

**Review Artcil** 

# Differential Susceptibility to Environmental Influences as a Theoretical Framework for Designing Genetic Nursing Research

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#### Abstract

The trend of personalized medicine will require more genetic studies to be done. Nurses are perfectly suited to conduct these types of studies. Designing these types of studies requires using a theoretical framework. Differential Susceptibility to Environmental Influence is a framework that describes a step-wise approach to designing these types of studies. Test of the independence of the susceptibility factor and the predictor, test of the association between the susceptibility factor and the outcome, comparison of the regression plot, test of the specificity of the model by replacing susceptibility factors and outcomes are the steps required to evaluate differential susceptibility.

**Keywords:** Environments; 5-HTTLPR; Differential susceptibility; GWAS

# Introduction

### Differential susceptibility to environmental influence

The National Institute of Health has identified precision health as a research initiative, including genetic studies. The advancement of technology has allowed for more genetic studies to be conducted than ever before. Nursing is in a prime position to conduct these types of studies. Nurses have studied how environments affect health since the Crimean War [1]. Now that technology makes studying genetics more accessible, nurses' roles must expand to study environmental effects on health with genetics as a variable. With new technology and information available, a theoretical framework must be used to design complicated genetic studies.

## **Theoretical framework**

Genetic studies that examine how genes interact with environments are gene-by-environment in nature. Variations occurring in identified candidate genes alter the genetic sequence. With interacting environmental stimuli, these variations lead to alterations in gene expression that code protein sequences and potentially change functional processes in the body [2].

Gene-by-environment theories have been described by several researchers [3,4]. A key factor in conducting genetic studies starts with candidate genes. Candidate genes are genes that have been identified in association with one or more diseases through large genome-wide association studies (GWAS). These studies have examined common genetic variations among those who share a certain diagnosis. Significant associations in large-scale GWAS studies are in the  $p=5 \times 10^{-8}$  range [5]. These types of studies are helpful in narrowing the potential genes influencing pathology. However, they are not comprehensive explanations to answer the question of why some individuals with genetic variations go on to develop disease, while others do not [3]. This is likely given small odds ratios that are found in GWAS. Single nucleotide polymorphisms explain very little about disease causes in complex disorders that have polygenetic variations.

The lack of replication for candidate genes alone has led researchers to consider these genes more as susceptibility genes. Susceptibility genes are those that modulate disease pathology in certain environmental contexts. In other words, genes may be thought of as analogous to the bullets in a gun, while the environment may be seen as pulling the trigger. Conceptualizing candidate genes as susceptibility genes, rather than vulnerability genes will create a framework for studying genes as they interact with the environment in both a negative and a positive way. Susceptibility helps to conceptualize the strength of the genetic risk, not just the presence or absence of genetic risk.

# Literature Review

Descriptive research can be used as the basis for identification of potential environmental triggers to study. Adverse experiences during childhood (ACE) have been studied in several contexts as an environmental exposure that can activate susceptibility genes. Individuals with MAOA genetic variants who experience ACE exposure, go on to develop antisocial personality traits [6]. Short allele carriers in 5-HTTLPR have been shown to affect individuals' perception of their environment, perceiving events as more negative compared to long allele carriers [7]. These are two of many examples of studies using a susceptibility gene framework with environmental variables included in research.

Belsky and colleagues developed a framework for evaluating an environmental effect in the presence of a susceptibility factor [8]. They used parenting behavior ratings to evaluate if infant negative emotionality, or temperament, was associated with high externalizing and inhibiting behavior at age three for Caucasian, firstborn boys. It was found that mothering was predictive of all externalizing problems ( $\beta$ =-0.23, p<0.05) and fathering only made a significant prediction of inhibitive behavior ( $\beta$ =0.31, p<0.01). Inhibiting behavior is described as withdrawn, fearful and anxious, while externalizing problems are described as argumentative, hitting others, and disobedient [7]. This means that mothering behavior was predictive of lower externalizing problems, such as the lack of aggression and defiance, and fathering was predictive of only inhibiting behaviors, such as withdrawn and

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anxious. The susceptibility factor in Belsky's original work was the temperament of the infant, high negative emotionality. The moderator was the ratings of the parenting behavior, assessing quality and quantity of parent/infant interactions during home visits. The outcome was the amount of externalizing behaviour and inhibition in the infant at age three. Susceptibility factor in the original work was the temperament of the infant at birth.

While the original work of Belsky and colleagues used temperament for the biological factor, it could be applied to genetics being the biological or susceptibility factor. For the purpose of this work, the theory will be explored with genetics as the susceptibility factor. When moderated by an environmental trigger, such as parenting, the interaction of the susceptibility factor and the environment or moderator is a necessary condition for differential susceptibility [9]. The concepts within differential susceptibility will be explored and evaluated to construct a framework for designing genetic nursing studies.

#### Differential susceptibility to environmental influences

differential susceptibility to environmental influences by Belsky and colleagues, defined the concepts of differential susceptibility and will provide a framework for application to research [10]. The concepts in differential susceptibility were first developed from work with externalizing behavior of infants. The negative behavior and the type of parenting those infants received was the focus of the study [8]. Belsky stated individuals are not all equally responsive to environmental inputs [8]. Belsky also aimed to evaluate the effect sizes with different outcomes, both parenting effects on attachment and parenting effects on cognitive development [9].

Differential susceptibility is based on the interaction between biological/genetic vulnerabilities and environmental vulnerabilities. The concepts go beyond a dual risk framework, where biological risks remain in the presence of both positive and negative environments. The strength of the vulnerabilities is important to highlight, as well as the type of environmental trigger- positive or negative. Consideration of the amount of risk a susceptibility carries helps to make the theory more applicable. Biological predispositions can be triggered by negative environmental stress that result in pathology. The stronger the biological predisposition, the less environmental stress required to trigger pathology. However, those with lower biological vulnerabilities require more environmental stress to trigger the pathological process. For example, an individual with a homozygous risk allele for a disease would need less environmental stress to trigger the disease phenotype compared to an individual with a heterozygous risk allele/wild (or normal) type allele.

Differential susceptibility has potential for application to a wide range of nursing research. The different combinations of variables, strength of associations, and the effect size of each variable make the theory very useful for many disciplines. With this potential application, guidelines need to be established to ensure the theory is applied correctly and comprehensively. The authors have provided guidelines for stepwise testing of differential susceptibility. The moderator is the environmental trigger and the susceptibility factor is the biological/genetic factor. The five-item list is a stepwise guide for testing differential susceptibility [8,10].

- 1. Statistical test for genuine cross-over interaction
- 2. Test of the independence of the susceptibility factor and the predictor
- 3. Test of the association between the susceptibility factor and the outcome.
- 4. Comparison of the regression plot
- 5. Test of the specificity of the model by replacing susceptibility factors and outcomes.

#### Statistical test for genuine cross-over interaction

Statistical analysis using correlations and regression coefficients should be used to test for combined increased susceptibility in the



| Candidate genes/SNPs | #1 | #2 | #3 | #4 |
|----------------------|----|----|----|----|
| #1                   |    | p= | p= | p= |
| #2                   | p= |    | p= | p= |
| #3                   | p= | p= |    | p= |
| #4                   | p= | p= | p= |    |

Table 1: Example of table showing linkage disequilibrium.

| Candidate gene    | Association with outcome |  |
|-------------------|--------------------------|--|
| Candidate gene #1 | p=10 × 5 <sup>-8</sup>   |  |
| Candidate gene #2 | p=10 × 5 <sup>-8</sup>   |  |
| Candidate gene #3 | p=10 × 5 <sup>-8</sup>   |  |
| Candidate gene #4 | ρ=10 × 5 <sup>-8</sup>   |  |

Table 2: Associations between susceptibility factor and outcome.

| Selected SNP      | Lack of association with another disease |
|-------------------|--|
| Candidate gene #1 | <i>p</i> >0.05                           |
| Candidate gene #2 | <i>p</i> >0.05                           |
| Candidate gene #3 | <i>p</i> >0.05                           |
| Candidate gene #4 | <i>p</i> >0.05                           |

Table 3: Lack of association between susceptibility factors and alternate outcome.

presence of the susceptibility factor, environmental trigger and the disease of interest [10] using conventional statistical criteria to evaluate the genuine cross-over interactions of outcomes with environmental triggers and susceptibility factors. Ensuring that regression lines do cross, as in the example in Figure 1A. These data can be found in GWAS studies examining the associations with the outcome and in studies examining the context where disease presentation occurs.

#### Discussion

# Test of the independence of the susceptibility factor and the predictor

Lack of association between the environmental moderator and susceptibility factors/genetic variants is the next step. In Belsky's work, the negative behavior of the infant was not associated with negative parenting [10]. The environment of negative parenting was an independent factor from the infant negative behavior, meaning the negative infant did not cause the negative parenting environment.

The independence of the susceptibly factors is an important step in evaluating Differential Susceptibility from dual risk. Ensuring that each candidate gene adds a unique risk factor requires examining linkage studies. Linkage disequilibrium is studied in genetics to examine whether different single nucleotide polymorphisms (SNPs) are causing the same risk for disease. Linkage disequilibrium is important to ensure that the candidate genes are truly a unique factor for the outcome of interest. Some SNPs may be linked to each other, meaning when one SNP has a variant, a linked neighbor SNP will also have a variant. This means they will not follow Mendelian transmission rules if in linkage. Selecting candidate genes and then comparing those to each other through linkage data can be shown in a Tables 1 and 2. All candidate genes should have a non-significant association ( $p \geq 0.05$ ) with the other candidate genes selected, showing they are not linked and can be considered as independent factors.

# Test of the association between the susceptibility factor and the outcome

Selected candidate genes or the biological susceptibility factors should be associated with the disease of interest in Differential Susceptibility frameworks. This can be shown through GWAS data that have significant associations many times as high as  $p = 5 \times 10^{-8}$  for

a strong association [11]. An example of a table used to show this stepin differential susceptibility evaluation is shown in Table 3.

#### Comparison of the regression plot

Comparison of the regression plots of the moderators/ environmental triggers overlaid onto the regression plots of the susceptibility factors is a way to examine if differential susceptibility is present. Figure 1A is an example Belsky uses to show Differential Susceptibility in comparison with other types of associations that may be present (Figures 1B-1D). The solid black line represents the genetic or biological susceptibility factor, and the dotted line represent the moderator or environmental trigger.

# Test of the specificity of the model by replacing susceptibility factors and outcomes

Step five can be shown by replacing the outcome with another phenomenon to examine the unique risk related to the specific outcome and not a risk of outcomes that may be similar or related in some way. Step five is important to eliminate common factors that may be a risk for many types of disease. Table 3 shows the associations with another outcome and the associations should be non-significant or p>0.05. These results should be non-significant.

Differential Susceptibility is not the only theoretical framework that considers both biological and environmental factors in the development of disease. The diathesis stress model, dual risk, and biological sensitivity to context thesis all include concepts of both nature (susceptibility factors) and nurture (moderators or environmental factors) [4,12]. However, differential susceptibility is the only framework that provides a step-wise approach to showing differential susceptibility. This aids in designing complex genetic studies and the complex analysis that is required. A major advantage to using this framework is the emphasis on nature shaping the differences in health outcomes while not excluding nurture and accounting for the influence of nurture. This is the predominant theme in Differential Susceptibility to Environmental Influences, while many other theories place an emphasis on the nature being the predominate influence [13,14].

### Conclusion

Selecting candidate genes using data from GWAS and linkage studies helps to select the most probable genes contributing a susceptibility factor to disease pathology. Ensuring samples are well characterized and accurately diagnosed and then replacing the outcome of interest increases the specificity of the research. With complex analysis required and a large amount of data to review prior to implementing a study, having a framework to follow as a guide will facilitate the design and conduct of genetic studies.

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