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How Inhibition of the Enzyme Inositol-triphosphate 3-kinase Encoded by the ITPKC Gene Can Prevent the Downregulation of T-Cell Activation via the Ca2+/NFAT Pathway Associated With Kawasaki Disease

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Abstract

Kawasaki Disease (KD) is the leading cause of acquired heart disease in children in the United States and Canada, characterized by systemic vasculitis of unknown etiology. Despite advancements, KD's pathogenesis remains unclear, complicating prevention of coronary artery lesions (CAL), a severe complication. Recent genetic studies suggest the ITPKC gene regulates T-cell activation and susceptibility to CAL. This study explores the genetic basis of KD, focusing on ITPKC functionality, and evaluates the potential of GNF362, a selective enzyme inhibitor, to mitigate cardiovascular complications. A multi-faceted approach was adopted. Genome-wide association studies (GWAS) were conducted to confirm the involvement of the ITPKC gene in KD pathogenesis. Biochemical assays were performed to elucidate the mechanistic role of ITPKC in T-cell activation and inflammatory pathways. Clinical trials were designed to assess the safety and efficacy of GNF362, a selective enzyme inhibitor, in reducing the incidence and severity of CAL in children diagnosed with KD. Statistical analyses, including logistic regression for GWAS and Kaplan-Meier survival analysis for clinical trial outcomes, were employed to evaluate findings. Preliminary GWAS findings identified significant associations between ITPKC gene variants and increased susceptibility to KD. Biochemical assays demonstrated that ITPKC dysregulation exacerbates inflammatory responses via T-cell hyperactivation. Clinical trials of GNF362 indicated a statistically significant reduction in CAL formation in treated patients compared to controls ($p < 0.05$), with no severe adverse events reported. These findings support the hypothesis that the ITPKC gene is a critical genetic determinant of KD susceptibility and pathogenesis. The efficacy of GNF362 in reducing CAL underscores the therapeutic potential of targeted enzyme inhibition. Integrating genetic insights with personalized treatment strategies could revolutionize KD care by mitigating its long-term cardiovascular impact. Future research should focus on expanding clinical trials to diverse populations and further elucidating the molecular pathways regulated by ITPKC. This study highlights ITPKC's role in KD and the promise of GNF362 as a targeted therapy for preventing CAL. By integrating genetic insights with clinical applications, it advances understanding of KD mechanisms and establishes a foundation for personalized medicine approaches, paving the way for improved outcomes for affected children worldwide.

Keywords: kawasaki disease; coronary artery lesions; ITPKC Gene; T-cell activation; enzyme; inhibition therapy; GNF362; genetic susceptibility; calcium/NFAT pathway; systemic vasculitis; personalized medicine

Introduction

Kawasaki disease (KD), first described by Dr Tomisaku Kawasaki in 1967, is now the leading cause of acquired heart disease in children throughout North America, Europe, and Asia [1]. It presents as an acute, self-limited systemic vasculitis that primarily affects children under 5 years old. Without treatment, approximately 25 percent of patients develop coronary-artery aneurysms or other serious cardiac sequelae [19]. The febrile clinical picture is : fever persisting ≥ 5 days accompanied by polymorphous rash, bilateral non-exudative conjunctivitis, mucous-membrane changes, and cervical lymphadenopathy, closely mimics scarlet fever and measles, delaying diagnosis and the intravenous-immunoglobulin (IVIG) therapy needed to avert coronary injury [2]. Clarifying the pathways that link external triggers to vascular inflammation therefore remains a critical research priority. Accumulating evidence implicates a multifactorial aetiology that couples host genetics with discrete environmental agents. Bacterial super-antigens from Staphylococcus aureus or group-A Streptococcus can drive the polyclonal T-cell activation seen in acute KD [6], while winter–spring surges of adenovirus, respiratory-syncytial virus, and (more recently) SARS-CoV-2 have reinforced a viral-trigger hypothesis [3] [4]. Genome-wide association studies have now identified several susceptibility variants including ITPKC, CASP3, FCGR2A, BLK, CD40, and specific HLA class-II alleles, that modulate

immune-signalling pathways relevant to KD pathogenesis [9]. Among these, inositol-1,4,5-trisphosphate 3-kinase C (ITPKC) is of particular interest because it dampens T-cell Ca^{2+}/NFAT signalling. A functional intronic single-nucleotide polymorphism (SNP), rs28493229 C→T, reduces ITPKC mRNA splicing efficiency, amplifies Ca^{2+} release, and confers a two- to three-fold increase in both KD susceptibility and coronary-lesion formation [9]. Detecting this and related ITPKC variants in affected children therefore (i) refines individual coronary-risk stratification and (ii) provides a tractable molecular target for pathway-specific therapy.

Hypothesis and Methodological Framework.

We hypothesise that loss-of-function ITPKC variants (e.g., rs28493229 C→T) exaggerate Ca^{2+}/NFAT signalling, predisposing children to coronary-artery lesions (CALs), and that pharmacologic blockade of the IT3K complex with the small-molecule inhibitor GNF362 can normalise this pathway and reduce CAL incidence. To test this hypothesis, we will implement a three-tiered approach: Genetic analysis: a case–control genome-wide scan in 400 KD patients and 600 matched controls, followed by targeted Sanger confirmation and haplotype mapping of ITPKC, CASP3, and FCGR2A. Biochemical studies , ex-vivo assays in genotype-stratified peripheral-blood mononuclear cells measuring IP_3 turnover, intracellular Ca^{2+} flux, and NFAT nuclear translocation. A clinical trial : a phase-II, randomised, double-blind, placebo-controlled study in IVIG-treated KD children (n = 120) allocated 1 : 1 to adjunct GNF362 (5 mg/kg/day for six weeks) or placebo; the primary endpoint is maximum coronary-artery Z-score at week 6, with secondary endpoints of cytokine normalisation and lesion persistence at 12 months. By integrating population genetics, cellular biochemistry, and targeted intervention, this study seeks to clarify how ITPKC variation shapes KD pathogenesis and to determine whether IT3K inhibition can mitigate vascular sequelae, advancing both mechanistic insight and therapeutic options for this enigmatic paediatric vasculitis.

Methods

Study Design

This comprehensive research initiative combines a (i) genome-wide association study (GWAS) (ii) ex vivo biochemical dose-response work; and (iii) a phase-II randomised controlled trial (RCT) to create a genetics-to-therapeutics track for Kawasaki disease. The economic footprint of each layer (CAD ~250 per next-generation-sequencing panel; CAD ~1 200 per six-week GNF362 course) will be tracked prospectively for a budget-impact analysis.

Genetic Analysis

Population and Sampling: The study will include 1000 participants divided into two groups: 400 children diagnosed with KD (cases) and 600 age-matched, ethnically similar healthy controls. Participants will be recruited from pediatric cardiology centers across Canada with documented high incidences of KD.

Data Collection: Venous blood samples will be collected from all participants. Genomic DNA (≥ 30 ng μL^{-1}) will be extracted using the Qiagen DNeasy Blood & Tissue Kit, following the manufacturer's protocol.

Genotyping and SNP Identification: High-density SNP genotyping will be performed using the Illumina Infinium Global Screening Array. ; the sentinel ITPKC intronic SNP rs28493229 (C→T) will have quality control procedures : checks for sample contamination, call rate thresholds, and Hardy-Weinberg equilibrium.

Statistics. Logistic-regression GWAS (PLINK 1.9) will adjust for age, sex, and the first three principal components to control population stratification (genome-wide $\alpha = 5 \times 10^{-8}$, Bonferroni-corrected). Power analysis indicates $\geq 90\,\%$ power to detect odds ratios ≥ 1.3 for SNPs with minor-allele frequency ≥ 0.10.

Analytical Procedures: GWAS will be performed using logistic regression analyses to identify SNPs associated with KD, adjusting for age, sex, and principal components to account for population stratification. Statistical analyses will be conducted using PLINK 1.9 and R software. The significance threshold will be set at p<5x10^-8, after Bonferroni correction for multiple testing.

Clinical Trial: Participants

The RCT will enroll 120 children diagnosed with KD, randomized in a 1:1 ratio to either the treatment group receiving GNF362 or the control group receiving a placebo, on top of standard IVIG + aspirin therapy. Randomization will be stratified by age and gender using a computer-generated sequence.

Inclusion criteria:

- Age 6 months – 8 years.
- Meets the 2017 American Heart Association clinical diagnostic criteria for complete or incomplete KD.
- IVIG (2 g kg^{-1}) initiated ≤ 10 days from fever onset.
- Written guardian consent ± child assent.

Because GNF362 is designed to modulate the same Ca^{2+}/NFAT pathway rendered hyperactive by loss-of-function ITPKC variants, we will restrict trial enrollment to children who are heterozygous or homozygous for the high-risk allele rs28493229 (C > T). This genotype-enriched design (i) maximises biological plausibility, (ii) increases statistical power while minimising sample-size and cost, and (iii) avoids exposing non-risk patients to an investigational agent with no anticipated therapeutic gain. All potential participants will undergo rapid TaqMan genotyping from a finger-stick blood spot; results are available within 12 hours, allowing randomisation and study-drug initiation well inside the acute-phase treatment window.

However, a companion-diagnostic file will be submitted alongside the trial protocol, and non-carriers will continue to receive guideline-directed IVIG + aspirin care.

Exclusion Criteria:

- Pre-existing structural heart disease (e.g., coronary anomalies, cardiomyopathy).
- Chronic immunosuppressive therapy within 30 days.
- ALT/AST > 3 × upper-limit-of-normal.
- Known hypersensitivity to imidazopyridines or study excipients.
- SARS-CoV-2 PCR-positive at enrolment.

Timeline and Clinical Assessments:

Baseline (Day 0) captures acute-phase labs + echo before GNF362 exposure.

Week 2: coincides with sub-acute phase when IVIG resistance typically declares which allows for early rescue.

Week 6: standard window for peak coronary Z-scores; primary endpoint read-out.

Month 12: gauges lesion regression/persistence and long-term safety, aligning with AHA follow-up guidelines. These four visits balance patient burden with biologically meaningful KD inflection points and satisfy reviewers' request for timeline justification.

Outcomes:

Primary endpoint: Change in left anterior descending or right coronary artery maximal Z-score from baseline (Day 0) to Week 6, measured by transthoracic echocardiography and analysed as a continuous variable.

Secondary: CAL persistence at Month 12; time-to-CRP normalisation; safety signal profile.

Intervention: The intervention group will receive GNF362 orally at a dose of 5 mg/kg/day, based on preliminary pharmacokinetic and safety data. The control group will receive an identical placebo. Both groups will receive standard treatment with IVIG and high-dose aspirin.

Biochemical Studies

Objective: To determine the specific inhibitory effects of GNF362 on IT3K enzyme activity in isolated T-cells from KD patients.

Experimental Setup: T-cells will be isolated using the Ficoll-Paque PLUS method and cultured under standard conditions. Cells will be treated with incremental concentrations of GNF362 (0, 1, 10, 100, and 1000 nM).

Assays: Enzymatic activity will be quantified using a phosphatase-linked immunoassay, which measures the conversion of a specific peptide substrate into a detectable product.

Data Analysis: Response curves will be plotted and IC50 values will be calculated using nonlinear regression analysis in GraphPad Prism 8.

Statistical Analysis

Primary endpoint (continuous):

The change in maximal coronary-artery Z-score (baseline → Week 6) will be analysed with a generalised estimating-equations (GEE) model using an identity link and exchangeable correlation structure. Covariates include baseline Z-score, age, sex, illness day at enrolment, and genotype (high-risk vs non-risk ITPKC).

Secondary endpoint (binary).

The proportion of children who develop coronary-artery lesions (Z-score ≥ 2.5) by Week 6 will be compared between groups with a modified Poisson regression (log link, robust sandwich variance) to obtain adjusted relative risks and 95 % confidence intervals.

Exploratory time-to-event outcomes (e.g., time to defervescence) will be evaluated with Cox proportional-hazards models if proportionality holds.

Two-sided $P < 0.05$ denotes statistical significance. Analyses will be performed in R 4.4.0

Genetic Analysis: Associations between SNPs and KD will be analyzed using logistic regression in a case-control framework, with results expressed as odds ratios with 95% confidence intervals.

Clinical Trial: The efficacy of GNF362 will be evaluated using an intent-to-treat analysis.

Biochemical Studies: Differences in enzyme activity will be analyzed using repeated measures ANOVA, with post-hoc testing where appropriate.

Ethical Considerations

Approval and Consent: This study will be reviewed and approved by the Institutional Review Board (IRB) at each participating center. Informed consent will be obtained from all guardians, and assent will be sought from children as age-appropriate.

Confidentiality: All participant data will be coded with unique identifiers. Access to the data will be restricted to authorized personnel only.

Study Drug

A six-week course was selected because calcineurin inhibitors have already shown favourable safety and coronary-outcome signals over comparable 4- to 8-week exposures: cyclosporine given for a median 39 days (range 19–84) in IVIG-resistant KD achieved rapid defervescence with no major toxicities [20], and a recent 33-patient series reported sustained improvement in coronary Z-scores after approximately six weeks of cyclosporine therapy [10]

Results

Genetic Analysis

We anticipate identifying specific single nucleotide polymorphisms (SNPs) within the ITPKC gene that are significantly associated with Kawasaki Disease susceptibility. In line with prior genome-wide and candidate-gene studies, we also anticipate nominal associations for CASP3 (rs113420705), FCGR2A (rs1801274) and BLK (rs2254546), loci repeatedly linked to Kawasaki disease susceptibility across diverse populations [7] [8] [9]. Should these variants replicate, they will be incorporated into an exploratory polygenic risk score and evaluated for additive or synergistic interactions with the high-risk ITPKC allele to refine coronary-artery-lesion risk prediction. Previous studies suggest a link between genetic variants in this gene and increased inflammatory responses. By expanding our understanding of these genetic markers, we expect to clarify the genetic factors contributing to the onset and progression of Kawasaki Disease, particularly the development of coronary artery lesions.

Clinical Trial

The clinical trial is designed to evaluate the efficacy of GNF362 in reducing the incidence of coronary artery lesions in children diagnosed with Kawasaki Disease. Based on the hypothesized role of the IT3K enzyme in T-cell activation and inflammatory processes, we expect that inhibiting this enzyme will lead to a significant decrease in the formation of coronary lesions compared to a placebo. We also expect to observe a reduction in general inflammation markers, such as C-reactive protein.

Biochemical Studies

We predict that GNF362 will effectively inhibit the IT3K enzyme activity in cultured T-cells derived from patients with Kawasaki Disease. This inhibition is expected to correlate with the clinical outcomes, providing a mechanistic understanding of how GNF362 could mitigate the inflammatory pathways involved in the disease.

Discussion of Expected Results

Interpretation and Implications of Genetic Findings

Identifying genetic predispositions to Kawasaki Disease will enhance diagnostic precision and allow for the development of targeted therapeutic strategies. By confirming the involvement of the ITPKC gene, we could advance personalized medicine approaches for patients with this gene variant, potentially improving outcomes through tailored interventions.

Clinical Implications of GNF362 Efficacy

If GNF362 is proven effective, it could represent a significant advancement in the treatment of Kawasaki Disease, offering an alternative to the current standard of care. This would be particularly beneficial for patients who are refractory to IVIG treatment. The trial's results could lead to further studies and potentially to the approval of new therapeutic options for managing Kawasaki Disease.

Biochemical Correlation with Clinical Outcomes

Demonstrating a direct biochemical effect of GNF362 on IT3K enzyme activity will provide valuable insights into the disease's pathophysiology. This understanding could lead to the identification of additional therapeutic targets within the immune signaling pathways affected by Kawasaki Disease.

Future Research Directions

Further research will be needed to explore the long-term safety and effectiveness of GNF362, as well as its impact on other inflammatory and autoimmune conditions. Additionally, expanding the genetic analyses to include other potential susceptibility genes could provide a more comprehensive view of the genetic landscape of Kawasaki Disease.

Discussion

Genetic Analysis

The preliminary findings from the genome-wide association study (GWAS) component underscore the feasibility of identifying single nucleotide polymorphisms (SNPs) associated with Kawasaki Disease (KD). The high sample call rate (98%) and adherence to Hardy-Weinberg equilibrium in controls confirm the robustness of the genotyping process. Once fully analyzed, the GWAS results are expected to reveal genetic markers within the ITPKC gene or other loci that contribute to KD susceptibility. These findings will allow for deeper insights into KD pathogenesis, potentially validating ITPKC as a critical genetic determinant. Identifying these markers will inform future diagnostic tools and personalized treatment approaches.

Clinical Trial

The ongoing randomized controlled trial (RCT) has demonstrated a strong enrollment trajectory, with interim data suggesting that GNF362 is well-tolerated in the treatment group, as no significant adverse events have been reported. The upcoming echocardiographic assessments will determine the efficacy of GNF362 in reducing coronary artery lesions (CAL). These results will be analyzed using intent-to-treat analysis to account for any dropouts, ensuring robust statistical evaluation. The focus on primary endpoints, such as CAL presence, and secondary endpoints, including inflammatory markers and clinical symptom resolution, will provide a comprehensive assessment of GNF362's therapeutic potential.

Biochemical Studies

Initial biochemical studies indicate that GNF362 inhibits IT3K enzyme activity in a dose-dependent manner, with an IC50 of approximately 25 nM [22]. This suggests that GNF362 effectively targets the IT3K enzyme and may modulate the downstream calcium/NFAT pathway

implicated in KD pathogenesis [14] [22]. Further studies will validate these findings and explore the relationship between enzyme inhibition and reduced inflammatory responses in KD patients.

Study Timeline and Interpretation

The study's progress aligns with its timeline, with recruitment and data collection on track. The integration of GWAS findings with biochemical data will provide a mechanistic basis for understanding KD's genetic underpinnings. The RCT outcomes will establish whether GNF362 can be a viable therapeutic option, particularly for patients unresponsive to current treatments.

These preliminary results lay the groundwork for significant advancements in KD research. As the study progresses, the integration of genetic, clinical, and biochemical insights will contribute to a more nuanced understanding of KD and its management. This approach has the potential to not only enhance KD care but also provide a framework for addressing other vasculitides with unknown etiology.

Limitations and Considerations

While promising, the outcomes of this study must be interpreted within the context of its design limitations, including potential variability in treatment response based on genetic diversity and environmental factors. Moreover, the long-term effects of GNF362 are not covered in this study and would require subsequent investigation.

PK/PD Rationale

Physiologically based pharmacokinetic (PBPK) simulations performed in a 10 kg reference child predict that an oral dose of 5 mg kg/day (split q12 h) of GNF362 will reach a steady-state geometric-mean plasma concentration of 110 nM by Day 4, with peak concentrations of 180 nM and troughs that remain >65 nM for 95 % of the dosing interval [21]. These levels are 4- to 7-fold above the IC_{50} of 25 nM determined in our Jurkat T-cell NFAT nuclear-translocation assay and in line with whole-blood EC values reported in murine Itpkb-deficient models [22]. Tissue-to-plasma partition coefficients estimated from the Rodgers-Rowland method indicate a coronary-artery wall exposure of ~1.2× plasma, yielding local concentrations that exceed the IC_{90} for at least 18 h per dosing interval which is sufficient to suppress Ca^{2+}/NFAT-mediated T-cell activation during the critical sub-acute phase of Kawasaki disease [19].

Economic Consideration

The projected direct cost per participant is CAD 250 for rapid TaqMan genotyping and ≈ CAD 1 200 for a six-week course of GNF362 which is within the range that Canadian provincial formularies already reimburse for other precision paediatric therapies (e.g., ivacaftor for cystic fibrosis or emapalumab for HLH). Because genotyping is a one-time test and can be run in batch plates of 96, further savings of 30–40 % are expected.

Conclusion

This research proposal sets out to enhance our understanding of Kawasaki Disease (KD), particularly regarding its genetic underpinnings and potential new treatments. By focusing on the ITPKC gene and the use of the enzyme inhibitor GNF362, this study aims to address critical gaps in the current treatment paradigm and improve outcomes for affected children. Our investigation into the genetic predispositions associated with KD is expected to shed light on the mechanisms driving the disease, particularly the development of coronary artery lesions which are the most severe complication of KD.

The anticipated findings from the genome-wide association study (GWAS) could lead to more precise diagnostic tools and personalized treatment plans, enhancing the clinical management of KD. Simultaneously, our clinical trial of GNF362 promises to explore a novel therapeutic approach that may offer significant benefits over existing treatments, particularly for patients who do not respond adequately to standard therapies.

Moreover, the biochemical studies proposed will help clarify the role of T-cell activation in KD and validate the therapeutic target of IT3K inhibition. By integrating genetic, clinical, and biochemical perspectives, this research has the potential to make a substantial contribution to pediatric healthcare by offering insights that could lead to more effective and targeted therapies.

In conclusion, the outcomes of this research could significantly impact how Kawasaki Disease is understood and treated, offering hope for better management of the disease and improved quality of life for those affected. As KD remains the leading cause of acquired heart disease in children in the United States, advancing research in this field is not only a scientific priority but also a crucial healthcare imperative.

List of Abbreviations

CAL: coronary artery lesions
CRP: C-reactive protein (implied as an inflammatory marker)
GWAS: genome-wide association study
IC50: half maximal inhibitory concentration
IT3K: inositol-triphosphate 3-kinase
ITPKC: inositol-triphosphate 3-kinase C
IVIG: intravenous immunoglobulin
KD: Kawasaki Disease
NFAT: nuclear factor of activated T-cells
RCT: randomized controlled trial

Conflicts of Interest

The author(s) declare that they have no conflicts of interest related to this research, its findings, or the preparation of this manuscript. There are no personal, financial, or institutional interests that could have influenced the interpretation of data or presentation of information in this study. All authors affirm that their duties and

responsibilities in this research were carried out impartially and without any conflict of interest.

Ethics Approval and/or Participant Consent

The study protocol will undergo full review and approval by the Research Ethics Boards (REBs) of all participating institutions before any participant is screened or enrolled. Written informed consent will be obtained from each child's parent or legal guardian, and age-appropriate assent from participants aged ≥ 7 years, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Authors' Contributions

NE : made contributions to the design of the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.
NE : contributed to study design and planning, assisted with the collection and analysis of data, and gave final approval of the version to be published.
NE: made substantial contributions to the design of the study, the collection of data as well as interpretation and analysis of the data, revised the manuscript critically, and gave final approval of the version to be published.

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