are consistent with findings of Rushton et al. (2011) who investigated the beliefs and practices of in-service chemistry teachers throughout their participation in a year-long inquiry professional development and found that teachers valued having opportunities to reflect on their teaching with colleagues after their enactments because it provided the opportunity to critique inquiry teaching techniques and solidify components of the model that were vital to student learning.

Rushton et al. (2011) questioned what happens following the "honeymoon" period during which "the enthusiasm and novelty of the approach, coupled with the pleasant memories of the [professional development] institute are sufficient to overcome the real and perceived barriers to inquiry instruction" (p. 44). Both Nina and Darcy expressed confidence in their own students' abilities after their Phase I experiences practice-teaching with students. Though Nina was able to sustain her beliefs, Darcy's

classroom experiences with her own students during other laboratory enactments caused a decrease of her confidence in her students' abilities to learn using the unit's technology. Darcy's example may suggest that perceived and real barriers to inquiry, such as organizational structure and types of learners, can cause a reversion to pre-professional development classroom practices after the "honeymoon" period. Through situated professional development support which included modeling of instructional strategies in her own classroom, Darcy was able to regain confidence in her students' abilities and improve her implementation of the curriculum. These observations support previous study suggestions regarding the use of repeated modeling of instructional strategies in multiple contexts to assist teacher learning (Singer et al. 2011, Luft 2001). Our extended professional development model included engaging teachers in the curriculum as learners, giving teachers practice experiences with colleagues and students outside of their own classroom, and offering opportunities to enact the unit with support and reflective feedback while using it with their own students. Through this model, teachers in our study acquired technical content, practice with the equipment, and management skills which helped them to enact the unit with greater levels of fidelity with each subsequent enactment.

3.6 IMPLICATIONS AND CONCLUSIONS

The implementation of technology-rich curriculum into a science classroom can be a difficult task for many teachers. Our study suggests professional development programs that support teaching experiences in formal and informal environments are needed to consistently and successfully engage students in the practices of scientists as suggested by the National Academy of Sciences and National Academy of Engineering (*A*

Framework… 2012). These situated teaching and learning experiences that include technical assistance, classroom management support, and content instruction, build teachers' scientific skills and teachers' self-perceived ability to successfully enact the curriculum. These supported beliefs can lead to enactments that are aligned with or enhance the curriculum designer's intent and fully engage students in the process of learning through scientific practices. .

A limitation of this study is rooted in the curriculum's tools. Both cases needed support with interpreting gel electrophoresis results with students during the Phase II enactments. Since the time of this study, a set of example results that can be used to demonstrate reading gels to provide more authentic experiences or to provide results when failure of the technology occurs has been included with the kit. Also, the current study was not specifically designed to evaluate factors related to types of learners or organizational structures that limit technology-rich curriculum implementation such as the amount of class time teachers have to work with students or administrative-level expectations of content. All of these factors can attribute to teachers' beliefs regarding students' abilities to learn content through scientific tools and therefore limit the fidelity of implementation. It is suggested that the association of these factors be further investigated in subsequent research.

Further work may explore how our situated model supports teachers through barriers of successful implementation. The barriers include those that are extrinsic, like organizational limitations, that have been discussed in previous work (Ertmer 1999; Waight and Abd-El-Khalick 2007) and those that are intrinsic and have been highlighted in this study-- teachers' beliefs about their ability to successfully enact the curriculum

and beliefs regarding students' ability to learn using technology (Waight and Abd-El-Khalick 2007; Falloon and Trewern 2013). Partnerships between research scientists and classroom educators founded in the consistent and successful use of technology-rich curriculum need to be prepared to invest the resources that successful institutionalization requires. These resources include not only pedagogical, content, and technology expertise that a science educator may provide but also a significant amount of time and a toolkit to deal with the barriers of successful implementation. Studies regarding how the resources of situated professional development models can be best used and allocated at the school, district, and state levels are needed to support successful NGSS- aligned curriculum implementations.

Table 3.1 Case demographic information

Teacher	Cohort Group	Years of Teaching	Highest Education Degree	2012 School Characteristic-- %Scoring ≥70 on Biology EOCT	2012 School Characteristic-- SC Annual Report Card Absolute Rating	2012 School Characteristic-- Enrollment
Darcy	2009-2010	27years in high school	B.S. in biology	81.5	Excellent	1789
Nina	2011-2012	6 years college, 3 years high school	Ph.D. in molecular biology	69.5	Average	1594

EOCT: South Carolina End of Course Test; students' score comprises 20% of their final grade in the course (SC District 2011)

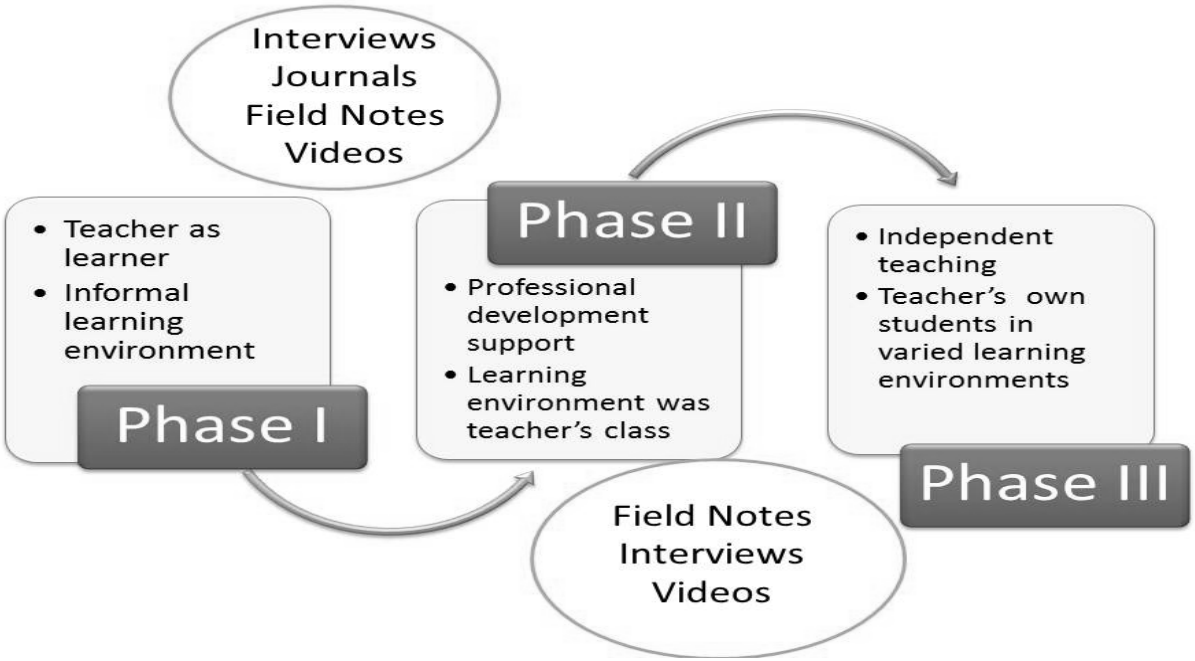

Figure 3.1 Taste receptor curriculum unit professional development model: this figure illustrates the components of each phase and the data collected between each phase of the professional development.

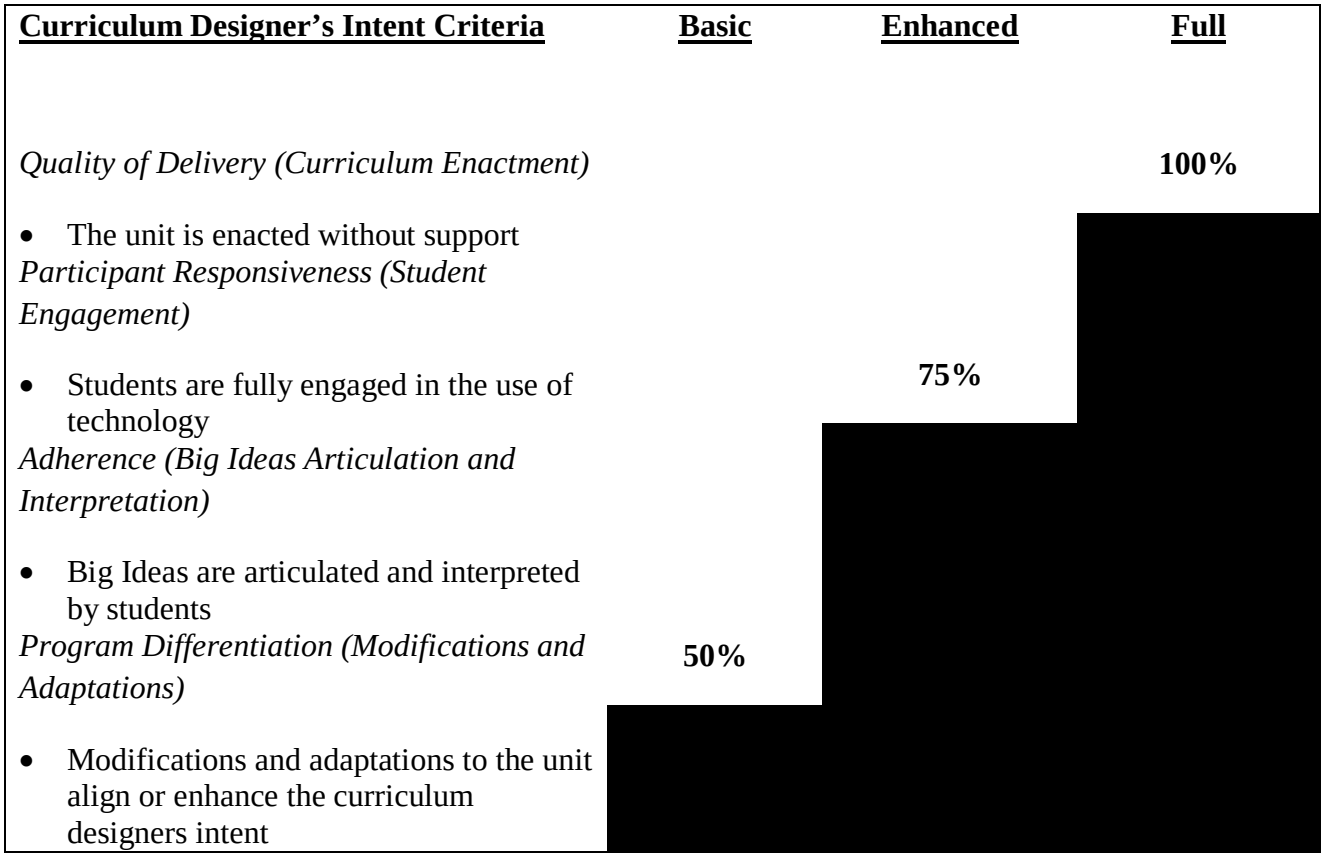

Figure 3.2 Criteria for measuring the degree of fidelity of implementation of the taste receptor curriculum unit enactment.

CHAPTER 4

CONCLUDING REMARKS

The results presented in this dissertation contribute to the literature regarding understanding breast cancer subtypes and science education teacher professional development. In study one, *Genetic Variation in Adiponectin Signaling Pathways May Influence Breast Cancer Prognosis*, we analyzed SNPs involved with adiponectin signaling. We found twelve associations between individual SNPs and patient or tumor characteristics that impact BrCa prognosis that support previous studies indicating several of these SNPs with cancer risk. Our results do not reflect correction for multiple tests, but they are consistent with the results from previous studies. Also, our study may be underpowered and should be repeated with larger sample sizes. Still, to our knowledge, this is the first study evaluating the association of these SNPs with risk for characteristics of BrCa subtype in both White and Black American populations. Our results, if corroborated by other studies in larger sample sizes, suggests further investigations regarding how these genetic changes may be associated with response to therapy and longterm outcomes.

Our results from study two, *Teachers' Beliefs of Technology Use to Teach Genetics*, inform science education professionals about the amount of support teachers need to implement technology-rich curriculum with a high level of fidelity of implementation. Through our comparative case analysis of two cases, we found that an

extended professional development model that included teaching of content knowledge, practice with the technology, modeling of classroom management skills, and reflective feedback of enactments in formal and informal environments increased teachers' self-efficacy, belief in students' ability, and the fidelity of implementation of the unit. The amount of modeling in the classroom was dependent on the teachers' background experience and perceived ability to engage their students in use of the technology. Our study's results may not be relevant for all science classrooms that vary by learner heterogeneity and school environment. However, our study does emphasize the role of science educators who have pedagogical, content, and technology expertise who can provide extended professional development in schools as states adopt Next Generation Science Standards. Future studies should explore the dynamics of professional development models that support school, district, and state-level NGSS-based curriculum integration throughout entire courses and the beliefs and enactments of teachers who participate in these models.

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