Case Report

Cornea Arcus and Dyslipidemia in Unrelated Adults With Monoallelic Germline Variants in the *Glucokinase Regulator* Gene

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Abstract

Variants in the *Glucokinase Regulator* (*GCKR*) gene are increasingly being detected with growing applications of genomic sequencing technologies. Despite the crucial roles of the *GCKR* gene in energy homeostasis, the clinical applications of *GCKR* variants are currently limited. We observed that a large proportion of *GCKR* variants that are available in gnomAD database (https://gnomad.broadinstitute.org/) lacked adequate evidence of pathogenicity or benign impact. We highlight the clinical need for an improved understanding of *GCKR* variants by presenting 2 compelling cases of unrelated families (3 individuals in total) who harbor rare *GCKR* variants in the context of cornea arcus and hyperlipidemia. Our observations underscore the burgeoning need for functional as well as family segregation studies to facilitate the clinical applications of *GCKR* variants.

Plain Language Summary

The Growing Need for an Improved Understanding of Variants in the Glucokinase Regulator Gene

The Glucokinase Regulator gene plays important roles in energy balance and cardiovascular disease risk. With increasing applications of genetic testing technologies, variants in the Glucokinase Regulator gene are increasingly being uncovered. There is a growing clinical need for an improved understanding of variants in the Glucokinase Regulator gene. We present the clinical history and findings from two unrelated patients as well as a pie chart that draws upon publicly available record of Glucokinase. Regulator gene variants to highlight this necessity.

Keywords

GCKR, GKRP, hyperlipidemia, dyslipidemia, variants, Cornea Arcus and Dyslipidemia in Unrelated Adults with Monoallelic Germline Variants in the *Glucokinase Regulator* Gene

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Introduction

Encoded by the *Glucokinase Regulator* (*GCKR*) at 2p23.3,[1] glucokinase regulatory protein (GKRP) plays important roles in energy and cardiovascular homeostasis.[2-4] The *GCKR* gene functions as the regulatory inhibitor of hepatic glucokinase (GCK), a key post-prandial glucose sensor. By modulating hepatic glucose uptake in response to nutritional state and cellular energy balance, the *GCKR* exerts a critical influence on systemic glucose and energy homeostasis.[5] Accordingly, genetic variation in the *GCKR* gene affects both glucose and lipid metabolism and is associated with a spectrum of metabolic phenotypes, including hypertriglyceridemia, broader dyslipidemia, altered fasting glucose regulation, increased susceptibility to type 2 diabetes mellitus, hepatic steatosis and elevated cardiometabolic disease risk.[6,7]

As *GCKR* variants are being increasingly associated with dyslipidemia,[6,8-11] the need for functional studies continues to rise. Functional studies using cell models, structural modeling, and fluorescent localization, have shown that *GCKR* variants can impair nuclear retention of GCK or disturb inhibition even without affecting localization.[6,10] *GCKR* variants have also been associated with gout,[12] type 2 diabetes mellitus,[13] fatty liver disease,[11] and coronary artery disease.[14] *GCKR* polymorphisms may have

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Table 1. Phenotypic Comparison of 3 Patients with Monoallelic GCKR Variants.

Domain	Parameter	Individual 1 41-year-old Female	Individual 2 70-year-old Female	Individual 3 48-year-old Male
Core lipid phenotype	Triglycerides (mg/dL) Reference interval (RI) = 0-150	47	133	92
	LDL-C (mg/dL) RI = 0-99	101	136	156.2
	HDL-C (mg/dL) RI ⩾ 50	79	55	41
	Total cholesterol (mg/dL) RI = 0-200	189	215*	213
Metabolic markers	BMI (kg/m^2)	23.34	26.60	27.674
Glycemic marker	HbA1c (%) and fasting blood glucose (FBG) levels	5.2, FBG levels are within normal limits (WNL)	5.0, FBG levels are WNL	Unknown, FBG levels are WNL
Liver and hepatic context	Liver function test results are WNL	Liver function test results are WNL	Liver function test results are WNL	Liver function test results are WNL
Secondary causes of dyslipidemia	Thyroid disease	No	No	No
	Renal disease, Estimated glomerular filtration rate (mL/min/ BSA) RI ⩾ 90 mL/min /BSA	75	69	57

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
The asterisk (*) indicates that Individual 2 has been on longstanding therapy (statins) for hyperlipidemia. Individual 2's lipid profile reported here in Table 1 are in the context of longstanding (several decades) pharmacotherapy with statins and dietary management.

complex multifactorial inheritance patterns, yet the possibilities of Mendelian risk transmission for rare *GCKR* variants remain (Mendelian Inheritance in Man [MIM][15] # 613463). To exemplify the growing clinical need for functional studies for rare *GCKR* variants, we present the clinical synopsis of 2 unrelated families (3 patients [2 females and 1 male] in total) with rare *GCKR* variants in the context of cornea arcus and hyperlipidemia.

Case Description

Individual 1, a 41-year-old woman underwent hyperlipidemia gene panel testing due to the clinical finding of corneal arcus and dyslipidemia. She has no known personal history of diabetes mellitus or hepatic steatosis or coronary artery disease or gout. Her family history includes hyperlipidemia in multiple first and second-degree relatives. The test identified a heterozygous variant, *GCKR* (NM_001486.3) c.1639 C>A p.(P547T). Although the c.1639 C>A variant was previously reported in another patient with hyperlipidemia[9] and is deemed to be rare (with gnomAD allele frequency of 0.0002), the variant is yet to fulfill the clinical criteria for classification as a pathogenic or likely pathogenic variant based on the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) Mendelian gene variant stratification framework[16] and is classified as a variant of uncertain significance (VUS). Even though cornea arcus has been associated with hereditary causes of hyperlipidemia,[17] this is the first reported case of cornea arcus in a patient with a *GCKR* variant.

Individual 2, a 70-year-old woman underwent whole genome sequencing in the context of her history of multisystemic illnesses including hyperlipidemia, migraine, bilateral cataracts, supraventricular tachycardia and atrial fibrillation (requiring ablation and external cardioversion), vertebra hemangioma, osteoporosis, enchondromas, obstructive sleep apnea and diverticulosis. She had no known history of impaired glucose metabolism, gout/hyperuricemia, fatty liver disease, or coronary artery disease. Additionally, she reported a family history of early-onset hyperlipidemia in first-degree relatives, including her brother, her father, and her son (Individual 3). Individual 2's lipid profile reported here in Table 1 are in the context of longstanding (several decades) pharmacotherapy with statins and dietary management. Genome sequencing revealed a heterozygous variant, *GCKR* (NM_001486.4) c.1135dup (p.Thr379Asnfs*36), amongst other variants. Classified as a VUS (with gnomAD allele frequency of 0.001 and global minor allele frequency of frequency [GMAF] 0.00060 [ClinVar Variation ID: 932562]), *GCKR* c.1135dup was the only variant identified by whole genome sequencing that could reasonably account for her longstanding dyslipidemia, which has been present since early adulthood. *GCKR* c.1135dup is predicted to cause premature protein truncation (due to a frameshift) and misfolding as well as abnormal protein trafficking.[10] *GCKR* c.1135dup was previously reported in patients with hyperlipidemia.[8,10] We reviewed gnomAD database (https://gnomad.broadinstitute.org/) on July 28, 2025, for *GCKR* variants and noticed that a large proportion (Figure 1 and Supplemental Table 1) of *GCKR* variants lacked adequate evidence of pathogenicity or benign impact.

Individual 3, a 48-year-old man with a history of dyslipidemia, chronic kidney disease, hypogonadism, and osteoarthritis, underwent family variant testing for the *GCKR* (NM_001486.4) c.1135dup (p.Thr379Asnfs*36) variant in the context of his mother's (Individual 2) history. At the time of the study, Individuals 1 and 3 were transitioning to pharmacotherapy following prior attempts at dietary management. All 3 individuals reported maintaining an active lifestyle with regular exercise.

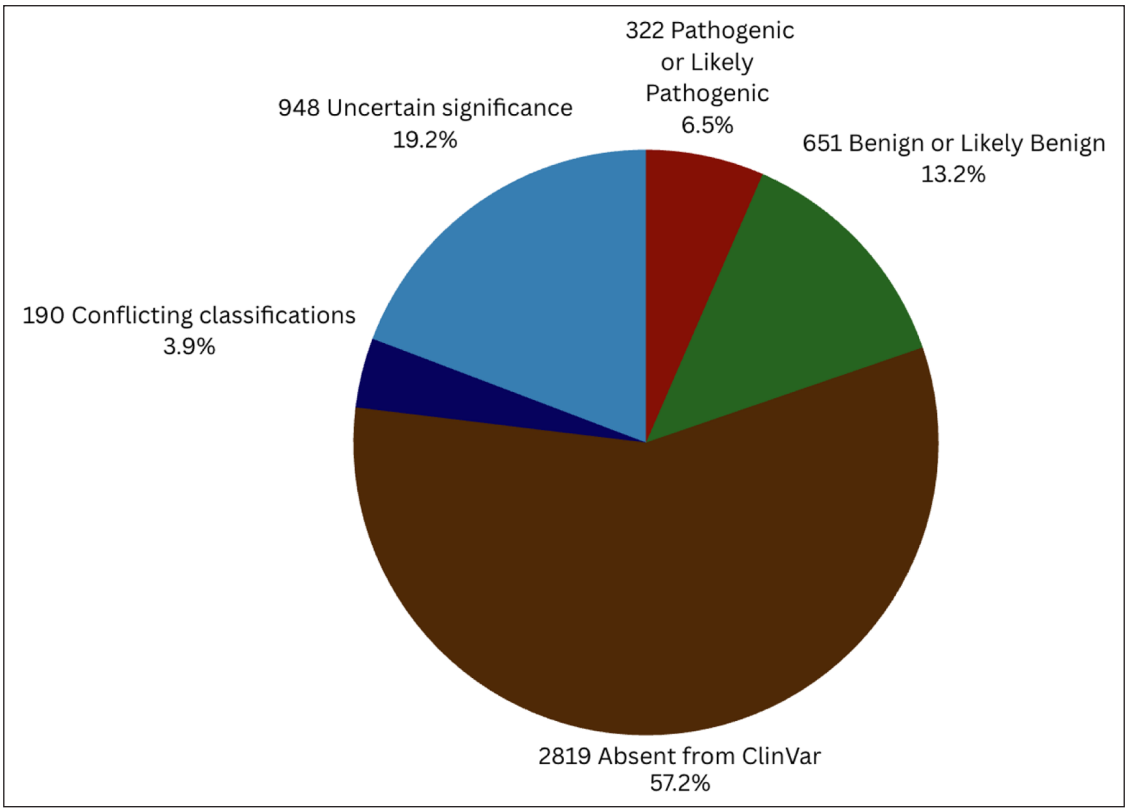

Figure 1. Distribution of *GCKR* variants that were present in the gnomAD database on July 28, 2025.

Discussion

Considering that VUS cannot be used for clinical purposes (to distinguish individuals at risk or to determine therapeutic options), these clinical cases and the review of *GCKR* variants in gnomAD database highlight the growing need for additional evidence base (potentially via functional biochemical studies and clinical case series as well as case-control studies) to facilitate the VUS resolution processes to help translate the growing knowledge of *GCKR* variants to benefit patient care. Given the growing applications of genetic sequencing technologies and the crucial role of *GCKR* in energy homeostasis, an improved understanding of known *GCKR* variants is critically needed. It is also noteworthy that all 3 individuals described in this report exhibited borderline low estimated glomerular filtration rate (eGFR), aligning with previous studies suggesting that GCKR variation may influence renal function.[18]

It is pertinent to note the role of crucial roles estrogen in hepatic lipid metabolism, insulin sensitivity, and VLDL secretion, and that these factors may influence lipid phenotypes in female patients.[19] It is currently unclear whether gender-based differences in metabolic traits may exist in individuals with *GCKR* variation. Although some population-based studies suggest sex-dependent lipid effects, the evidence remains limited.[20]

Conclusion

This study highlights the growing clinical need for an improved understanding of *GCKR* variants. Functional as well as family segregation studies that can help facilitate the clinical applications of *GCKR* variants are increasingly warranted.

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Ethical Considerations

This study was deemed to be exempt from review by the Mayo Clinic Institutional Review Board.

Consent to Participate

Informed written consent was obtained from the patients for the study. Informed written consent was obtained from the patients for publication.

Author Contributions

Bukola A Olarewaju: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing. Ileana Trujillo: Investigation; Methodology; Writing – review & editing. Mayowa A. Osundiji: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; Writing – review & editing.

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Declaration of Conflicting Interests

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CARE Guideline Adherence Statement

This case report was prepared in accordance with the CARE (CAse REport) guidelines.

Supplemental Material

Supplemental material for this article is available online.

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