OPEN ACCESS

Scholars International Journal of Chemistry and Material Sciences

Abbreviated Key Title: Sch Int J Chem Mater Sci
ISSN 2616-8669 (Print) | ISSN 2617-6556 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: http://saudijournals.com

Original Research Article

TRB3 Q84 Levels as New Biochemical Marker for the Early Detection and Diagnosis of Permanent Corneal Damage in Patients with Heart Failure

Noor Ali Gebur[1*]

[1*]Department of Chemistry, College of Science, University of Al-Qadisiyah, Diwaniyah, Iraq

DOI: https://doi.org/10.36348/sijcms.2025.v08i05.010 | **Received:** 05.08.2025 | **Accepted:** 03.10.2025 | **Published:** 27.10.2025

[1]***Corresponding author:** Noor Ali Gebur
Department of Chemistry, College of Science, University of Al-Qadisiyah, Diwaniyah, Iraq

Abstract

***Background and aim**:* Failure of heart (HF) represents a cause of illness and death. A common single nucleotide polymorphism (SNP), identified as rs2295490, within the human gene tribbles pseudokinase 3 – glutamine at position 84 (TRB3 Q84) has been linked to a predisposition for early diagnosis of insulin resistance at a young age and type 2 diabetes. This study aimed to assess serum TRB3 Q84 levels in individuals with heart failure and to explore potential associations with selected biochemical markers. ***Materials and methods**:* A study was conducted involving 120 Iraqi participants, 60 heart failure patients; their ages ranged from <40 – 70> years (35 males and 25 females). To compare the results, 60 healthy adults were included as a control group; their ages ranged from <40 – 70> years (35 males and 25 females). The serum of TRB3 Q84 levels and markers of metabolic like BMI, W/H, SBP, DBP, creatinine, urea, AST, ALT, BNP, FSG, insulin, HOMA-IR, QUICKI and TGF-β were measured. The results were measured by statistical analysis. ***Results**:* As comparison between the groups of heart failure and control, respectively, the *mean* of the biomarkers showed a significantly increased of BNP levels (140±9 versus 50±7, P=0.02), FSG (104.3±8 versus 82.5±6, P=0.03), insulin (10±0.5 versus 6±0.2, P=0.05), *HOMA-IR* (4.1±0.3 versus 2.5±0.2, P=0.02), TGF-β (4.5±0.4 versus 3±0.2, P=0.02) and TRB3 Q84 (3±0.2 versus 1.85±0.1, P=0.01), while the mean of QUICKI levels showed a significantly decreased in the group of heart failure as compared with the group of control, respectively (0.38±0.02 versus 0.59±0.03, P=0.01). A strong significant direct correlation between TRB3 Q84 and BNP, FBS, insulin, HOMA-IR and TGF-β levels, while QUICKI levels *showed* a strong* *significant* *indirect* correlation with *TRB3 Q84* level. ***Conclusions**:* A *significant* *strong* - *positive* *correlation* was observed* between* TRB3 Q84, BNP, FSG, insulin, HOMA-IR and TGF-β biomarkers, while a significant strong negative correlation was identified between TRB3 Q84 and QUICKI in heart failure patients. Therefore, TRB3 Q84 levels may be used as an early diagnostic marker to identify permanent corneal fibrosis in heart failure patients.

Keywords: Failure of Heart • Tribbles - Pseudokinase 3 – Glutamine at Position 84 (TRB3 Q84) • Creatinine • Urea • Brain Natriuretic Peptide (BNP) • Permanent Corneal Damage • Insulin – Resistance* of Homeostatic* – Model* - Assessment (HOMA-IR) • Growth* – Factor*- of -Transforming* - Beta (TGF-β) • Aspartate Aminotransferase (AST) • Fasting Serum Glucose (FSG) • Check – Index*- of – Quantitative*– Insulin*- Sensitivity (QUICKI) • Alanine Aminotransferase (ALT).

INTRODUCTION

Failure of heart (HF) represents a cause of illness and death [1]. The primary contributors to HF include cardiorenal syndrome (CRS), coronary heart disease (CHD), hypertension and diabetes [2]. CRS encompasses a group of metabolic conditions such as high blood pressure, obesity, abnormalities affecting both the heart muscle, kidneys and insulin resistance. This syndrome significantly elevates the risk of type 2 mellitus of diabetes (T2DM) and disorders of cardiovascular including CHD and HF and renal [3].

In the United States cardiorenal syndrome (CRS) affects at least a quarter of the adult population. Its prevalence is rapidly increasing, driven by the aging population alongside widespread overnutrition and sedentary lifestyles [4]. Epidemiological data reveal that more than 40% of those over 60 years old suffer from CRS and over 60% of American adults are classified as overweight. Moreover, continuing into

adulthood and obesity beginning in childhood is becoming a significant global health concern, as it increases susceptibility to CRS and type 2 mellitus of diabetes (T2DM) [5]. Failure of heart, with the risk of developing T2DM often precedes the onset of insulin resistance being 18% to 22% higher over a decade compared to individuals with treated hypertension [6-7].

A common single nucleotide polymorphism (SNP), identified as rs2295490, within the human gene tribbles pseudokinase 3 – glutamine at position 84 (TRB3 Q84) has been linked to a predisposition for early diagnosis of insulin resistance at a young age and type 2 diabetes [8-9]. The frequency of this allele varies among populations, being approximately 13% in Europeans and Africans, while rising to 25–27% in Japanese and Chinese groups. This genetic variant with several metabolic and cardiovascular conditions including diabetic nephropathy, chronic kidney disease, impaired glucose regulation, atherosclerosis, metabolic syndrome and cardiovascular disease [10-11].

The single of nucleotide polymorphism (SNP) in a TRIB3 Q84 linked to insulin resistance causes a mutation that replaces at position 84 a polar glutamine (Q) within the kinase with a basic arginine (R). This position is consistently occupied by arginine in the related proteins TRIB1 and TRIB2 [12-13]. Notably, an R107L mutation in TRIB1 located at the equivalent site has been associated with acute megakaryocytic leukemia (AML) promote degradation of the transcription factor C/EBPα, highlighting its critical regulatory role. Correspondingly, the R84 form exhibits higher affinity binding to AKT compared to the Q84 form [14-15]. Functionally, the R84 variant impairs secretion of insulin more efficiently in β-cells pancreatic and modulates endothelial cell function by reducing release of nitric oxide and increasing activity of MAPK, early events involved in atherosclerosis development [16-17].

Tribble's proteins were originally discovered in drosophila, where members of this family have a conserved role across metazoans, they bind critical regulatory proteins and target them for proteasomal degradation, thereby modulating multiple signaling pathways. In drosophila, insulin signaling constitutes a highly conserved pathway that connects nutrient status to various developmental outcomes such as body size regulation and sexual maturation [18-19].

Tribbles family proteins exhibit strong sequence conservation within their kinase central, including the motif containing the R/Q residue linked to metabolic disorders in humans. Importantly, mutations at the R141 position specifically disrupt Akt-related signaling without impairing Trbl's robust inhibition of developmental pathways controlled by its other targets, such as C/EBP (Slbo) and Cdc25 phosphatase (String) [20-21]. Moreover, expression of the mouse Trib3 R variant in flies strongly suppresses Akt activation, underscoring the evolutionary conservation of this functional site. To explore the functional significance of this site, we examined its role in Trbl-mediated regulation in drosophila. This findings reveal that, similar to humans, the variant R in flies binds Akt more effectively and acts as a stronger inhibitor of Akt-driven signaling of insulin compared to a genetically engineered Q variant [22-23]. Since alterations at R141 do not affect other Trbl-regulated developmental of processes, this residue presents an attractive target for developing small molecules aimed at enhancing insulin sensitivity in specific tissues [24-25].

Diabetes mellitus* (DM)* is a disease of impacting people* *worldwide more than 500 million. Within the eye, DM affects not only the retina but also the anterior segment and adnexal structures [26-28]. This sharp increase is anticipated across most developed and developing nations. Beyond the retina, diabetes also induces changes on the surface of ocular, resulting in a higher occurrence of ocular diseases such as dry eye syndrome among affected individuals [29–31]. In particular, diabetic retinopathy, caused by neovascularization and microvascular damage in the retina, remains a major contributor to vision impairment and blindness [32-33]. Furthermore, DM is linked to other eye conditions, including glaucoma and cataract formation [34-35].

Diabetic keratopathy (DK) is a chronic condition that threatens vision by disrupting normal corneal wound healing, primarily due to damage to corneal nerves. It presents a range of clinical signs including superficial punctate keratopathy, recurrent epithelial erosions and reduced corneal sensitivity [36-38]. Although DK shares clinical similarities with neurotrophic keratopathy (NK), the two conditions differ in their underlying causes: NK results solely from neuropathic damage, while DK primarily involves inflammation driven by immune cell mechanisms that remain incompletely understood [39-41].

The mediated pathological of immune cells in the diabetic cornea is crucial to elucidate their role in the onset and diabetic keratopathy (DK) progression. These myeloid cells exhibit many functional similarities to other bone marrow-derived immune cells but generally maintain a predominantly immune-quiescent state in the cornea [42-45]. The experimental approach utilized two mouse models, the deficient insulin streptozotocin (STZ)-induced model of *diabetes* of *type 1* and the *insulin* *resistant*- *diabetes* of *type 2* model. The findings enhanced characteristics of corneas proinflammatory of both T2D and T1D mice, coinciding with the onset of DK clinical symptoms. Employing established cellular and molecular assays associated with imaging clinical of intravital [46-49].

This study aimed to assess serum of TRB3 Q84 levels in individuals with heart failure and to investigate potential associations with the evaluated biochemical markers.

EXPERIMENTAL

Individuals and study design

Ethical clearance for conducting this study was obtained from the University of Al-Qadisiyah / Faculty of Science. This study was designed as two different groups included 120 subjects, 60 heart failure patients (35 males and 25 females), their ages ranged from <40 – 70> years. In "Diwaniya Teaching Hospital" in Al-Qadisiyah, Iraq, patients were registered throughout the period from May 2025 to July 2025. To compare the results, 60 healthy adults were included as a control group, their ages ranged from <40 to 70> years, (35 males and 25 females).

Exclusion criteria

Individuals suffering from other chronic conditions such as advanced renal failure, chronic liver disease, or active autoimmune disorders were excluded. Patients with acute or chronic infections at the time of sample collection were also excluded, as well as those taking high doses of corticosteroids or immunosuppressive medications. In addition, the study did not include clinically unstable patients, those admitted to intensive care units, or those on mechanical ventilation. Pregnant or breastfeeding women, as well as patients who had received a blood transfusion within the past three months, were also excluded.

Collection of samples

Blood samples were collected from both control and patients at fasting of 8–12 hours using 23-gauge needles through antecubital venipuncture. The collected blood was then left to clot at room temperature in plain tubes. Subsequently, the samples were centrifuged, allowing for serum separation.

Anthropometric evaluation

To assessment the index of body mass; by the equation: BMI=(weight in kg)/ (height in meters)

Biochemical evaluation

The serum level of (BNP) was quantified using a commercial ELISA kit from CORTEZ (USA), employing an ELISA microplate washer and reader, in accordance with the enzyme-linked immunosorbent assay methodology. The (FSG) concentration was assessed through a spectrophotometric assay (Type 3) by using a kit provided by Monobind Inc. (USA). By using a commercial TBARS-based assay kit supplied by LTA (Italy) to measure insulin concentration, by the thiobarbituric acid of reactive substances (TBARS) assay. To determine the serum (TRB3 Q84) levels, enzyme-linked immunosorbent assay kits from MELSIN (China) were utilized. The (TGF-β) content in serum was measured by using a kit from LTA (Italy), according to spectrophotometric assay guidelines. The determination of (ALT) and (AST) concentrations by using a spectrophotometric kit from LiNEAR (Spain). By using spectrophotometric assay kits from MELSIN (China) were utilized, to determine the serum creatinine and urea levels. The calculation of resistance of insulin and the extent of sensitivity by using (HOMA-IR) and (QUICK) equations [50-51].

Bio-statistical analysis

By using Microsoft Excel 2010 in conjunction with SPSS software (version 24) to analyze the collected data. The determination of the significant differences of the investigated groups were conducted by comparative statistical tests. Additionally, the analysis was employed to examine potential associations among the parameters by pearson's correlation coefficient.

RESULTS

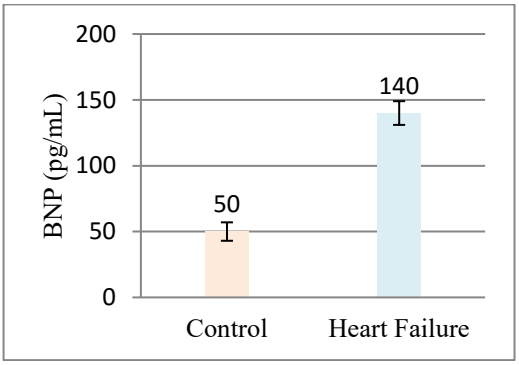
As shown in Table 1, Figure 1 (A, B, C, D, E, F, G), that display the mean of age, gender, BMI, W/H, SBP, DBP, creatinine, urea, AST and ALT levels that demonstrated no* - *significant* differences *between the groups of *heart *failure* and *control. While the mean of BNP, FSG, insulin, HOMA-IR, TGF-β and TRB3 Q84 levels showed a significantly increased in the group* of *heart* failure* as *compared* with *the *group* of *control, while the *mean* of QUICKI *levels* showed a significantly decreased in the heart failure group as compared with the control group.

Table 1: Demographic and biochemical data for the heart failure and the control groups

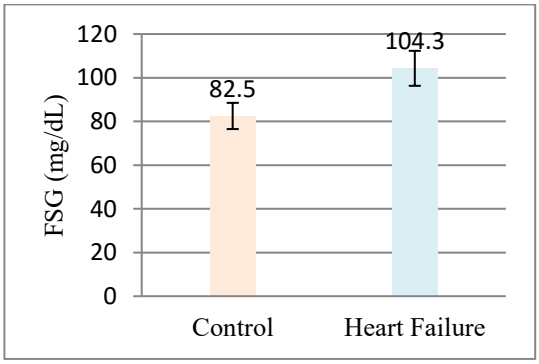
Parameters	Groups		P-value
	Control Mean ±SD (n=60)	Heart failure Mean ±SD (n=60)	
Age (year)	**55±3**	**55±3**	**0.15**
Gender Males/Females	35(58.3%)/25(41.7%)	35(58.3%)/25(41.7%)	0.85
BMI (kg/m2)	21.5±2	27.5±4	0.73
W/H	0.72±0.01	0.95±0.02	0.45
SBP (mmHg)	120±10	130±12	0.31
DBP (mmHg)	75±5	91±7	0.86

BNP (pg/mL)	50±7	140 ±9	0.02
FSG (mg/dL)	82.5 ± 6	104.3 ± 8	0. 03
Insulin (µU/mL)	6 ± 0.2	10 ± 0.5	0.05
HOMA-IR	2.5 ± 0.2	4.1 ± 0.3	0.02
QUICKI	0.59 ± 0.03	0.38 ± 0.02	0.01
Creatinine (mg/dL)	0.85±0.02	1±0.01	0.12
Urea (mg/dL)	13±1	15±2	0.23
AST (U/L)	25±4	30±6	0.09
ALT (U/L)	31±2	39±7	0.08
TGF-β (ng/mL)	3±0.2	4.5±0.4	0.02
TRB3 Q84 (ng/mL)	1.85±0.1	3± 0.2	0.01

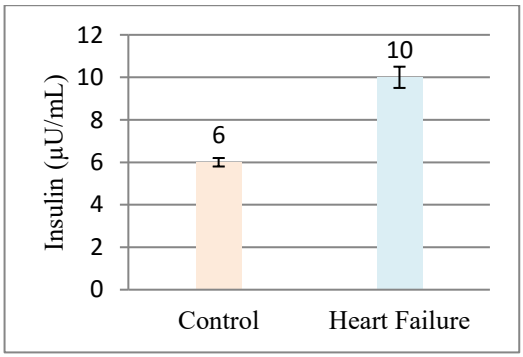
Significance: A p-value of ≤ 0.05 was *considered <significant>, n: <Number* -of- *subjects>, Mean ± SD; SD: <Deviation* – of – Stander*>, W/H: <Ratio* – of - *Waist -to- *Hip>, BMI: <Index* - of - *Body - *Mass>, DBP: <The Blood*- Pressure - of - Diastolic>, SBP: <The Blood*- Pressure - of - Systolic>, BNP: <*Peptide of Brain* - *Natriuretic*>, HOMA-IR: <Insulin – Resistance* of Homeostatic* – Model* - Assessment>, FSG: <Serum – Glucose*- of - Fasting>, QUICKI: <Check – Index*- of – Quantitative*– Insulin*- Sensitivity>, ALT: <Alanine* - *Aminotransferase>, AST: <Aspartate* - *Aminotransferase>, TGF-β: < Growth* – Factor*- of -Transforming* - Beta>, TRB3 Q84: <Tribbles* - Pseudokinase 3 – Glutamine* at Position 84>.



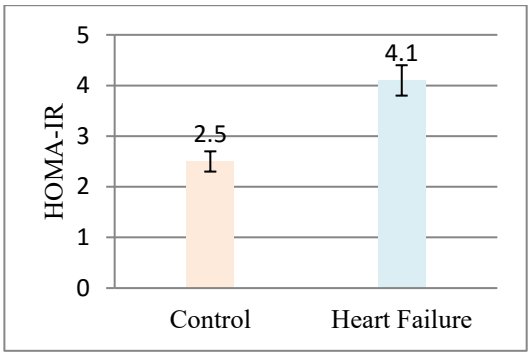
A



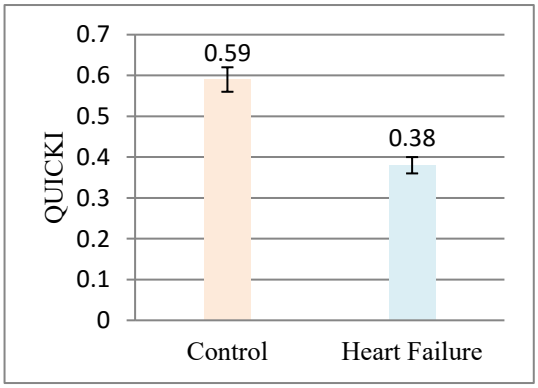
B



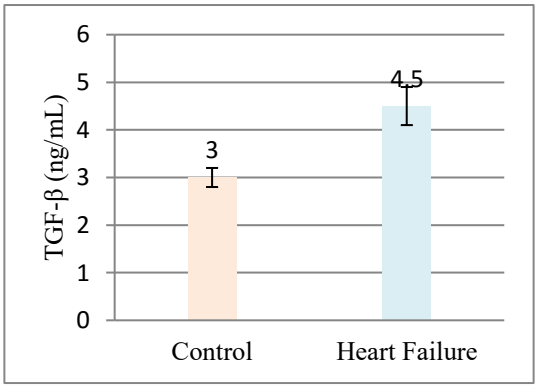
C



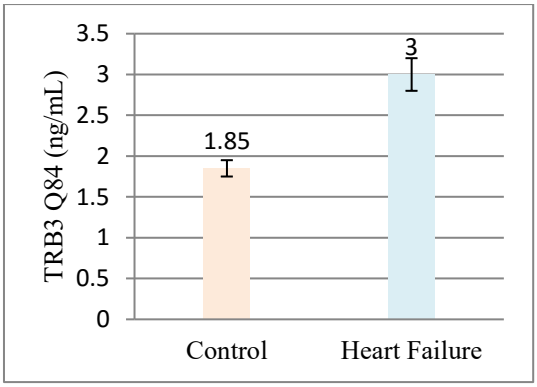
D



E



F



G

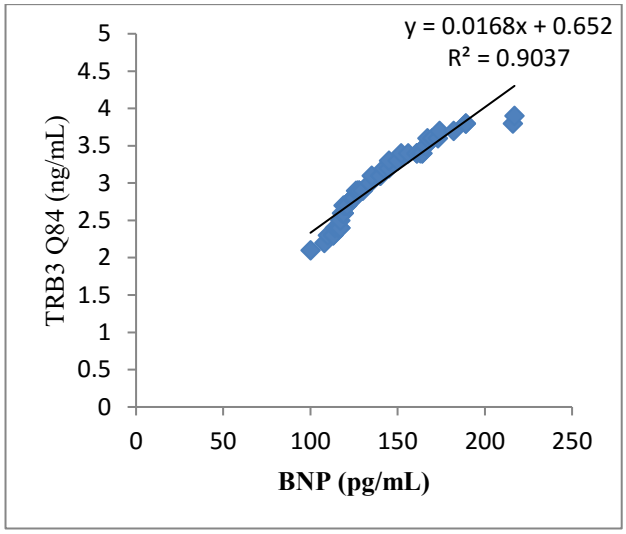
Figure 1: Comparison of serum A: BNP, B: FSG, C: Insulin, D: HOMA-IR, E: QUICKI, F: TGF-β and G: TRB3 Q84 levels between the heart failure and the control groups

As shown in Table 2, Figure 2 (A, B, C, D, E, F), that display the linear regression analysis results that assessing the relationship between levels of serum TRB3 Q84 concentrations and selected demographic and biochemical parameters in individuals with heart failure. The findings revealed that no - strong - significant - correlation - between TRB3 Q84 and other studied demographic - and - biochemical parameters, except that BNP, FBS, insulin, HOMA-IR and TGF-β levels showed a strong - significant - positive - correlation with TRB3 Q84 level, while QUICKI levels showed a strong - significant - negative - correlation with TRB3 Q84 level.

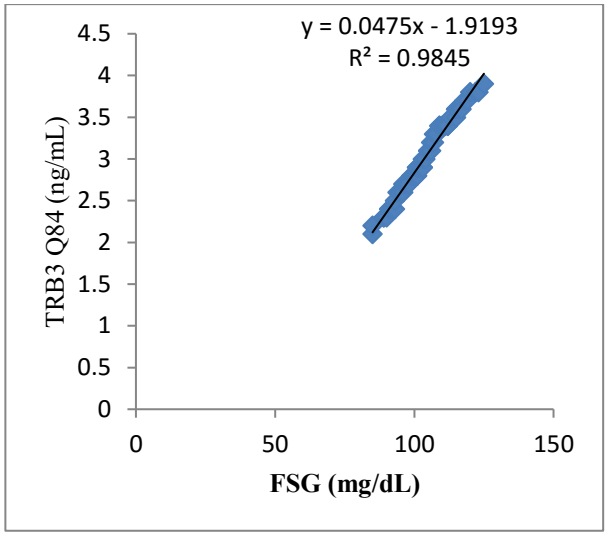
Table 2: Correlation between serum TRB3 Q84 levels and others demographic and biochemical parameters in the heart failure group

Parameters	TRB3 Q84 (ng/mL)	
Age (year)	r P-value	0.52 0.83
BMI (Kg/m2)	r P-value	0.45 0.94
W/H	r P-value	0.27 0.81
SBP (mmHg)	r P-value	0.51 0.78
DBP (mmHg)	r P-value	0.37 0.91
BNP (pg/mL)	r P-value	0.98 0.02
FSG (mg/dL)	r P-value	0.98 0.04
Insulin (µU/mL)	r P-value	0.96 0.01
HOMA-IR	r P-value	0.94 0.03
QUICKI	r P-value	-0.91 0.05
Creatinine (mg/dL)	r P-value	0.31 0.58
Urea (mg/dL)	r P-value	0.42 0.36
AST (U/L)	r P-value	0.14 0.36
ALT (U/L)	r P-value	0.28 0.36
TGF-β (ng/mL)	r P-value	0.97 0.03

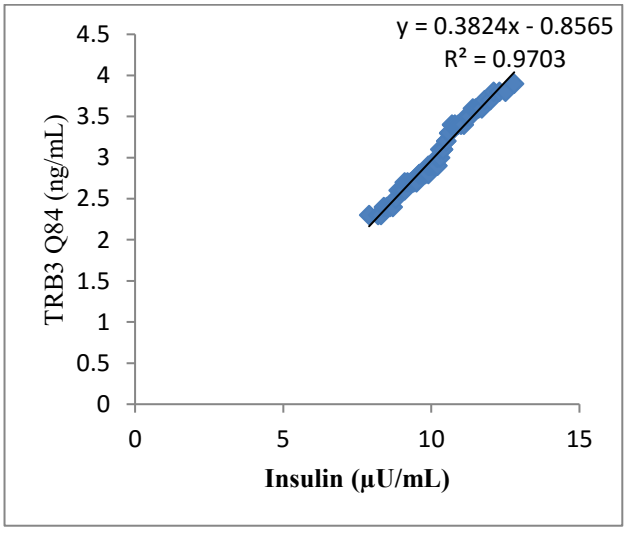
A p-value of ≤ 0.05 was considered, r: <correlation* coefficient* - of - Person>, W/H: <Ratio* – of - Waist -to-Hip>, BMI: <Index of* - Body - Mass>, DBP: <The Blood*- Pressure - of - Diastolic>, SBP: <The Blood*- Pressure - of - Systolic>, BNP: <<*Peptide of Brain* - *Natriuretic*>, HOMA-IR: <Insulin – Resistance* of Homeostatic* – Model* - Assessment>, FSG: <Serum – Glucose*- of - Fasting>, QUICKI: <Check – Index*- of – Quantitative*– Insulin*-Sensitivity>, ALT: <Alanine* - *Aminotransferase>, AST: <Aspartate* - *Aminotransferase>, TGF-β: < Growth* – Factor*- of -Transforming* - Beta>, TRB3 Q84: <Tribbles* - Pseudokinase 3 – Glutamine* at Position 84>.



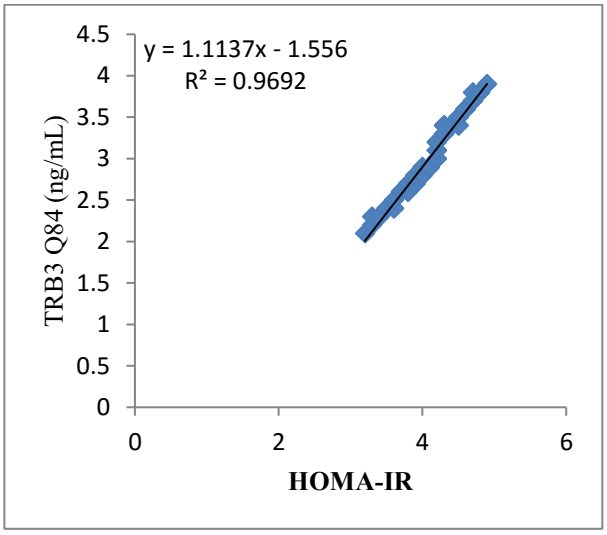
A



B



C



D

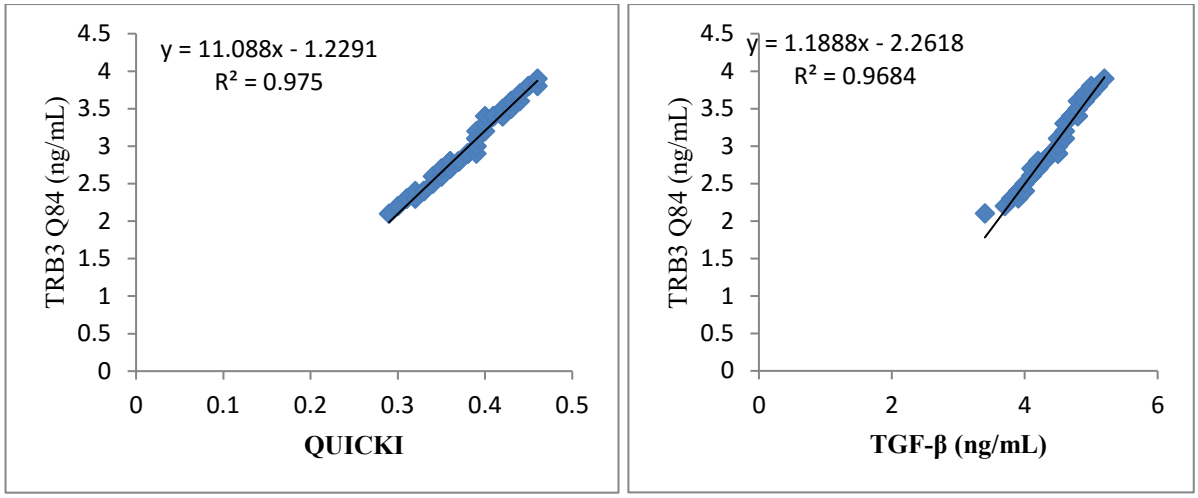


Figure 2: Correlation between serum TRB3 Q84 levels and A: BNP, B: FSG, C: Insulin, D: HOMA-IR, E: QUICKI and F: TGF-β in the heart failure group.

Table 3 presents the ROC curve analysis for TRB3 Q84, revealing a cut-off point of 93.3% for detecting heart failure patients. The *area* - *under* - the *curve* (AUC) was *calculated* at 0.952, reflecting high diagnostic performance. TRB3 Q84 demonstrated a sensitivity of 93.3% and a specificity of 100%, as - shown - in Figure 3.

Table 3: Receiver operating characteristic (ROC) and area under the curve (AUC) analysis of TRB3 Q84 in diagnosis heart failure patients

Variable	Group	Cut-off concentration %	Sensitivity %	Specificity %	AUC	Std. Error	95% CI of AUC	P-value
TRB3 Q84	Heart Hailure	93.3	93.3	100	0.952	0.025	0.903-1.000	0.001

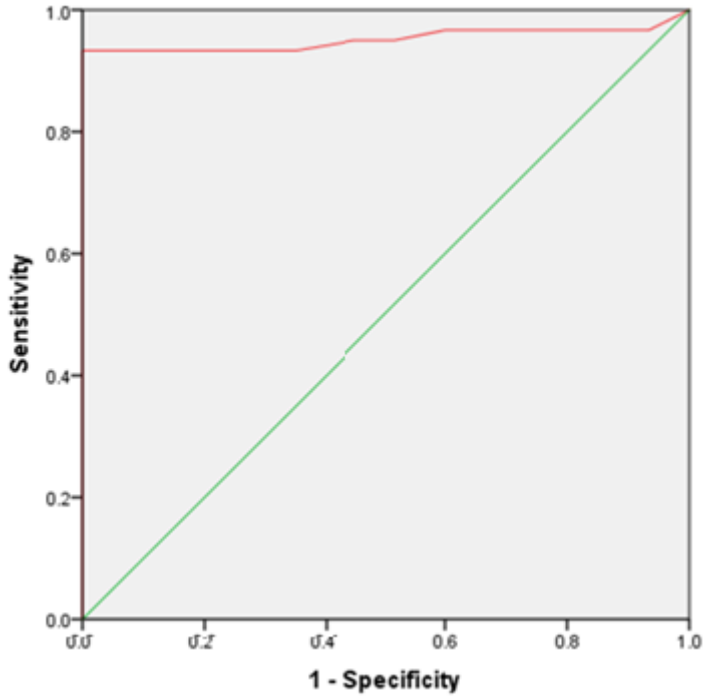


Figure 3: Receiver operating characteristic (ROC) curve analysis of TRB3 Q84 in diagnosing heart failure patients

DISCUSSION

The present study revealed a significantly increased in serum TRB3 Q84 levels, alongside a notable increased in BNP, FSG, insulin, HOMA-IR and TGF-β levels and decreased in QUICKI levels biomarkers among individuals with heart failure. In these patients a significant strong positive correlation was identified between TRB3 Q84, BNP, FSG, insulin, HOMA-IR and TGF-β biomarkers, while a significant strong negative correlation was identified between TRB3 Q84 and QUICKI. The fact of this pattern can be explained by that when heart failure occurs, the pumping of blood to the muscles, liver, and other tissues weakens, leading to hypoperfusion (reduced blood flow). This decreased blood flow reduces the delivery of oxygen and glucose to the cells, especially muscle cells. As a result, these cells have a diminished ability to absorb glucose and become less responsive to insulin due to impaired insulin receptor signaling, which depends on adequate tissue perfusion. Excess glucose entering the mitochondria within the cells is metabolized to produce energy through the electron transport chain. However, this leads to hight production of species of reactive oxygen (ROS) such as superoxide, which causes damage to proteins, lipids, and DNA inside the cell. Ultimately, hyperglycemia* of *chronic *causes *damage* of small blood vessels and peripheral nerves, particularly in the cornea. This damage leads to impaired corneal nutrition and nerve function, reducing the cornea's ability to heal and regenerate. Additionally, the accumulation of end products of advanced glycation (AGEs) increases inflammation and deteriorates the corneal structure, resulting in permanent corneal damage that may cause serious vision complications. This damage triggers a state of cellular stress, activating defense mechanisms including the expression of proteins such as TRB3 Q84, at his stage TRB3 Q84 reduces cellular metabolism and slows cell growth to protect the cell from further injury. Consequently, elevated TRB3 Q84 levels could potentially serve as an early biomarker indicating increased risk for permanent corneal damage in individuals with heart failure.

Previous work demonstrated a conserved role in regulating the pathway of insulin signaling of modulating Akt activity by the drosophila protein Trbl [52]. Corresponding to the human TRIB3 single nucleotide polymorphism (SNP) variant R84 known to be linked with insulin resistance is also crucial for insulin signaling modulation in flies [53]. Building on these findings, showed that an amino acid conserved at Trbl site. Similarly, when the analogous residue in Trbl drosophila (R141) is Q (R141Q) mutated, they observed diminished binding of Trbl to Akt, which leads to enhanced larval growth and increased anabolic activity. Functional analyses in human cells and organ cultures have revealed that the TRIB3 Q84 variant binds and inhibits AKT less effectively than the R84 variant [54]. Supporting this, they also found that expression of mouse Trib3, which carries the R variant, in the drosophila fat body suppresses Akt activation to a degree comparable to wild-type Trbl. These findings collectively indicate that the arginine residue is essential for Akt binding and inhibition.

Previous study suggested that the variant TRIB3 Q84 emerged relatively in human evolution was late. The Q residue variant found predominantly in modern humans is distinctive to both humans and Neanderthals, whereas the residue R is highly across nearly metazoan Tribbles (Trib) proteins conserved. Interestingly, human orthologs of TRIB1 and TRIB2 retain the conserved R residue, underscoring its functional importance within this protein family. Given that short-term nutrient deprivation elevates TRIB3 Q84 in the tissue of adipose [55], and that TRIB3 Q84 levels increase in human cells subjected to glucose and amino acid starvation [56], one hypothesis is that the variant Q84 allows for some Akt activity residual during physical prolonged exertion such as running of endurance a trait that is particularly characteristic of hominids [57]. While the negative impact of the Q/R substitution on function has been established [58], it remains an open question what selective advantage this motif may have conferred during the evolutionary divergence of humans and neanderthals.

The drosophila model of insulin resistance provides a valuable system to investigate the specific effects of these TRIrB3 Q84 SNPs across different developmental stages, tissues, and dietary conditions [59]. Beyond the well-known variant Q and R SNP in populations of human, several other non-synonymous SNPs exist within the genomic of the TRIB3 Q84 gene of human, though their functions and biological significance remain largely unexplored. Since Trib3 expression is influenced by diet, experiments involving Trbl under high sugar and fat dietary regimens conducted efficiently [60]. This allows in drosophila the powerful genetic tools use is available to either overexpress or knock down Trbl in targeted tissues. Moreover, vertebrate Trib3 exhibits tissue-specific roles in the liver, endothelium, and pancreatic islets organs with functional counterparts in flies. Additionally, considering TRIB3's established function as a molecular link between diabetes and cancer, these insights can guide investigations of Trbl in recently developed drosophila tumor models regulated by insulin signaling [61].

In the previous study, they demonstrated that the mutation of R141Q does not disrupt Trbl's capacity by cell division inhibition triggered by Cdc25 phosphatase or to regulate cell migration mediated by C/EBP. Mutations affecting the conserved DLK motif have been shown to significantly weaken tribbles family proteins interaction of with key partners such as Akt [62]. This finding indicates that the DLK motif may represent a promising therapeutic target for selectively

reducing insulin resistance while preserving other essential cellular roles of Trbl. The tribbles roles in mammals in regulation of insulin are complex, notably TRIB2 has recently been identified as an Akt activator [63] and has been linked to leukemogenesis by promoting phosphorylation of ERK [64].

Subsequently incorporated the mutation to evaluate its effects in vivo in flies. In vivo studies confirmed that the R141E variant binds Akt with increased affinity, suggesting it may act dominantly to inhibit activity of Akt more effectively than wild-type Trbl. The fly model, characterized by a single tribbles isoform, presents a valuable platform for rapid investigation of molecular defects linked to tribbles disease alleles in human, thereby advancing the understanding of their roles in diabetes of type 2 and cancer [65-66].

CONCLUSION

The results of this study indicated a significant strong positive correlation between TRB3 Q84, BNP, FSG, insulin, HOMA-IR and TGF-β biomarkers, while a *significant* strong *negative* correlation was identified *between* TRB3 Q84 and QUICKI in *heart* failure* *patients. Therefore, TRB3 Q84 levels as new biochemical marker for the early detection and diagnosis of permanent corneal damage in *heart* failure* *patients. It is recommended to include TRB3 Q84 measurement as part of early screening protocols for development of permanent corneal damage in heart failure patients and ophthalmologic evaluations should be integrated into the routine follow-up of patients with heart failure, with particular attention to early corneal nerve damage and tear film abnormalities.

ACKNOWLEDGEMENT

The participants were thanked by author for their cooperation, as well as the medical personnel and laboratory staff in Al Qadisiyah at Diwaniya Teaching Hospital, Iraq, were thanked by author for their valuable support in sample collection and the execution of essential laboratory analyses.

CONFLICT OF INTERESTS

There *was* no *conflict* of *interest.

FUNDING

Self*-*funding.

REFERENCES

1. Norton C, Georgiopoulou V and Kalogeropoulos A, Epidemiology and cost of advanced heart failure, *Prog Cardiovasc Dis*, 2011 ; 54:78–85.
2. Sowers J, Whaley A and Hayden M, The Role of Overweight and Obesity in the Cardiorenal Syndrome, *Cardiorenal Med*, 2011; 1:5–12.
3. Falcão I and Leite A, Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment, *Heart Fail Rev*, 2011; 3:1-7.
4. Reaven G, Insulin resistance: the link between obesity and cardiovascular disease, *Med Clin North Am*, 2011; 95:875–92.
5. Mamas M, Deaton C and Rutter M, Impaired glucose tolerance and insulin resistance in heart failure: underrecognized and undertreated, *J Card Fail*, 2010; 16:761–68.
6. Heck P and Dutka D, Insulin resistance and heart failure, *Curr Heart Fail Rep*, 2009; 6:89–94.
7. Coats A and Anker S, Insulin resistance in chronic heart failure, *J Cardiovasc Pharmacol*, 2000; 35:9–14.
8. Andreozzi F, Formoso G and Prudente S, TRIB3 R84 variant is associated with impaired insulin-mediated nitric oxide production in human endothelial cells, *Arterioscler. Thromb. Vasc Biol*, 2008; 28:1355-1360.
9. Prudente S, Bailetti D and Mendonca C, Infrequent TRIB3 coding variants and coronary artery disease in type 2 diabetes, *Atherosclerosis*, 2015; 242:334-339.
10. Prudente S, Dallapiccola B and Pellegrini F, Genetic prediction of common diseases. Still no help for the clinical diabetologist, *Nutr. Metab. Cardiovasc. Dis*, 2012; 22:929-936.
11. Yokoyama T, Toki T ad Aoki Y, Identification of TRIB1 R107L gain- of-function mutation in human acute megakaryocytic leukemia, *Blood*, 2012; 119:2608-2611.
12. Gong H, Wang Z and Jiang H, TRIB3 functional Q84R polymorphism is a risk factor for metabolic syndrome and carotid atherosclerosis, *Diabetes Care*, 2009; 32:1311-1313.
13. Prudente S, Hribal M and Flex E, The functional Q84R polymorphism of mammalian Tribbles homolog TRB3 is associated with insulin resistance and related cardiovascular risk in Caucasians from Italy, *Diabetes*, 2005; 54:2807-2811.
14. Formoso G, Tomo P and Andreozzi F, The TRIB3 R84 variant is associated with increased carotid intima-media thickness in vivo and with enhanced MAPK signalling in human endothelial cells, *Cardiovasc. Res*, 2011; 89:184-192.
15. Dobens L and Bouyain S, Developmental roles of tribbles protein family members, *Dev. Dyn*, 2012; 241: 1239-1248.
16. Koyama T, Mendes C and Mirth C, Mechanisms regulating nutrition-dependent developmental plasticity through organ-specific effects in insects, *Front. Physiol*, 2013 ; 4:263-275.
17. Das R and Dobens L, Conservation of gene and tissue networks regulating insulin signalling in flies and vertebrates, *Biochem. Soc. Trans*, 2015; 43:1057-1062.
18. Krishna G, Bir S and Kevil C, Endothelial Dysfunction and Diabetes: Effects on

Angiogenesis, Vascular Remodeling, and Wound Healing, *Int. J. Vasc. Med*, 2012; 20:30-36.
19. Sayin N, Kara N and Pekel G, Ocular Complications of Diabetes Mellitus, *World J. Diabetes*, 2015; 6:92–108.
20. DeMill D, Hussain M and Pop R, Ocular Surface Disease in Patients with Diabetic Peripheral Neuropathy, *Br. J. Ophthalmol,* 2016; 100:924–928.
21. Vieira V, Karamichos D and Lee D, Ocular Complications of Diabetes and Therapeutic Approaches, *Biomed. Res. Int*, 2016; 20:38-47.
22. Lutty G, Effects of Diabetes on the Eye, *Investig. Ophthalmol. Vis. Sci*, 2013; 54:81–87.
23. Semeraro F, Cancarini A and Rezzola S, Diabetic Retinopathy: Vascular and Inflammatory Disease, *J. Diabetes Res*, 2015; 2015:58-64.
24. Yu F, Yin J, Lee P and Hwang F, Sensory Nerve Regeneration after Epithelium Wounding in Normal and Diabetic Corneas, *Expert. Rev. Ophthalmol*, 2015; 10:383–392.
25. Kaji Y, Prevention of Diabetic Keratopathy, *Br. J. Ophthalmol,* 2005; 89:254–255.
26. Negi A, Stephen M, Vernon A and Frcophth D, An Overview of the Eye in Diabetes, *J. R. Soc. Med*, 2003; 96:266–272.
27. Klein B, Klein R and Moss S, Incidence of Cataract Surgery in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, *Am. J. Ophthalmol*, 1995; 119:295–300.
28. Messmer E, Schmid C, Zapp D and Kampik A, In Vivo Confocal Microscopy of Corneal Small Fiber Damage in Diabetes Mellitus, *Graefe's Arch. Clin. Exp. Ophthalmol*, 2010; 248:1307–1312.
29. Nitoda E, Kallinikos P, Pallikaris A, Moschandrea J, Amoiridis G, Ganotakis E and Tsilimbaris M, Correlation of Diabetic Retinopathy and Corneal Neuropathy Using Confocal Microscopy, *Curr. Eye Res*, 2012; 37:898–906.
30. Naik K, Magdum R, Ahuja A and Kaul S, Ocular Surface Diseases in Patients with Diabetes, *Cureus*, 2022; 14:23-40.
31. Zhang Z, Zou X, Xue W, Zhang P, Wang S and Zou H, Ocular Surface Microbiota in Diabetic Patients with Dry Eye Disease, *Investig. Ophthalmol. Vis. Sci*, 2021; 62:13-20.
32. King A, The Use of Animal Models in Diabetes Research, *Br. J. Pharmacol*, 2012; 166:877–894.
33. Di A, Coassin M, Micera A and Mori T, Ocular Surface Diabetic Disease: A Neurogenic Condition, *Ocul. Surf*, 2021; 19:218–223.
34. Chopra V, Varma R, Francis B and Wu J, Type 2 Diabetes Mellitus and the Risk of Open-Angle Glaucoma: The Los Angeles Latino Eye Study, *Ophthalmology*, 2008; 115:227–232.
35. Saw S, Wong T, Ting S, Foong A and Foster P, The Relationship Between Anterior Chamber Depth and the Presence of Diabetes in the Tanjong Pagar Survey, *Am. J. Ophthalmol*, 2007; 144:325–326.
36. Huang S, Palla S, Ruzycki P and Varma R, Aldo-Keto Reductases in the Eye, *J. Ophthalmol,* 2010; 20:52-58.
37. Priyadarsini S, Whelchel A, Nicholas S and Sharif R, Diabetic Keratopathy: Insights and Challenges, *Surv. Ophthalmol,* 2020; 65:5-13.
38. Shih K, Lam K and Tong L, A Systematic Review on the Impact of Diabetes Mellitus on the Ocular Surface, *Nutr. Diabetes*, 2017; 7:2-5.
39. Han S, Yang H and Hyon J, Influence of Diabetes Mellitus on Anterior Segment of the Eye, *Clin. Interv. Aging*, 2019; 14:53–63.
40. Sellers E, Clark I, Tavakoli M, Dean H, McGavock J and Malik R, The Acceptability and Feasibility of Corneal Confocal Microscopy to Detect Early Diabetic Neuropathy in Children: A Pilot Study, *Diabet. Med*, 2013; 30:630–631.
41. Barsegian A, Lee J, Salifu M and Mcfarlane S, Corneal Neuropathy: An Underrated Manifestation of Diabetes Mellitus, *J. Clin. Endocrinol. Diabetes*, 2018; 20:1-11.
42. NaPier E, Camacho M, McDevitt T and Sweeney A, Neurotrophic Keratopathy : Current Challenges and Future Prospects, *Ann. Med*, 2022; 54:6-12.
43. Zhou Q, Yang L, Wang Q, Li Y, Wei C and Xie L, Mechanistic Investigations of Diabetic Ocular Surface Diseases, *Front. Endocrinol*, 2022; 13:107-115.
44. Ljubimov A, Diabetic Complications in the Cornea, *Vis. Res*, 2017; 139:8-13.
45. Hamrah P, Liu Y, Zhang Q and Dana M, The Corneal Stroma Is Endowed with a Significant Number of Resident Dendritic Cells, *Investig. Ophthalmol. Vis. Sci*, 2003; 44:581–589.
46. Hamrah P, Liu Y, Zhang Q and Dana M, Alterations in Corneal Stromal Dendritic Cell Phenotype and Distribution in Inflammation, *Arch. Ophthalmol*, 2003; 121:1132–1140.
47. Hamrah P, Zhang Q, Liu Y and Dana M, Novel Characterization of MHC Class II-Negative Population of Resident Corneal Langerhans Cell-Type Dendritic Cells, *Investig. Ophthalmol. Vis. Sci*, 2002; 43:639–646.
48. Amouzegar A, Chauhan S and Dana R, Alloimmunity and Tolerance in Corneal Transplantation, *J. Immunol*, 2016; 196:3983–3991.
49. Huq S, Liu Y, Benichou G and Dana M, Relevance of the Direct Pathway of Sensitization in Corneal Transplantation Is Dictated by the Graft Bed Microenvironment, *J. Immunol*, 2004; 173:4464–4469.
50. Grzesiuk W, Dorota S and Katarzyna J, Insulin Resistance in Endocrinopathies, *Endocrinol Obes Metab Disorder*, 2008; 5:38-44.
51. Szurkowska M, Krystyna S, Aleksandra J and Zbigniew S, Insulin Resistance Indices in Population-Based Study and their Predictive Value in Defining Metabolic Syndrome, *Przegl Epidemiol*, 2005; 59:743-751.

52. Das R, Sebo Z, Pence L and Dobens L, Drosophila tribbles antagonizes insulin signaling-mediated growth and metabolism via interactions with Akt kinase, *PLoS ONE*, 2014; 8:109-130.
53. Prudente S, Hribal M, Flex E and Turchi F, The functional Q84R polymorphism of mammalian Tribbles homolog TRB3 is associated with insulin resistance and related cardiovascular risk in Caucasians from Italy, *Diabetes*, 2005; 54:2807-2811.
54. Andreozzi F, Formoso G, Prudente S, Hribal M and Pandolfi A, TRIB3 R84 variant is associated with impaired insulin-mediated nitric oxide production in human endothelial cells, *Arterioscler. Thromb. Vasc. Biol,* 2008; 28:1355-1360.
55. Prudente S, Bailetti D, Mendonca C and Mannino G, Infrequent TRIB3 coding variants and coronary artery disease in type 2 diabetes, *Atherosclerosis*, *2015*; 242:334-339.
56. Liu J, Zhang W, Chuang G and Hill H, Role of TRIB3 in regulation of insulin sensitivity and nutrient metabolism during short-term fasting and nutrient excess, *Am. J. Physiol. Endocrinol. Metab*, 2012; 303:908-916.
57. Schwarzer R, Dames S, Tondera D, Klippel A and Kaufmann J, TRB3 is a PI 3-kinase dependent indicator for nutrient starvation, *Cell. Signal*, 2006; 18:899-909.
58. Bramble D and Lieberman D, Endurance running and the evolution of Homo, *Nature*, 2004 ; 432 :345-352.
59. Musselman L, Fink J, Narzinski K, Ramachandran P, Hathiramani S, Cagan R and Baranski T, A high-sugar diet produces obesity and insulin resistance in wild-type Drosophila, *Dis. Model. Mech*, 2011; 4:842-849.
60. Izrailit J, Berman H, Datti A, Wrana J and Reedijk M, High throughput kinase inhibitor screens reveal TRB3 and MAPK-ERK/TGFbeta pathways as fundamental Notch regulators in breast cancer, *Proc. Natl. Acad. Sci. USA*, 2013; 110:1714-1719.
61. Figueroa A and Bilder D, Malignant Drosophila tumors interrupt insulin signaling to induce cachexia-like wasting, *Dev. Cell*, 2015; 33:47-55.
62. Masoner V, Das R, Pence L, Anand G, Laferriere H, Zars T, Bouyain S and Dobens L, the kinase domain of Drosophila Tribbles is required for turnover of fly C/EBP during cell migration, *Dev. Biol*, 2013; 375:33-44.
63. Hill R, Madureira P, Ferreira B, Baptista I, Machado S, Colaço L, Dos M, Liu N, Dopazo A and Ugurel S, TRIB2 confers resistance to anti-cancer therapy by activating the serine/threonine protein kinase AKT, *Nat. Commun*, 2017; 8:14-18.
64. Yokoyama T, Toki T, Aoki Y, Kanezaki R and Park M, Identification of TRIB1 R107L gain- of-function mutation in human acute megakaryocytic leukemia, *Blood*, 2012; 119:2608-2611.
65. Alfa R and Kim S, Using Drosophila to discover mechanisms underlying type 2 diabetes, *Dis. Model. Mech*, 2016; 9:365-376.
66. Liew C, Bochenski J, Kawamori D, Hu J and Leech C, The pseudokinase tribbles homolog 3 interacts with ATF4 to negatively regulate insulin exocytosis in human and mouse beta cells, *J. Clin. Invest*, 2010; 120:2876-2888.

