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Original Article

Functional Characterization of IL-17F Polymorphism Using Computational Tools

Nazia Hadi[1], Wagma Gul[1], Tayyaba Iftikhar[2], Naveed Khan[1]

[1] Department of Biotechnology, Abdul Wali Khan University, Mardan, Pakistan

[2] Department of Pharmacy, Abdul Wali Khan University, Mardan, Pakistan

Correspondence: naveedkhan@awkum.edu.pk
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ABSTRACT

Background: Obesity is a complex disorder influenced by both environmental exposures and genetic predisposition, with inflammatory cytokines playing a central role. Interleukin-17F (IL-17F), a pro-inflammatory mediator, has been linked to multiple immune-related diseases, but the contribution of its coding variants to disease susceptibility remains poorly defined. Objective: This study aimed to identify potentially deleterious nonsynonymous single-nucleotide polymorphisms (nsSNPs) in IL-17F and evaluate their structural and functional impact using computational tools. Methods: Missense variants were retrieved from public databases and screened with prediction algorithms (SIFT, PolyPhen-2, PhD-SNP, SNPs&GO, and PANTHER). Stability was assessed using I-Mutant 3.0 and MUpro, functional effects with MutPred, and evolutionary conservation with ConSurf. Three-dimensional protein structures were modeled by I-TASSER and compared with TM-align. Gene and protein interaction networks were examined using GeneMANIA and STRING, while phosphorylation and ubiquitination sites were predicted with GPS/NetPhos and BDM-PUB. Results: From 2,230 IL-17F variants, 158 were missense substitutions. Cross-tool consensus highlighted 23 nsSNPs with deleterious potential. Most substitutions reduced protein stability, particularly R77S, P81S, and V155G. MutPred scores indicated that cysteine substitutions at positions 107 and 152 were especially disruptive (>0.91). ConSurf revealed that the majority of these variants occur at conserved residues, while structural modeling demonstrated RMSD deviations up to 3.2 Å, consistent with conformational disturbance. Predicted phosphorylation and ubiquitination hotspots suggested that some variants may also alter regulatory post-translational modifications. Conclusion: Computational analysis identified multiple IL-17F nsSNPs likely to compromise protein structure and function. These findings provide a prioritized set of variants for experimental validation and genetic association studies, contributing to understanding the role of IL-17F in obesity and related inflammatory conditions.
Keywords: Interleukin-17F, nonsynonymous SNPs, protein stability, structural bioinformatics, obesity, post-translational modifications.

INTRODUCTION

Obesity is a chronic metabolic disorder marked by excessive fat accumulation that impairs health and contributes to a wide range of comorbidities. Although lifestyle factors such as diet and physical inactivity are well-recognized contributors, substantial evidence indicates that genetic predisposition accounts for a significant proportion of variability in susceptibility, with heritability estimates ranging between 40% and 70% (1,2). Advances in genome-wide association studies have uncovered hundreds of loci implicated in energy balance, glucose regulation, and immune pathways, suggesting that obesity is influenced by an intricate network of metabolic and inflammatory signals (3,4).

Among the genes linked with immune regulation, interleukin-17F (IL-17F) has emerged as a particularly important candidate. IL-17F encodes a pro-inflammatory cytokine involved in host defense and immune-mediated processes, and its polymorphisms have been associated with several inflammatory disorders, including osteoarthritis, inflammatory bowel disease, ulcerative colitis, and gastric malignancies (5–7). Specific nonsynonymous single-nucleotide polymorphisms (nsSNPs), such as rs2397084 (E126G) and His161Arg, have been reported to alter susceptibility to immune-related conditions and chronic inflammatory states (8,9). These findings highlight IL-17F as a gene of interest not only in classical immune dysregulation but also in obesity, which is increasingly recognized as a low-grade inflammatory condition.

Despite the growing body of literature on IL-17F polymorphisms in disease, there is a lack of comprehensive evaluation of potentially deleterious nsSNPs in this gene using in silico approaches. To date, no systematic computational analysis has been performed to identify functional variants that may disrupt IL-17F protein stability, structural conformation, or interaction with signaling partners. Addressing this gap is essential for prioritizing variants for experimental validation and for understanding their potential role in the genetic architecture

of obesity and related disorders. This study therefore applied multiple bioinformatics tools to predict and characterize the functional impact of IL-17F nsSNPs, aiming to identify high-risk variants that could contribute to disease pathogenesis.

MATERIAL AND METHODS

This investigation was an in silico analysis of coding variants in the human IL-17F gene. Variants were retrieved from public repositories and passed through a predefined pipeline that assessed pathogenicity, stability, conservation, structural consequences, interaction context, and post-translational modification (PTM) propensity. Unless stated otherwise, default parameters were used and analyses were performed on data accessed in January 2023.

Single-nucleotide polymorphisms (SNPs) were gathered from dbSNP and Ensembl, while the canonical IL-17F protein sequence was taken from UniProt (10–12). We restricted the dataset to missense variants mapped to the canonical coding transcript; synonymous, UTR, intronic, and duplicate entries were excluded. Amino-acid substitutions were harmonized against the UniProt reference sequence to ensure consistent residue indexing.

Prediction of functional impact used a panel of complementary algorithms. SIFT, PolyPhen-2, PhD-SNP, SNPs&GO, and PANTHER were applied to each missense variant (13–17). Variants with SIFT scores <0.05 were considered intolerant; PolyPhen-2 scores >0.85 were labeled “probably damaging” and >0.50 “possibly damaging”; PhD-SNP and SNPs&GO outputs were recorded as disease/neutral with their associated probabilities; PANTHER subPSEC scores were interpreted on the deleteriousness gradient. To prioritize hits, we used a consensus rule: variants predicted damaging by at least three of the five tools advanced to downstream analyses.

To evaluate changes in thermodynamic stability, we ran I-Mutant 3.0 and MUpro using the IL-17F sequence as input at pH 7.0 and 25 °C (18,19). Predicted ΔΔG values (mutant–wild type) below 0 indicated decreased stability; the magnitude of change was used to rank candidates.

Putative functional consequences beyond stability were explored with MutPred, which yields a general score (g) and mechanistic hypotheses (20). Following conventional practice, $g > 0.50$ flagged potentially damaging substitutions and $g \geq 0.75$ denoted high-confidence effects, with specific property alterations retained for interpretation.

Evolutionary constraint was quantified with ConSurf, which infers residue-level conservation from homologous sequences and assigns grades from 1 (variable) to 9 (highly conserved), while also classifying residues as buried or exposed (21). Variants occurring at conserved and/or functionally exposed sites were considered higher priority.

For structural consequences, we generated three-dimensional models for the wild-type protein and each shortlisted mutant using I-TASSER, selecting top models by C-score (22). UCSF Chimera was used for visualization and qualitative inspection of local changes, such as side-chain packing or interface perturbations (23). Structural similarity between wild-type and mutant models was quantified with TM-align, reporting TM-score (0–1) and backbone RMSD as global deviation metrics (24).

To place variants within a systems context, we examined gene-gene relationships with GeneMANIA—capturing co-expression, physical interactions, pathway co-membership, and shared domains—and protein-protein interactions with STRING (v11), recording network density and enrichment statistics (25,26). These analyses helped identify whether affected residues sat in proteins central to inflammatory signaling clusters.

Finally, PTM liabilities were profiled across the IL-17F sequence. Lysine methylation candidates were predicted with GPS-MSP 3.0 (27). Serine/threonine/tyrosine phosphorylation sites were inferred independently with GPS 3.0 and NetPhos 3.1, retaining residues above the default confidence thresholds and noting overlaps (28,29). Ubiquitination candidates on lysines were predicted using BDM-PUB with its balanced cut-off (30). Concordant calls across tools were prioritized, and any variant that disrupted or created a high-confidence PTM motif was flagged.

No human or animal subjects were involved. The study is computational and reproducible from the cited databases, software, and stated thresholds. References correspond to tool and database citations and should be completed in the bibliography as per journal style.

RESULTS

Variant retrieval and functional prediction

Interrogation of the Ensembl database identified 2,230 variants mapped to the IL-17F locus. These included 158 nonsynonymous (missense) substitutions, 73 synonymous changes, 38 variants in the 5′ untranslated region, 70 in the 3′ untranslated region, and approximately 1,756 intronic alterations (Figure 1). Given their potential impact on protein sequence, the 158 missense variants were carried forward for functional screening.

Five independent algorithms were applied to evaluate the pathogenic potential of these substitutions: SIFT, PolyPhen-2, PhD-SNP, SNPs&GO, and PANTHER. SIFT classified 133 variants as functionally intolerant (score <0.05) and 25 as tolerated. PolyPhen-2 identified 66 variants as “probably damaging,” 22 as “possibly damaging,” and the remainder as benign. PhD-SNP predicted 44 nsSNPs as disease-related, while 114 were considered neutral. SNPs&GO marked 33 variants as deleterious and 125 as non-damaging, whereas PANTHER estimated 41 as probably damaging, 21 as possibly damaging, and 95 benign.

When predictions were cross-compared, a consensus set of 23 nsSNPs consistently emerged as deleterious across three or more of the five tools (Figure 2, Table 1). These included recurrent substitutions at positions R77, S78, P81, D89, R92, A100, C107, G112, I123, V129, R131, R132, C152, T153, V155, and P157. Each of these variants was prioritized for further analysis of stability, functional impact, and structural modeling.

Table 1. Consensus deleterious nsSNPs in IL-17F predicted by five computational tools

SNP ID	Substitution	SIFT	PhD-SNP	SNPs&GO	PANTHER	PolyPhen-2
rs770953888	R77S	NT (0.00)	D	D (0.746)	PD	PD (1.000)
rs770953888	R77C	NT (0.00)	D	D (0.712)	PD	PD (1.000)
rs1764012735	S78Y	NT (0.03)	D	D (0.571)	PD	PD (1.000)
rs530331585	P81S	NT (0.00)	D	D (0.773)	PD	PD (1.000)
rs1444198450	D89H	NT (0.00)	D	D (0.824)	PD	PD (1.000)
rs142962486	R92G	NT (0.00)	D	D (0.709)	PD	PD (1.000)
rs142962486	R92W	NT (0.00)	D	D (0.722)	PD	PD (1.000)
rs376780230	R92Q	NT (0.00)	D	D (0.782)	PD	PD (1.000)
rs1325665616	A100T	NT (0.00)	D	D (0.739)	PD	PD (1.000)
rs1369700788	A100V	NT (0.00)	D	D (0.597)	PD	PD (1.000)
rs901898355	C107R	NT (0.00)	D	D (0.829)	PD	PD (1.000)
rs1213524690	G112R	NT (0.02)	D	D (0.687)	PD	PD (1.000)
rs570911210	I123T	NT (0.01)	D	D (0.595)	PD	PD (1.000)
rs201184682	V129A	NT (0.00)	D	D (0.538)	PD	PD (1.000)
rs147873628	R131W	NT (0.00)	D	D (0.513)	PD	PD (1.000)
rs760408480	R132S	NT (0.01)	D	D (0.721)	PD	PD (1.000)
rs762731838	C152R	NT (0.00)	D	D (0.888)	PD	PD (1.000)
rs777210315	C152Y	NT (0.00)	D	D (0.879)	PD	PD (1.000)
rs777210315	C152F	NT (0.00)	D	D (0.876)	PD	PD (1.000)
rs1297601336	T153A	NT (0.00)	D	D (0.719)	PD	PD (1.000)
rs769299818	T153I	NT (0.00)	D	D (0.645)	PD	PD (0.999)
rs746053425	V155G	NT (0.00)	D	D (0.736)	PoD	PD (1.000)
rs757261387	P157L	NT (0.01)	D	D (0.566)	PD	PD (1.000)

Abbreviations: NT = Not tolerated; D = Disease-related; PD = Probably damaging; PoD = Possibly damaging.

Protein stability and functional effects

The 23 high-risk nsSNPs were assessed for their influence on IL-17F protein stability. Predictions from I-Mutant 3.0 and MUpro were consistent for nearly all variants, showing a general decrease in thermodynamic stability. Most ΔΔG values were negative, confirming destabilization. Substitutions such as R77S (−3.87 kcal/mol), V155G (−3.71 kcal/mol), and P81S (−2.33 kcal/mol) produced the strongest destabilizing effects, while A100V was predicted as nearly neutral or mildly stabilizing (Table 2).

MutPred scores indicated that cysteine substitutions at positions 107 and 152 (C107R, C152R, C152Y, C152F) were the most disruptive (>0.91), consistent with disruption of disulfide bonds. Other high-confidence damaging mutations included R92G (0.864), S78Y (0.824), A100V (0.812), and G112R (0.806). By contrast, R131W and R132S were predicted to have only moderate functional impact (scores near 0.55). These findings suggest that both stability loss and altered functional properties are major mechanisms by which these variants may impair IL-17F function.

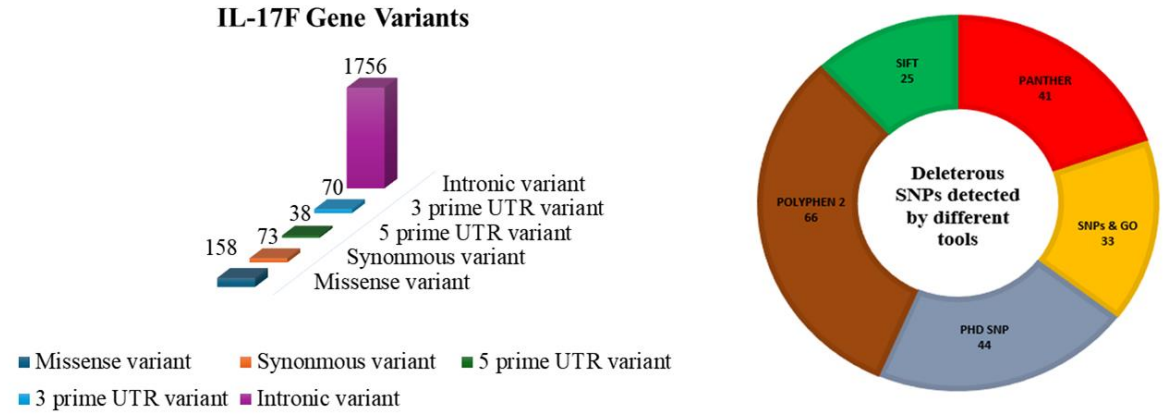

Figure 1 Distribution of IL-17F gene variants and predicted deleterious substitutions. Left panel: classification of 2,230 variants retrieved from Ensembl, including missense, synonymous, untranslated region (UTR), and intronic categories. Right panel: consensus deleterious nonsynonymous SNPs identified by five computational tools (SIFT, PolyPhen-2, PhD-SNP, SNPs&GO, and PANTHER), highlighting overlap across prediction methods.

Table 2. Stability predictions for deleterious nsSNPs in IL-17F

SNP ID	Substitution	I-Mutant ΔΔG (kcal/mol)	Effect	MUpro ΔΔG	Effect
R77S	−3.87	Decrease	−0.95	Decrease	
R77C	−1.27	Decrease	−0.64	Decrease	
S78Y	−0.63	Decrease	−0.82	Decrease	
P81S	−2.33	Decrease	−1.25	Decrease	
D89H	−0.88	Decrease	−0.79	Decrease	
R92G	−2.10	Decrease	−1.55	Decrease	
R92W	−0.80	Decrease	−0.96	Decrease	
R92Q	−1.68	Decrease	−1.06	Decrease	
A100T	−0.76	Decrease	−0.34	Decrease	
A100V	−0.04	Neutral	+0.22	Increase	
C107R	−0.84	Decrease	−1.18	Decrease	
G112R	−0.88	Decrease	−1.06	Decrease	
I123T	−2.33	Decrease	−2.02	Decrease	
V129A	−1.74	Decrease	−0.96	Decrease	
R131W	−0.36	Decrease	−1.30	Decrease	
R132S	−2.18	Decrease	−1.49	Decrease	
C152R	−0.02	Neutral	−0.91	Decrease	
C152Y	−1.02	Decrease	−0.77	Decrease	
C152F	−1.29	Decrease	−0.45	Decrease	
T153A	−0.69	Decrease	−0.42	Decrease	
T153I	−0.17	Neutral	−0.02	Decrease	
V155G	−3.71	Decrease	−1.88	Decrease	
P157L	−0.35	Decrease	−0.11	Decrease	

Table 3. Functional effect prediction of deleterious nsSNPs in IL-17F (MutPred)

Substitution	Score	Effect	Substitution	Score	Effect
R77S	0.808	High	A100V	0.812	High
R77H	0.675	Moderate	C107R	0.926	High
S78Y	0.824	High	G112R	0.806	High
P81S	0.759	High	I123T	0.611	Moderate
D89H	0.726	Moderate	V129A	0.683	Moderate
R92G	0.864	High	R131W	0.542	Low
R92W	0.786	High	R132S	0.554	Low
R92Q	0.692	Moderate	C152R	0.941	High
T153A	0.707	Moderate	C152Y	0.917	High
T153I	0.745	High	C152F	0.920	High
V155G	0.802	High	P157L	0.787	High

Thresholds: >0.75 = high confidence deleterious; 0.50–0.75 = moderate impact.

Conservation and structural modeling

ConSurf analysis indicated that many deleterious nsSNPs mapped to conserved regions. Several were both conserved and surface-exposed, including R77, S78, P81, D89, R92, G112, R132, and P157. Other substitutions (A100, C107, I123, V129, C152, T153) were predicted to be buried yet highly conserved, suggesting destabilization of the protein core. I-TASSER modeling followed by TM-align revealed moderate structural deviations between mutant and wild-type proteins. TM-scores ranged from 0.80 to 0.88, while RMSD values varied from 1.8 to 3.2 Å.

The largest deviations were observed for C107R and substitutions at C152 (R, Y, F), with RMSD above 3.0 Å, consistent with disruption of disulfide bonds. Mutations R77C, P81S, and A100T also produced RMSD shifts above 2.5 Å. In contrast, T153A and T153I showed minimal structural deviation (RMSD <2.0 Å), suggesting limited global impact (Table 4).

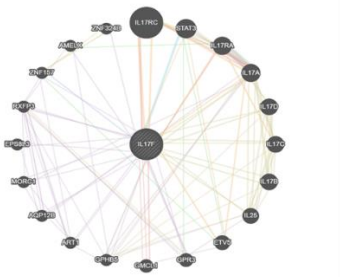

Figure 2 Conservation profile and interaction networks of IL-17F. Left panel:

ConSurf analysis showing residue conservation across IL-17F, with color-coded scores indicating variable to highly conserved positions and annotation of exposed, buried, functional, and structural residues. Middle panel: gene–gene interaction network generated by GeneMANIA, illustrating co-expression, co-localization, and shared domains of IL-17F with related genes. Right panel: protein–protein interaction network from STRING, highlighting IL-17F connectivity with other IL-17 family members and immune-related signaling partners.

Table 4. Structural alignment scores of IL-17F deleterious nsSNPs (TM-align)

Substitution	TM-score	RMSD (Å)	Substitution	TM-score	RMSD (Å)
R77S	0.868	2.19	**I123T**	0.860	2.25
R77C	0.832	2.91	**V129A**	0.868	2.41
S78Y	0.837	2.41	**R131W**	0.858	2.39
P81S	0.805	2.78	**R132S**	0.842	2.11
D89H	0.835	2.54	**C152R**	0.814	3.03
R92G	0.863	2.45	**C152Y**	0.800	2.85
R92W	0.851	2.48	**C152F**	0.838	2.18
R92Q	0.828	2.57	**T153A**	0.875	1.85
A100T	0.822	2.65	**T153I**	0.882	1.83
A100V	0.878	2.37	**V155G**	0.851	2.44
C107R	0.813	3.16	**P157L**	0.844	2.64
G112R	0.855	2.35	–	–	–

Interaction networks and post-translational modifications GeneMANIA analysis indicated that IL-17F interacts directly with IL17RA, IL17RC, and GMCL1, while co-expressing with genes including MORC1, GPHB5, EPS8L3, ART1, ZNF157, ZNF324B, GPR3, AMELX, RXFP3, and AQP12B. It also co-localizes with ZNF157 and shares pathway-level interactions with IL17A and STAT3. STRING analysis confirmed a dense protein interaction network with 11 nodes and 50 edges, average degree of 9.1, clustering coefficient of 0.923, and enrichment p-value of 1.11×10^{-16}.

PTM predictions identified no methylation sites. Phosphorylation was widespread, with GPS 3.0 identifying 34 residues and NetPhos 3.1 confirming 14 high-confidence sites. Overlapping predictions highlighted key serine and threonine residues (e.g., Ser26, Ser69, Ser71, Ser78, Ser80, Ser95, Ser138, Thr2, Thr39, Thr79, Thr87, Thr149, Thr156) as candidate regulatory sites (Table 5). Ubiquitination analysis identified lysines at positions 4, 13, 32, 35, and 113 as potential modification sites, with scores above the prediction threshold (Table 6).

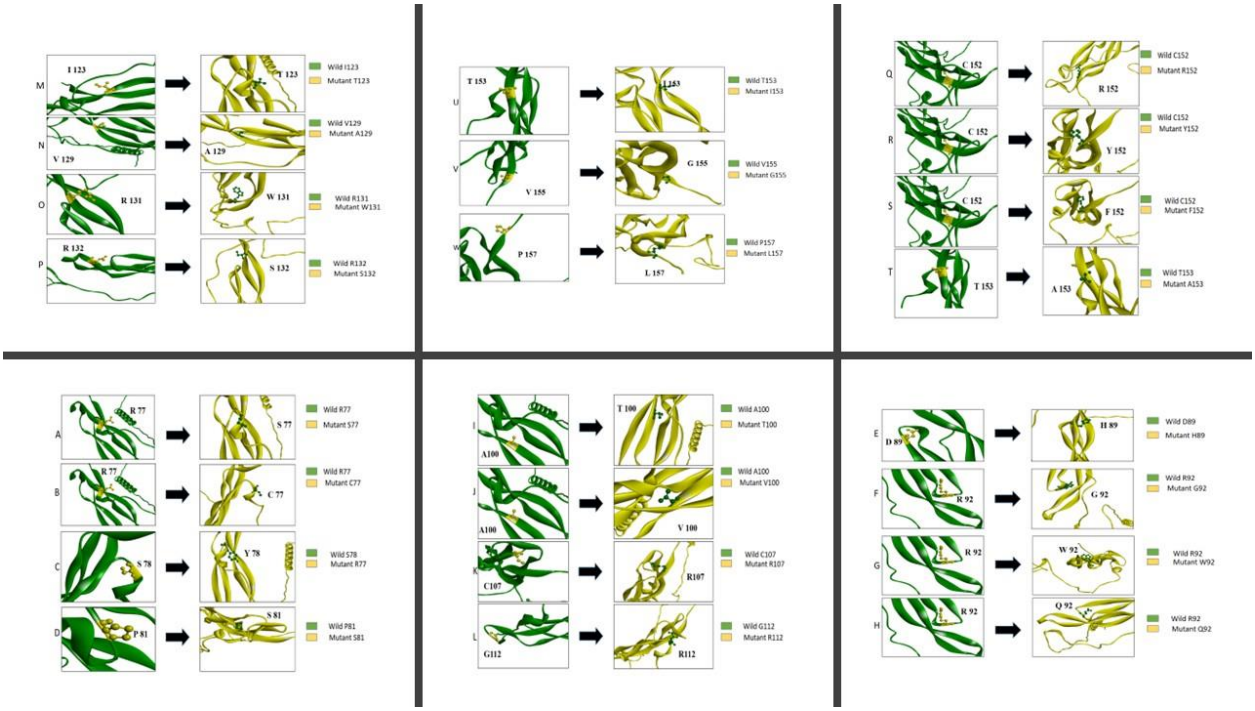

Figure 3 Structural comparison of wild-type and mutant IL-17F proteins.

Ribbon models generated by I-TASSER and visualized in Chimera illustrate conformational changes introduced by the 23 prioritized nonsynonymous substitutions. Each panel shows the wild-type residue (green) alongside its mutant form (yellow), highlighting alterations in side-chain orientation and local structural context. Variants at conserved cysteine (C107, C152) and arginine (R77, R92, R132) positions demonstrate pronounced distortions, while other substitutions such as A100V, I123T, and V155G produce notable shifts in backbone geometry. These comparisons emphasize the structural destabilization predicted for deleterious IL-17F variants.

Table 5. Consensus phosphorylation sites in IL-17F predicted by GPS 3.0 and NetPhos 3.1

Residue	Position	Score (NetPhos 3.1)	Kinases (NetPhos 3.1)	Score (GPS 3.1)	Kinase (GPS 3.1)
Ser	26	0.503	CKII	0.5017	AGC
Ser	54	0.613	unsp	0.1756	CAMK
Ser	69	0.995	unsp	0.2471	CAMK
Ser	71	0.525	cdc2	0.3139	CAMK
Ser	78	0.502	cdc2	0.2791	CK1
Ser	80	0.993	unsp	0.2719	CK1
Ser	95	0.975	unsp	0.4096	CK1
Ser	138	0.720	PKC	0.3586	AGC
Thr	2	0.693	PKC	0.4219	CK1
Thr	39	0.778	PKC	0.3721	CK1
Thr	79	0.615	unsp	0.3124	CK1
Thr	87	0.638	PKC	0.2578	CK1
Thr	149	0.743	PKC	0.4352	CK1
Thr	156	0.542	p38MAPK	0.2644	CK1

Table 6. Predicted ubiquitination sites in IL-17F (BDM-PUB)

Position	Peptide motif	Score	Threshold
4	****MTVKTLHGPAM	1.92	0.3
13	LHGPAMVKYLLLSIL	1.36	0.3
32	LSEAAARKIPKVGHT	2.09	0.3
35	AAARKIPKVGHTFFQ	0.58	0.3
113	GCINAQGKEDISMNS	0.55	0.3

DISCUSSION

Obesity arises from the interplay of lifestyle, environmental, and genetic factors, and increasing evidence highlights a major role for inherited susceptibility in determining individual risk. Estimates from twin and family studies suggest that 40–70% of variability in obesity-related traits can be attributed to heritable components (1,2). Genome-wide studies have identified numerous loci linked with adiposity, many of which are embedded in inflammatory and metabolic pathways (3,4). Among these, cytokine genes are of particular interest because obesity is characterized by low-grade chronic inflammation.

The present study focused on IL-17F, a pro-inflammatory cytokine implicated in several immune-mediated disorders including inflammatory bowel disease, ulcerative colitis, osteoarthritis, and gastric cancer (5–7). Variants such as rs2397084 (E126G) and His161Arg have previously been studied in specific disease contexts, but a comprehensive bioinformatics analysis of nonsynonymous substitutions across the IL-17F gene has not been reported. By combining multiple predictive algorithms, we identified 23 candidate nsSNPs with high likelihood of functional disruption. This integrated approach provides greater reliability than relying on a single tool, as the algorithms differ in their sensitivity and specificity (8–10).

Our findings highlight several recurrent themes. First, cysteine substitutions at positions 107 and 152 consistently produced destabilizing effects and high functional impact scores. These residues are central to disulfide bond formation, and their alteration is predicted to compromise protein folding and stability, a phenomenon described in other cytokine family members (11). Arginine substitutions at positions 77, 92, and 132 also emerged as deleterious, underscoring the structural importance of charged residues in maintaining protein–protein interfaces. Second, ConSurf analysis showed that the majority of these variants occur at conserved sites, reinforcing the likelihood of functional impairment. Third, structural modeling suggested that several mutations (e.g., C107R, C152R/Y/F) produce RMSD deviations above 3 Å, supporting major conformational shifts.

The functional impact of these variants extends beyond structural changes. MutPred suggested disruption of post-translational modifications such as phosphorylation, ubiquitination, and altered disordered regions, which could impair downstream signaling. Our PTM analysis revealed phosphorylation-prone serine and threonine residues at positions 26, 69, 71, 78, 80, and 95, as well as multiple lysines susceptible to ubiquitination. Variants affecting these regions may therefore interfere with signal transduction and protein turnover, processes that are essential for cytokine regulation in inflammatory networks (12,13). In addition, network analysis demonstrated that IL-17F interacts closely with IL17RA, IL17RC, and STAT3, positioning it within critical immune pathways. Perturbations at the genetic level may therefore have system-wide effects.

These results add to growing evidence that genetic variants in inflammatory cytokines contribute to metabolic and immune dysregulation. However, it is important to recognize the limitations of this study. All predictions are computational and based on models that estimate rather than directly measure biological impact. Functional validation using in vitro and in vivo models is required to confirm the consequences of these variants. Furthermore, the frequency of these SNPs in different populations was not assessed, limiting conclusions about their epidemiological relevance. Finally, obesity is polygenic and multifactorial; IL-17F variants are likely to interact with many other loci and environmental factors.

Despite these limitations, our work provides a prioritized list of IL-17F variants that warrant experimental investigation. These candidates may serve as useful markers for population-based genetic association studies and, in the longer term, inform the development of personalized therapeutic strategies targeting obesity-related inflammation.

CONCLUSION

This comprehensive bioinformatics study identified 23 high-risk nonsynonymous variants in IL-17F that are predicted to impair protein stability, disrupt conserved domains, and alter post-translational modification sites. Variants at cysteine and arginine residues were particularly disruptive, with structural modeling showing significant deviations from the wild type. Functional predictions further indicated that these mutations may affect phosphorylation and ubiquitination, thereby influencing IL-17F's role in immune signaling. Collectively, these findings highlight candidate SNPs for further laboratory and population-based research. Future experimental validation is necessary to confirm their role in disease susceptibility and to explore their potential as biomarkers in obesity and related inflammatory disorders.

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