ASSOCIATION BETWEEN KIRs AND LEUKEMIA SUSCEPTIBILITY

A Thesis Submitted

In the partial fulfillment of the requirement for the degree of

MASTER OF SCIENCE

in

BIOTECHNOLOGY

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May, 2025

ACKNOWLEDGEMENT

I would like to express my sincerest appreciation and gratitude to all those who have supported me and guided me towards the completion of my MSc. Dissertation. I would like to express my heartfelt gratitude to my mentor, Dr. Asmita Das, Department of Biotechnology, Delhi Technological University, for helping me identify and refine my thesis topic and providing guidance and insightful feedback. Her direction and knowledge have been instrumental in shaping the direction and quality of my work. Without her dedicated academic excellence and patience, this project would not have been possible.

I would equally like to express my gratitude to the PhD Scholars in my lab, for always being approachable and willing to help me with their constant encouragement and technical assistance. Their willingness to share their knowledge has made this project more insightful and enriching.

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DECLARATION

I, Anushka Mishra, 2K23/MSCBIO/58 student of M.Sc. Biotechnology hereby declares that the Dissertation Project entitled "ASSOCIATION BETWEEN KIRs AND LEUKEMIA SUSCEPTIBILITY" is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Science. This work is original and not copied from any source without paper citation. I have honored the principles of academic integrity and have upheld the normal student code of academic conduct in the completion of this work.

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This is to certify that the Dissertation Project titled "Association between KIRs and Leukemia Susceptibility" which is being submitted by Anushka Mishra 2K23/MSCBIO/58, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Science is a record of the work carried out by the student under my supervision. To the best of my knowledge, this work has not been submitted in part or full for any Degree or Diploma to this University or elsewhere.

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ASSOCIATION BETWEEN KIRs AND LEUKEMIA SUSCEPTIBILITY

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ABSTRACT

Aim: - Natural Killer (NK) cells are critical components of the innate immune system, serving as an essential first-line defense mechanism against malignancies such as leukemia. Their activity is controlled by a group of genes called Killer-cell Immunoglobulin-like Receptors (KIRs), which can either activate or inhibit NK cell function. Polymorphisms in these genes may influence how well NK cells can detect and destroy cancer cells. This review explores the association between germline KIR frequency and predisposition to leukemia, additionally also aims to get insight on whether activating KIR3DS1 gene is associated with an increased or decreased risk of developing leukemia. Among different cancers, the heterogeneity of leukemia, provides a window to explore the disease-specific and shared mechanism.

Using data from previously published case-control studies, the results for KIR3DS1 gene was combined and analyzed using chi-square test.

Result: - Data from two independent Iranian studies (Mirzazadeh et al., 2023; Alavianmehr et al., 2020) were pooled to investigate the association of the activating KIR gene KIR3DS1 with leukemia susceptibility. A chi-square test was performed on the combined dataset, which included a total of 276 cases and 290 controls. The analysis yielded a chi-square value of 17.647, with a p-value < 0.001, indicating a statistically significant association. The calculated odds ratio (OR) was 0.522, suggesting that individuals carrying the KIR3DS1 gene were approximately 48% less likely to develop leukemia compared to non-carriers in this dataset, suggesting a protective role.

Conclusion: - These findings suggest that activating KIRs do not always raise leukemia risk, and their effect may depend on other immune factors such as inhibitory KIRs and HLA ligands. More research is needed, combining genetic and functional studies across different populations to better understand these immune interactions and their role in leukemia. More extensive research on this topic could support the development of more targeted treatments for blood cancers.

While the current study is not a full meta-analysis, it shows the value of pooled statistical evaluation in a small scale gene association research.

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LIST OF ABBREVIATIONS

NK	Natural Killer
KIR	Killer cell immunoglobulin–like receptor
MHC	Major Histocompatibility Complex
ULBP	UL16-binding proteins
HLA	Human Leukocyte Antigen
LRC	Leukocyte Receptor Complex
iKIR	Inhibitory Killer cell immunoglobulin–like receptor
aKIR	Activating Killer cell immunoglobulin–like receptor
AML	Acute Myeloid Leukemia
ALL	Acute Lymphoblastic Leukemia
CLL	Chronic Lymphoblastic Leukemia
C-ALL	childhood Acute Lymphoblastic Leukemia
B-ALL	B cell Acute Lymphoblastic Leukemia
T-ALL	T cell Acute Lymphoblastic Leukemia
OR	Odds Ratio
LIR	Leukocyte Immunoglobulin-like Receptor
CNV	Copy Number Variation

Association Between KIR Genes and Leukemia Susceptibility

1. Introduction

1.1 Background on Natural Killer (NK) cells and their role in immune surveillance

Natural killer (NK) cells are vital components of the innate immunity and they are responsible for limiting tumour growth and viral infections by lysing transformed/altered or infected cells [37]. These cells play an active role in immune responses through their cytotoxic functions, cytokine secretion, and regulatory effects on T lymphocytes and dendritic cells [1]. They make up approximately 10% of the circulating lymphocyte population and are recognized as the primary facilitators of cancer immunosurveillance [1] [2] [19]. NK cell action is the result of the dialogue that takes place between the NK cell receptors and their corresponding ligand. Inhibitory signals are relayed upon the recognition of Major Histocompatibility Complex (MHC) class I molecules by the NK cell inhibitory receptor. While the activation depends on the balance between activating and inhibitory signals. Activating signals are transmitted by (1) recognition of molecules that bind to activating receptors such as NKG2D which recognizes ligands like MICA/B and ULBPs (UL16-binding proteins) [3] [4] and/or (2) due to the downregulation/absence of MHC-I molecules on the cell's surface known as the "missing-self" hypothesis, which describes how NK cells are capable of mediating cytotoxicity without prior sensitization by recognizing the absence or downregulation of MHC-I molecules on target cells. This lack of MHC class I expression fails to engage NK cell inhibitory receptors, thereby rendering the target cells susceptible to NK cell mediated lysis [2]. NK cells get activated and cytotoxicity is triggered against target cells if activating signals predominate.[3] [4]

Interestingly, the inhibitory signalling pathway dominates the regulation of homeostatic functions in mature NK cells, including those expressing inhibitory and activating receptors for identical ligand. [5]

1.2 Overview of Killer-cell Immunoglobulin-like Receptors (KIRs)

In humans, the KIR gene cluster is situated on chromosome 19q13.4 and covers a 150 kb region within the leukocyte receptor complex (LRC) consisting of a centromeric and telomeric region. Thus far, 14 KIR genes have been described along with 2 pseudogenes that do not code for a functional KIR molecule (namely, KIR2DP1 and KIR3DP1). [6]

Killer-cell immunoglobulin-like receptors (KIRs) are a family of highly polymorphic and diverse surface receptors predominantly expressed on natural killer (NK) cells and a subset of T cells. These receptors play a critical role in controlling immune responses by interpreting signals that govern the activation or inhibition of cytotoxic activity and cytokine production. [8]

KIRs interact with class I human leukocyte antigen (HLA-I) molecules, allowing NK cells to discriminate between healthy self-cells and those that are infected, transformed, or altered in some other way. KIRs are divided into two broad categories:

1. Inhibitory KIRs, which possess long cytoplasmic tails containing immunoreceptor tyrosine-based inhibitory motifs (ITIMs) and deliver negative signals upon HLA recognition. Involved in NK cell education

Encoded by 7 genes KIR3DL1-3, KIR2DL1-3 AND KIR2DL5

- Activating KIRs, characterized by short cytoplasmic tails, which transmit activating signals through immunoreceptor tyrosine-based activation motifs (ITAMs).

  Encoded by 6 genes KIR3DS1 AND KIR2DS1-5

KIR2DL4 performs both inhibitory and activating functions, but inhibitory functions dominate as it contains ITIMs in its cytoplasmic domain similar to iKIRs.

Four KIR genes, 3DL3, 3DP1, 2DL4, and 3DL2, are present on all haplotypes and are called framework loci [7]

KIRs exhibit extensive allelic and haplotypic polymorphism. KIR haplotypes are broadly classified into A and B haplotypes. A haplotypes typically contain more inhibitory KIRs and are relatively conserved, whereas B haplotypes include a greater number and variety of activating KIRs. [6] [7] [8]

As both the receptors and their ligands are independently inherited KIR-HLA interactions are not fixed, resulting in a high degree of combinatorial diversity that influences individual immune responses. This diversity has been linked to disease susceptibility, progression, and outcomes, including in viral infections, autoimmune disorders, cancer, and pregnancy complications. [5] [9]

1.3 Leukemia subtypes and pathophysiology

Leukemia refers to a heterogenous group of blood cancers that develop due to abnormal growth of immature white blood cells. It is categorized as either acute or chronic depending on the speed of disease progression, and as myeloid or lymphoid based on the type of blood cell affected. Acute leukemia is defined by the presence of more than 20% blast cells in the peripheral blood or bone marrow while chronic leukemia is typically marked by an elevated white blood cell count. [11]

The main types include acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), which originate from the myeloid lineage, as well as acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL), which arise from the lymphoid lineage. There are also rarer forms, such as leukemias involving mature B cells, T cells, and natural killer (NK) cells. ALL more commonly occurs in children, as 80% of ALL cases are observed to affect children.

Leukemia develops when pluripotent hematopoietic stem cells capable of giving rise to both myeloid and lymphoid lineages undergo malignant transformation. In acute forms of leukemia, the cancerous cells are typically immature and poorly differentiated leukocytes, known as blasts, which may be either lymphoblasts or myeloblasts. These abnormal cells multiply uncontrollably, replacing normal blood-forming cells and disrupting normal blood cell development and function, which leads to the clinical manifestations of the disease. [11][12][13]

1.4 Rationale for Focusing on Leukemia Susceptibility

Generally, it has been observed that hematopoietic cancers have responded better than solid tumors to NK cell therapies and the reasons for that are tied to the fact that the hematopoietic origin of leukemia directly involves cells that are primary targets of NK cell surveillance.

Given the close interaction between NK cells and hematopoietic cells, variations in KIR genes are likely to have a more immediate and measurable impact on leukemia development compared to solid tumors. The challenge arises from the difficulty of NK cell infiltration into the tumor site and the presence of inhibitory signals within the immunosuppressive tumor microenvironment, contributing to the exhaustion of NK cells.

Moreover, among different cancers, the heterogeneity of leukemia, (acute and chronic, lymphoid and myeloid forms) provides a window to explore the disease-specific and shared mechanism.

Considering the extensive body of research examining KIR-HLA genotypes and their influence on leukemia susceptibility and prognosis, this review specifically explores the impact of germline KIR variation on the initial susceptibility to various leukemia subtypes. Moreover, the copy number of KIR genes influences the proportion of cells expressing KIR and may be associated with the efficacy of immune responses against infections and malignancies. [7]

2. Literature Review

2.1 Importance of KIR-HLA interactions in immune regulation

The main function of KIRs interacting with HLA class I molecules is to help the immune system detect and eliminate abnormal cells while protecting healthy ones. Inhibitory KIRs stop immune cells from attacking normal tissues unless there is a loss or change in HLA class I due to infection or mutation, while activating KIRs assist in recognizing and targeting diseased cells. [17] [10]

When inhibitory KIRs interact with HLA class I molecules, they help educate NK cells to recognize those ligands as a normal part of healthy tissue. The traditional model explaining NK cell activation is known as the "missing self" hypothesis. According to this idea, NK cells are able to destroy target cells without needing prior exposure, because cells that lose or reduce their MHC class I expression become susceptible. This happens because they no longer engage inhibitory receptors on NK cells, allowing the NK cells to attack. [14] [10]

Multiple evidences indicate that KIRs and the combinations with their corresponding ligands exhibit polymorphisms which have an essential role in susceptibility or immunity to different diseased conditions, including pregnancy complications, viral infection, and autoimmune diseases [14] [15] [16] [18]

2.2 KIR Polymorphism and Leukemia Susceptibility

A wide range of researches have investigated the relationship between specific KIR genotypes and the probability of developing different forms of leukemia, including AML, CLL and CML.

The underlying mechanisms by which KIR polymorphism influences leukemia susceptibility are not fully elucidated, but several hypotheses have been proposed. Aberrant cytokine signaling and disruption of the leukemia stem cell hierarchy are considered to have a crucial role in the pathogenesis of these hematological malignancies. [10] [36]

2.3 Influence of activating vs. inhibitory KIRs

2.3.1 Predisposition to leukemia due to increased iKIRs/decreased aKIRs

A widely accepted immunogenetic hypothesis concerning KIR polymorphism and leukemia susceptibility posits that an increased presence of inhibitory KIRs (iKIRs) contributes to immune evasion by malignant cells. In this model, elevated iKIR expression on NK cells transmits strong inhibitory signals following the recognition of self-HLA class I molecules, leading to downregulation or termination of activity or anergy of killer cells. The immunosuppressive microenvironment also provides the opportunity to leukemic cells to circumvent innate immune surveillance and proliferate unchecked.

Several studies support this theory. Karabon et al. (2011) [20] reported a significantly higher ratio of inhibitory to activating KIR genes in leukemia patients (0.67 : 0.17), suggesting an immunogenetic skew toward suppression of NK cell activity. Moreover, a lower occurrence of the activating genes KIR2DS3 and KIR2DL5 was identified in individuals with B-CLL when compared to controls, with the decrease in KIR2DS3 reaching statistical significance in female patients, further implying a role of diminished activation in leukemogenesis. [20]

In a Chinese cohort, Zhang et al. (2010) [21] observed a significant increase in KIR2DS4 frequency among CML patients, whereas KIR2DS3 was significantly reduced in ALL patients, implying its probable protective role [21]. Correspondingly, an Iranian study by Shahsavar et al. (2010) [22] also noted decreased KIR2DS3 frequencies in both AML and ALL patients, although statistical significance was not achieved in ALL cases. [22]

The recurring theme of an increased iKIR frequency among leukemia patients has led to the hypothesis that a higher inhibitory-to-activating KIR ratio may impair NK cell cytotoxic function, thereby facilitating immune escape. In contrast, experimentally it has also been observed that higher expression levels of activating aKIRs are correlated with favourable disease prognosis in hematologic malignancies, suggesting their involvement in effective antitumor responses. [20] [21] [22] [23]

Functional experiments have demonstrated that blocking inhibitory receptors such as iKIRs, CD94/NKG2A, and leukocyte immunoglobulin-like receptor-1 (LIR-1) significantly enhances NK cell-mediated lysis of leukemic blasts, reinforcing the idea that inhibitory signalling contributes to immune evasion. [24] [25]

2.3.2 Predisposition to leukemia due to increased aKIRs/decreased iKIRs

More recent studies suggest that an increase in activating KIRs and/or a reduction in inhibitory KIRs may contribute to a heightened leukemia risk.

In a 2023 study by Mirzazadeh et al., of AML patients reported a significantly higher frequency of aKIR/HLA class I combinations in patients compared to healthy controls [26]. The control group exhibited an increased prevalence of aKIRs without their corresponding HLA classIigands. Notably, the frequency of KIR3DS1 was considerably higher in patients, corroborating the study by Alavianmehr et al. (2020) on 167 Persian AML patients, who observed a similar enrichment of aKIRs, particularly

KIR3DS1, alongside an enhanced frequency of iKIRs in the control population [27]. Mirzazadeh also observed a greater frequency of iKIR/HLA class I combinations in controls, further reinforcing that these genotypes may confer protection. [26]

Halimi et al. (2024) examined 154 Iranian patients with acute lymphoblastic leukemia (affecting B-cell) and found similar trends. The patient cohort demonstrated elevated frequencies of aKIRs again with KIR3DS1 reaching statistical significance and increased aKIR/HLA class I ligand combinations [28]. Additionally, patients more commonly possessed iKIRs without their respective HLA ligands, indicating a lack of functional inhibitory signalling causing them to be hyporesponsive [28].

In contrast, iKIR/HLA combinations were present in elevated frequency in the control group, potentially implying their protective effect.

Supporting these findings, a study by Misra et al. (2016) on a North Indian ALL cohort reported a decreased occurrence of inhibitory KIRs among patients [29]. Specifically, KIR2DL3 and KIR2DL5 were associated with a protective effect in B-ALL cases, while aKIRs were implicated as risk factors for both B-ALL and T-ALL.

While these results may appear counterintuitive, they can be explained by current models of natural killer (NK) cell education. A deficiency in iKIR/HLA signaling may impair the development of NK cell functionality, rendering them hyporesponsive and ineffective in tumor surveillance [31]. During development, NK cells are "licensed" through interactions between iKIRs and self-HLA ligands. This process makes them self-tolerance while also conditioning the NK cells for effective cytotoxic responses. In the absence of adequate inhibitory signaling as in individuals with fewer iKIR-HLA ligand interactions, NK cells fail to undergo proper education, resulting in a hyporesponsive or unlicensed phenotype. Such NK cells exhibit reduced cytotoxicity, even in the presence of activating ligands, and are therefore less effective at recognizing and eliminating transformed cells. [3] [31]

However, it is important to note that NK cell hyporesponsiveness resulting from the absence of ITIM mediated signalling can be partially subdued by cytokines. Consequently, the lack of licensing may not significantly impair NK cell functionality alone under inflammatory conditions. [3]

Conversely, excessive aKIR signaling mainly in the circumstance where HLA class I is downregulatedor absent may result in chronic activation of NK cell and eventual exhaustion, thereby facilitating the immune evasion and progression of malignant cells [30].

2.4 Summary of findings

Studies where a significant association between KIRs and leukemia was observed showed one of the following 2 results:

1. Predisposition due to inhibitory KIRs, where the trend of upregulation of iKIRs was observed among patients, often suggesting a protective profile with regards to activating KIRs. Hyporesponsiveness of NK cells due to the neutralisation of or overpowering the activation signal is attributed as the reason behind these observations.

Table 1. Summary of findings across different studies

2. Predisposition due to activating KIRs, where an increased frequency of aKIRs was likely the

Study	Population	Leukemia Type	Sample Size (n)	Comments
Mirzazadeh et al., 2023	Iranian	AML	181	increased frequency of 3DS1
Halimi et al., 2024	Iranian	B-ALL	154	increased frequency of 3DS1; iKIR/HLA - 1 more in control
Misra et al., 2016	North Indian	childhood ALL	137	increased frequency of aKIRs oserved in patients
Alavianmehr et al., 2020	Persian	AML	167	increased frequency of 3DS1; aKIR > iKIR in patients
Kołtan et al., 2021	Polish	childhood ALL	49	aKIR > iKIR in patients
Karabon et al., 2011	Polish	CLL	197	decreased frequency of 2DS3 reaching significance in women
Varbanova et al., 2019	Bulgarian	AML	17	decreased frequency of 3DS1; protective for AML
Shahsavar et al., 2010	Iranian	AML	40	decreased frequency of 2DS3 iKIR > aKIR in patients
Shahsavar et al., 2010	Iranian	ALL	38	no specific association for individual KIRs

culprit behind susceptibility to leukemia. Inefficient NK cell education due to decreased iKIRs, coupled with the exhaustion of NK cells due to overactivation could also cause susceptibility to leukemia.

Studies which did not observe strongly significant associations between the two factors being examined must also be noted. In a German cohort studied by Babor et al. no significant difference was observed between the case and control. [32] Adam et al performed a study on childhood ALL patients and failed to observe an association between KIR genotype and non Hispanic white children, however hispanic children showed significant association in KIR genotype between patients and controls. [33] A large study involving 1,767 German patients with AML found no association between the presence or absence of individual KIR genes and disease susceptibility. However, a minor trend was observed suggesting a potential protective effect associated with a lower number of inhibitory KIRs and their corresponding HLA ligands. [34]

These conflicting results can be due to a number of factors, such as genetic variation across different populations and environmental variations that influence the pathogenesis and clinical manifestation of leukemia.

2.5 Research Gaps

Although the existing research provides valuable insights into the interaction between NK cell surface receptors and their corresponding ligands in the case of various leukemia subtypes, further investigation must be carried on while keeping a note of the following gaps:

1. Small sample sizes

To arrive at a credible conclusion, studies should include larger sample sizes to encompass the maximum number of genetic variations in a cohort. Most studies adopted smaller sample sizes; Varbanova et al. did a case control study on AML patients with a sample size of 17, Shahsavar et al. with 40 AML cases and 38 ALL cases with an inconsistently matched control group of 200. This might skew the result, potentially introducing bias and straying further from the true degree of association.

2. Variation in KIR typing techniques and data reporting
   The variation in genotyping techniques and exclusion of certain aspects of the data such as allelic variation, makes combining the results of different studies less reliable, giving rise to challenges in performing meta- analysis.

3. Lack of cross population studies
   Most studies focus only on a certain ethnic group, limiting the opportunity to make generalizations about the association being population dependent or being universal.

4. Lack of pooled data analysis
   Due to the high level of heterogeneity among the studies it becomes a challenge to find data that is compatible for drawing well-grounded conclusions. Pooling data increases the statistical power and helps in providing an estimate of association.

3. Methodology

3.1 Study Design

In an effort to investigate the level of association between KIR genes and leukemia susceptibility, a pooled dataset was created using data from the two independent studies conducted by Ali Alavianmehr et al. (2020) [27] and Sara Mirzazadeh et al. (2023) [26] on AML patients, examining the frequency of KIR genes in an Iranian cohort.

3.2 Data collection

Both studies reported a significant risk association of KIR3DS1 with AML and had comparable data along with similar ethnic backgrounds. This provided favourable conditions to perform a chi-square test. The following information was extracted from each study:

- Number of cases and controls
- Number of individuals with and without the KIR3DS1 gene in each group

3.3 Data Pooling

Table 2. Data extracted from the study by Ali Alavianmehr et al. (2020)

Group	**KIR3DS1+**	**KIR3DS1-**	**Total**
Cases	85	82	167

Controls	67	102	169

Table 3. Data extracted from the study by Sara Mirzazadeh et al. (2023)

Group	**KIR3DS1+**	**KIR3DS1-**	**Total**
Cases	90	102	181
Controls	54	127	181

Table 4. Pooled Contingency Table for chi-square test

Group	**KIR3DS1+**	**KIR3DS1-**	**Total**
Cases	175	173	348
Controls	121	229	350

3.4 Statistical Analysis

A Chi-square test of independence was performed using JASP 0.19.3 to determine whether there was a statistically significant association between the presence of KIR3DS1 and leukemia status. The Chi-square value (χ^2), p-value, and odds ratio (OR) with a 95% confidence interval were calculated.

- Chi-square (χ^2): 17.647
- p-value: < 0.001
- Odds Ratio (OR): 0.522

A p-value < 0.05 was considered statistically significant.

Chi-Squared Tests

	Value	df	p
X^2	17.647	1	< .001
N	698		

Odds Ratio

		95% Confidence Intervals		
	Odds Ratio	Lower	Upper	p
Odds ratio	0.522	0.385	0.708	

Results obtained using JASP 0.19.3

3.5 Interpretation

The chi-square value of 17.647 along with a p-value that is less than 0.001 indicates a statistically significant association between the presence of the activating KIR gene KIR3DS1 and leukemia susceptibility in the pooled dataset from the two studies.

The odds ratio of 0.522 suggests that individuals carrying the KIR3DS1 gene have approximately 48% lower odds of developing leukemia compared to those without this gene. This implies a potential protective effect of KIR3DS1 against leukemia in the studied populations.

4. Results

A combined analysis of data from Ali Alavianmehr et al. (2020) and Sara Mirzazadeh et al. (2023) was performed to investigate the association between the activating KIR gene KIR3DS1 and leukemia susceptibility.

The pooled chi-square analysis demonstrated a statistically significant association ($\chi^2 = 17.647$, $p < 0.001$), indicating a non-random distribution of KIR3DS1 between cases and controls. The calculated odds ratio of 0.522 (95% CI) suggests that the presence of KIR3DS1 is associated with a reduced risk of leukemia. These findings support the hypothesis that KIR3DS1 may confer a protective effect against leukemia in the studied populations.

5. Discussion

The analysis of KIRs and leukemia susceptibility indicated a complex and nuanced association between the two. Specifically, the pooled analysis of KIR3DS1 from the studies by Sara Mirzazadeh et al. (2023) and Alavianmehr et al. (2020) revealed a statistically significant association, with a chi-square value of 17.647 and a p-value < 0.001, suggesting a protective role (OR = 0.522) of KIR3DS1 in the combined dataset. This result contrasts with the conclusions drawn in the individual studies, where both the studies reported 3DS1 as a potential risk factor in AML patients, but aligns with other studies which report 3DS1 as a protective factor in other populations as observed by Varbanova et al. in Bulgarian cohort for AML cases.

There are many factors which come into play in order to confer susceptibility to the various subtypes of leukemia, which may explain the inconsistencies observed in study results. It is important to note that variations in KIR receptor frequency do not influence leukemia risk alone. Instead, they represent one aspect of the broader biological mechanism that play a role in predisposing individuals to leukemia.

Additional factors like copy number variation (CNV), allelic polymorphism and translation differences among KIR genes affect leukemia susceptibility, often, certain alleles are not expressed or the KIR genes may fuse [33]. Also, variation in sequence directly impacts the effector functions such as ligand affinity or specificity [5].

Population immunogenetic studies do not always encompass for these factors which play a critical role on NK cell function which eventually affects leukemia susceptibility.

6. Conclusion

This study analyzed the association of activating KIR genes, particularly KIR3DS1, with leukemia susceptibility using pooled data from published case-control studies. While individual studies suggested an increased risk associated with certain aKIRs, the combined statistical analysis identified a significant protective association of KIR3DS1.

The results suggest that aKIRs may not universally increase leukemia risk, and their role may vary depending on coexisting inhibitory KIRs, ligand availability, and other immunological factors.

These findings provide a foundation for further investigation and call for more comprehensive studies that integrate KIR-HLA genotyping with NK cell functional studies across diverse populations to clarify the immunogenetic mechanisms underlying leukemia susceptibility and whether certain ethnic populations are genetically more susceptible to leukemia. This would help in the development of combinatorial therapies for the treatment of hematological malignancies.

7. References

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