

# ***Diseases to Watch***

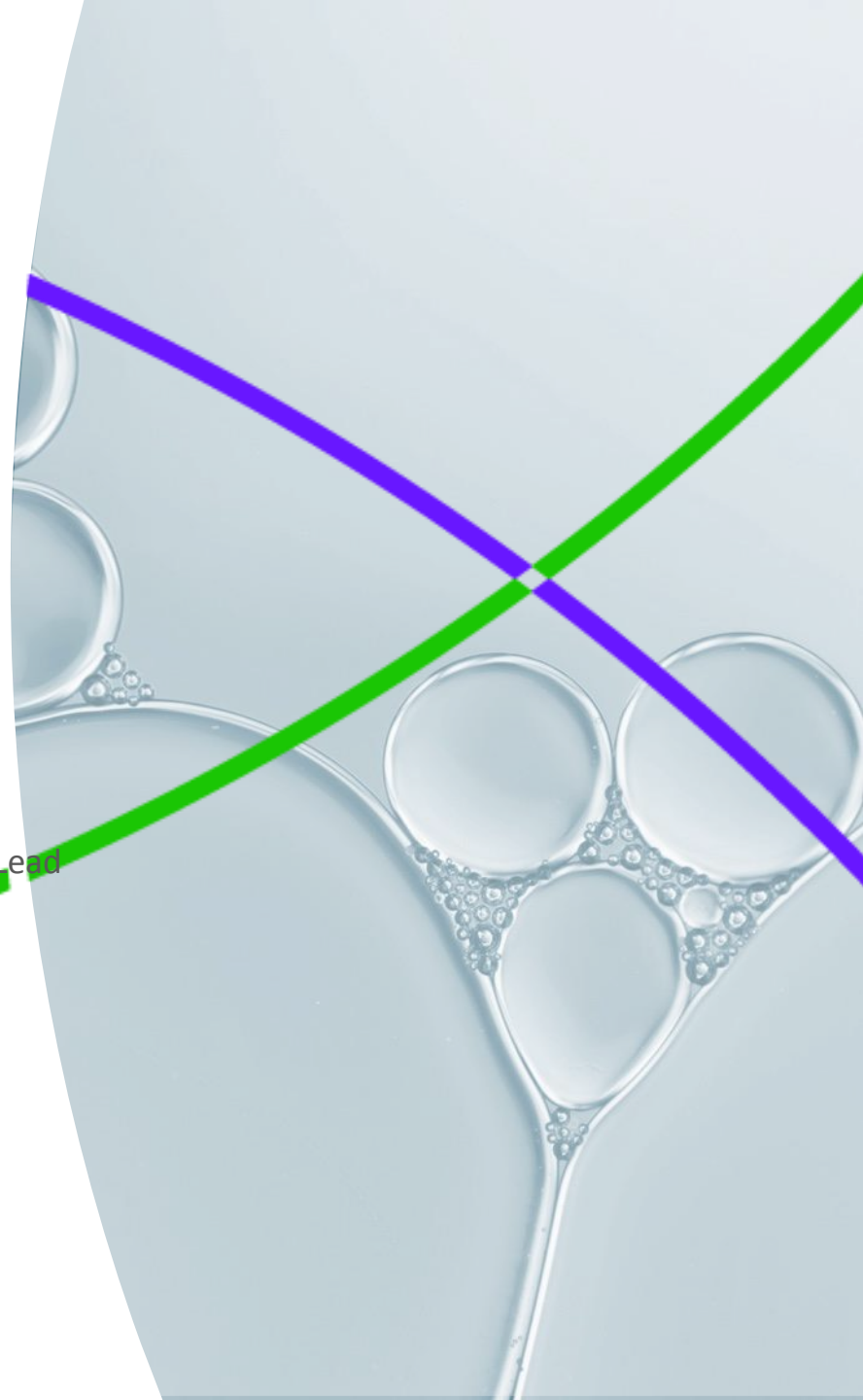
## **Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-alcoholic steatohepatitis (NASH)**

- Prevalence and Symptoms
- Risk Factors and Potential treatments
- Target identification for NASH

Robert Poolman  
Director of Preclinical Products

Carolyn Finch  
Solution Scientist Team Lead

August 2018



## Featured Speakers

### **Dr. Robert Poolman**

Director of Preclinical Products

Clarivate Analytics



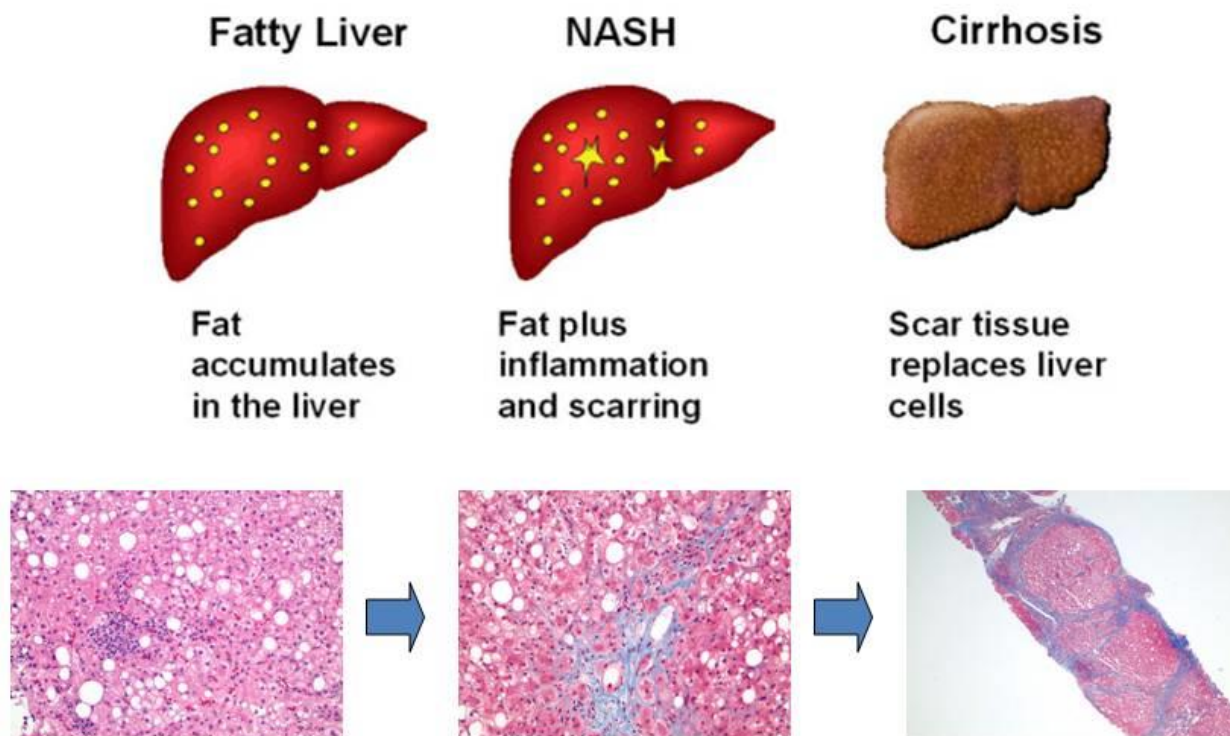
### **Carolyn Finch**

Solution Scientist Team Lead

Clarivate Analytics

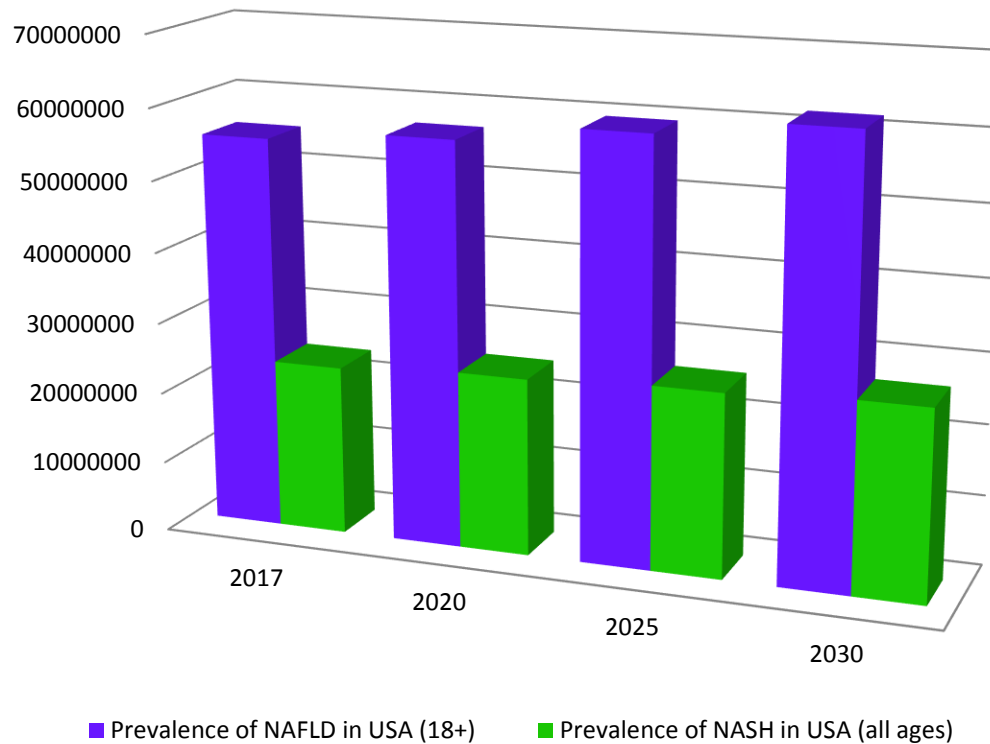


# What is Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH)?



- Fat (triglyceride) accumulation in the liver in >5% of hepatocytes, in the absence of excessive alcohol consumption
- Inflammation, oxidative damage, scar tissue and eventually fibrosis
- Progressive disease
  - Can lead to cirrhosis, fibrosis and liver cancer
- Reversible until Cirrhosis

## What is the prevalence of NAFLD and NASH?

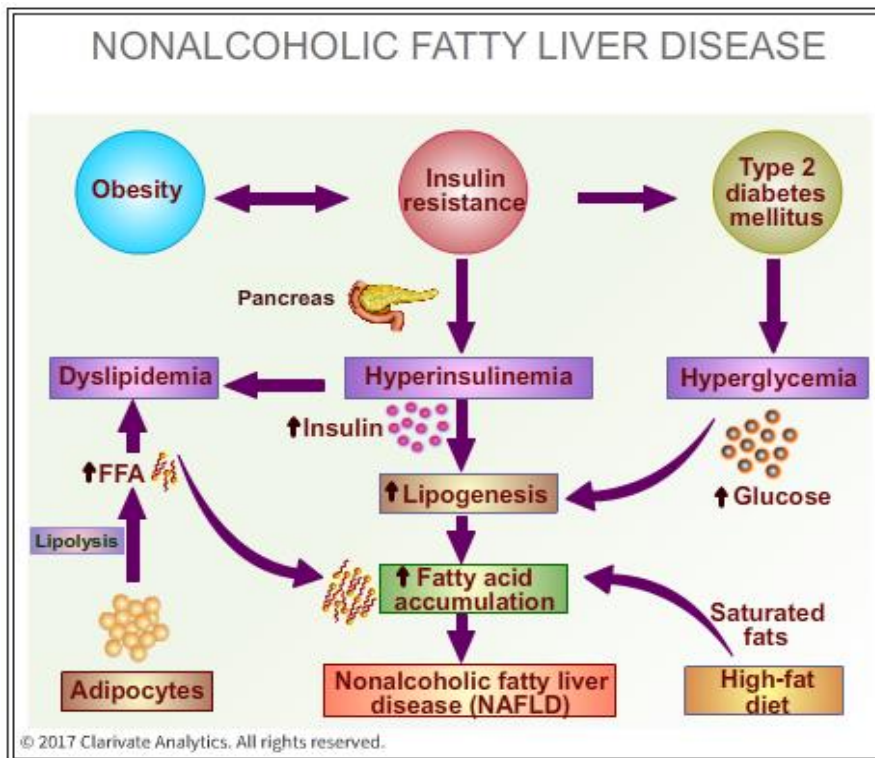


- Until recently considered to be relatively rare and harmless
- Growing global obesity epidemic
- NAFLD is the most prevalent chronic liver disease
- Projected to be the leading indication for liver transplant within the decade
- 2017 Prevalence
  - NAFLD – 24% North America, 25% Europe, 27% Asia, 30% South America
  - NASH – 7.5% USA, 5% UK, 5% Japan, 4% Worldwide

## What are the symptoms and risk factors for NAFLD and NASH?

### Symptoms:

- Usually asymptomatic
- Abdominal discomfort
- Tiredness
- NASH:
  - jaundice
  - abdominal swelling
  - bleeding
  - fluid retention



### Diagnosis:

- Liver function tests
- Liver enzyme tests
- Ultrasound or MRI
- Biopsy

### Risk Factors:

- Obesity and old age
- Predisposing conditions - diabetes, hypertension and hyperlipidemia
- Ethnicity – e.g. Asian and Hispanic populations
- Lifestyle – high fat diets, smoking and inactivity
- Genetic factors – genetic polymorphisms
- Alterations in gut microbiome composition

## What are the potential treatments for NAFLD and NASH?

- First line: Intense lifestyle modifications



- Second line: Medical and surgical treatments BUT No approved drug for NASH
- Drugs being investigated for NAFLD and NASH

Drug Category	Representative	Mode of action
Anti-diabetics	Metformin, Pioglitazone	Improve insulin sensitivity
GLP1 analogues	Exenatide, Liraglutide	Suppress appetite, increase weight loss and increase insulin production
DPP4 inhibitors	Sitagliptin, Linagliptin	Enhances insulin production
Anti-oxidants	Vitamin E	Reduce oxidative stress
Statins	Atorvastatin	Lowers plasma lipids
Lipase inhibitors	Orlistat	Decrease fat absorption from intestine
Farnesoid XR agonist	Obeticholic acid	Reduce steatosis and inflammation
PPAR- $\alpha/\gamma$ agonist	Elafibranor	Reduce steatosis, inflammation and fibrosis

# How to discover novel druggable targets for NASH and NAFLD?

## Problem:

- Complex genetic factors and Multi-factorial disease
- Lack of validated clinical trial endpoints
- Scattered information
- Difficulty in prioritizing druggable targets

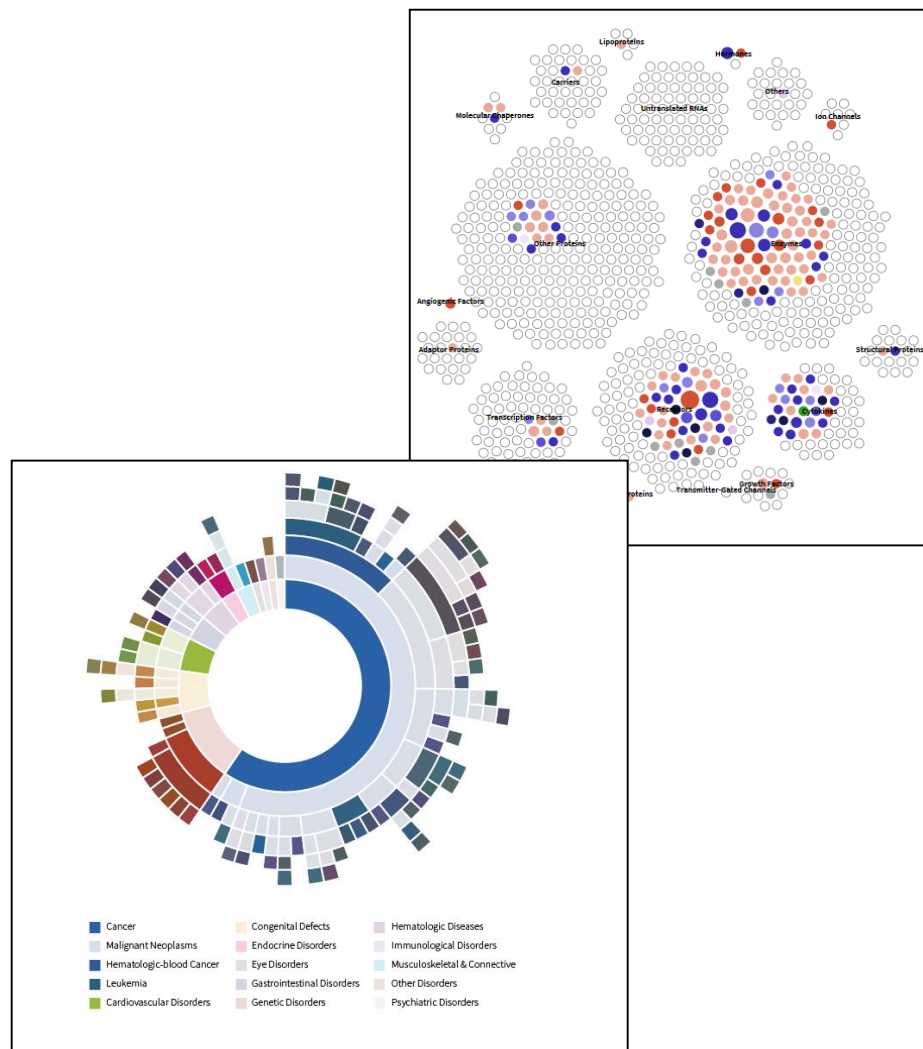
## Solution:

- Database of curated scientific data which rank targets based on evidence to support target/disease association
  - Identify novel targets in causative areas (metabolic, inflammation, fibrosis)
  - Consider a combination approach

## Target Druggability

- Allows users to effectively visualize and analyze target/disease information
- Enhanced target information – Integrity and Metacore
- Simple, easy to use interface
- Customized Exploration views – group by target family, highest phase or genetic evidence
- Protein Atlas tissue expression information
- Animal models, References, Patents and Biomarker information

- **LIVE Demo** - Drug Research Advisor (DRA)



## Novel targets for NASH

A search of [Drug Research Advisor](#) for NASH retrieves 209 Targets (109 enzymes + receptors).

**Clarivate Analytics**

Drug Research Advisor Target Druggability Search Saved work

209 targets for Non-alcoholic steatohepatitis Export | Save search

Filters **1** Table Exploration

View targets by Reset

Group by  
Target families

Color by  
Drug highest phase

Size by  
Drug count

Legend ^

Color by

- Phase III
- Phase II / III
- Phase II
- Phase I / II
- Phase I
- Discontinued
- Preclinical
- Biological testing
- Not determined
- No related drugs

Size by

Least 


 Most

**Receptors (37)**

Back Select targets 109 Deselect

- ✓ Bile acid receptor NR1H4  
Drugs: 65
- ✓ Peroxisome proliferator-activated receptor alpha PPARA  
Drugs: 14
- ✓ Peroxisome proliferator-activated receptor delta PPARD  
Drugs: 14
- ✓ Peroxisome proliferator-activated receptor gamma PPARG  
Drugs: 12
- ✓ Glucagon-like peptide 1 receptor GLP1R  
Drugs: 5
- ✓ Thyroid hormone receptor beta THRBB  
Drugs: 4
- ✓ Adiponectin receptor protein 2 ADIPOR2  
Drugs: 3
- ✓ Cannabinoid receptor 1 CNR1  
Drugs: 3
- ✓ Peroxisome Proliferator-Activated Receptors (PPAR) (nonspecified subtype)  
Drugs: 3
- ✓ C-C chemokine receptor type 2

## Narrowing the search for a novel target for NASH

If these 109 enzymes + receptors are prioritized by “Complete novelty,” **Patatin-like phospholipase domain-containing protein 3 (PNPLA3)** is ranked 3rd.

Clarivate Analytics

Drug Research Advisor Target Druggability Search Saved work

109 targets for Non-alcoholic steatohepatitis

Export | Save search

Filters 1

Target prioritization Complete novelty Condition novelty Early development No prioritization

Rank	Target		Number of related records				
	Target main name	Gene symbol	Drugs	Experimental pharmacology	Animal models	Biomarker uses	Genetic evidence
	<input checked="" type="checkbox"/> Select targets <input type="checkbox"/> Deselect		filtered (total)	filtered (total)	filtered (total)	filtered (total)	filtered (total)
1	<input checked="" type="checkbox"/> Methylenetetrahydrofolate reductase	[SYN] MTHFR		2	0 (6)	0 (268)	2 (1169)
2	<input checked="" type="checkbox"/> Superoxide dismutase [Mn], mitochondrial	[SYN] SOD2		43	0 (28)	4 (806)	1 (172)
3	<input checked="" type="checkbox"/> Patatin-like phospholipase domain-containing protein 3	[SYN] PNPLA3		1	0 (3)	5 (113)	27 (231)
4	<input checked="" type="checkbox"/> Cytochrome b-245 light chain	[SYN] CYBA		13	0 (6)	2 (185)	1 (97)
5	<input checked="" type="checkbox"/> NADH-ubiquinone oxidoreductase chain 6	[SYN] ND6		1	0 (2)	2 (85)	1 (76)
6	<input checked="" type="checkbox"/> 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2	[SYN] PLCG2		14	0 (1)	0 (239)	1 (59)
7	<input checked="" type="checkbox"/> Choline-phosphate cytidyltransferase A	[SYN] PCYT1A				0 (65)	1 (19)
8	<input checked="" type="checkbox"/> Elongation of very long chain fatty acids protein 5	[SYN] ELOVL5		9		0 (116)	1 (11)
9	<input checked="" type="checkbox"/> Long-chain-fatty-acid--CoA ligase 4	[SYN] ACSL4		8		1 (103)	2 (11)
10	<input checked="" type="checkbox"/> Phosphatidylethanolamine N-methyltransferase	[SYN] PEMT			3 (8)	0 (18)	1 (11)
11	<input checked="" type="checkbox"/> Calcium-dependent phospholipase A2	[SYN] PLA2G5		32	0 (3)	0 (45)	1 (7)
12	<input checked="" type="checkbox"/> FAD synthase	[SYN] FLAD1				0 (42)	1 (9)
13	<input checked="" type="checkbox"/> Group IIE secretory phospholipase A2	[SYN] PLA2G2E				0 (18)	1 (6)
	<input checked="" type="checkbox"/> 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-1	[SYN] PLCG1	0 (4)	61	0 (1)	0 (226)	1 (51)
	<input checked="" type="checkbox"/> Acetyl-CoA carboxylase 1	[SYN] ACACA	2 (138)	192	0 (11)	8 (225)	0 (23)
	<input checked="" type="checkbox"/> Acetyl-CoA carboxylase 2	[SYN] ACACB	1 (359)	391	0 (7)	1 (111)	0 (30)
	<input checked="" type="checkbox"/> Acetyl-CoA Carboxylases (ACC) (nonspecified subtype)	[SYN] -	2 (184)	117	0 (11)		

## Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

**Patatin-like phospholipase domain-containing protein 3**, also known as adiponutrin, is a membrane protein with triacylglycerol lipase activity that mediates triacylglycerol hydrolysis in adipocytes. It may be involved in the balance of energy usage/storage in adipocytes.

Drug Research Advisor Target Druggability Search Saved work


Patatin-like phospholipase domain-containing protein 3  
PNPLA3 [SYN]

Overview Drugs Experimental pharmacology Biomarker uses

Condition evidence ⓘ

Sunburst Table

Cancer  
 Cardiovascular Disorders  
 Diagnostics  
 Endocrine Disorders  
 Gastrointestinal Disorders  
 Metabolic Disorders  
 Neurological Disorders  
 Other Diseases  
 Other disorders (systemic [...])  
 Substance abuse end [...]



Main family  
Enzymes

Main family group  
Enzymes

Protein/RNA description  
Multifunctional enzyme which has both triacylglycerol lipase and acylglycerol O-acyltransferase activities.

Gene description  
The protein encoded by this gene is a triacylglycerol lipase that mediates triacylglycerol hydrolysis in adipocytes. The encoded protein, which appears to be membrane bound, may be involved in the balance of energy usage/storage in adipocytes. [provided by RefSeq, Jul 2008]

Molecular function

Biological process

Subcellular location

Protein  
Chromosomal location: 22q13.31  
Molecular weight: 52865  
Organism: Homo sapiens

Lists

- Drugs
- Pathway maps
- Animal models
- Genetic evidence citations
- Patents
- References

Tissue Expression  
Human Protein Atlas

Integrity

Targets and Genomics

External links

- EMBL
- Ensembl Gene
- Ensembl Protein
- Ensembl Transcript
- Entrez Gene
- GenBank
- HUGO
- KEGG
- OMIM
- UniProtKB

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## Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

Tissue expression of Patatin-like phospholipase domain-containing protein 3 can be viewed from the Link for The Human Protein Atlas.

Patatin-like phospholipase domain-containing protein 3  
PNPLA3 [SYN]

Overview Drugs Experimental pharmacology Biomarker uses

Condition evidence ⓘ

Sunburst Table

Legend:

- Cancer
- Cardiovascular Disorders
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Tissue Expression  
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Targets and Genomics

External links

EMBL  
Ensembl Gene  
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# Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

THE HUMAN PROTEIN ATLAS

MENU HELP NEWS

PNPLA3

TISSUE CELL PATHOLOGY

**TISSUE ATLAS**

PRIMARY DATA

GENE/PROTEIN

Antibody validation

Dictionary

Tissue proteome

**GENERAL INFORMATION**

Gene name<sup>1</sup> PNPLA3

Gene description<sup>1</sup> Patatin like phospholipase domain containing 3

Protein class<sup>1</sup> Disease related genes  
Enzymes  
Plasma proteins  
Potential drug targets  
Predicted intracellular proteins

Predicted localization<sup>1</sup> Intracellular

Number of transcripts<sup>1</sup> 2

[SHOW MORE](#)

**HUMAN PROTEIN ATLAS INFORMATION**

RNA tissue category<sup>1</sup> HPA: Tissue enhanced (liver)  
GTEx: Tissue enhanced (liver, skin)  
FANTOM5: Group enriched (liver, retina)

Protein evidence<sup>1</sup> Evidence at protein level

Protein expression<sup>1</sup> Expression in kidney and liver.

**IMMUNOHISTOCHEMISTRY DATA RELIABILITY**

Data reliability description<sup>1</sup> Antibody staining mainly consistent with RNA expression data. Pending external verification.

Reliability score<sup>1</sup> Approved

Antibodies<sup>1</sup> HPA058058

[SHOW MORE](#)

**RNA AND PROTEIN EXPRESSION SUMMARY<sup>1</sup>**

RNA expression (TPM)<sup>1</sup> Protein expression (score)<sup>1</sup>

Brain

Endocrine tissues

Bone marrow & immune system

Muscle tissues

Lung

Liver & gallbladder

Pancreas

Gastrointestinal tract

Kidney & urinary bladder

Male tissues

Female tissues

Adipose & soft tissue

Skin

Cerebral cortex

Lymph node

Liver

Colon

Kidney

Testis

## Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

### Genetic Evidence

Genetic evidence for Patatin-like phospholipase domain-containing protein 3 as a target in NASH can be viewed from the 55 literature, conference and patent citations which have identified specific genetic polymorphisms in Genetic evidence for Patatin-like phospholipase domain-containing protein 3 that are associated with a greater risk of NASH.

Condition evidence 

Sunburst

Table

Condition (Showing 6 of total 33)



Number of related records

Condition	Drugs	Animal models	Genetic evidence	Biomarker uses
liver				
Cancer, <b>liver</b> (hepatocellular carcinoma)			25	6
Fatty <b>liver</b> disease, alcoholic			3	1
Injury, <b>liver</b>			2	
<b>Liver</b> Cirrhosis			2	
<b>Liver</b> diseases			5	1
Non-alcoholic fatty <b>liver</b> disease (NAFLD)			46	13

## Genetic evidence for Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH

### References

Examination of references suggests that Genetic evidence for Patatin-like phospholipase domain-containing protein 3 could be a valid target for the treatment of NASH.

#### Genetic evidence citations

Filtered by **Non-alcoholic fatty liver disease (NAFLD)**

46 genetic evidence records related to the following 55 references

##### CONFERENCE

#### PNPLA3 but not TM6SF2 polymorphisms were associated with higher degrees of steatosis and liver fibrosis among Brazilian NAFLD patients

Author: Mazo, D.F. | Malta, F. | Stefano, J.T. | et al.

Publication: Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) - 2017-10-20 / 2017-10-20 - Washington, D.C., United States

**Non-alcoholic fatty liver disease (NAFLD)** **Relevant**

##### CONFERENCE

#### The association of nonalcoholic fatty liver disease with genetic polymorphisms: A multicenter study

Author: Uygun, A. | Ozturk, K. | Demirci, H. | et al.

Publication: Annual Meeting of the European Association for the Study of the Liver (EASL) - 2017-04-19 / 2017-04-19 - Amsterdam, Netherlands

**Non-alcoholic fatty liver disease (NAFLD)** **Relevant**

##### ARTICLE

#### APOC3 rs2070666 is associated with the hepatic steatosis independently of PNPLA3 rs738409 in chinese han patients with nonalcoholic fatty liver diseases

Author: Zhang, R.N. | Zheng, R.D. | Mi, Y.Q. | Zhou, D. | Shen, F. | Chen, G.X. | Zhu, C.Y. | Pan, Q. | Fan, J.G.

Publication: Digestive Diseases and Sciences | PUBLISHED:2016 | VOL:61 | ISSUE:8 | PAGE:2284

PubMed ID: 27059980 [↗](#)

DOI: 10.1007/s10620-016-4120-7

**Non-alcoholic fatty liver disease (NAFLD)** **Relevant**

##### CONFERENCE

#### Adiponutrin (rs738409) gene polymorphisms increase the risk and progression of nonalcoholic steatohepatitis (NASH) in Asian Indians

Author: Vernekar, M. | Chandak, S. | Shah, N. | Parekh, S. | Amerapurkar, D.N.

Publication: Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) - 2016-11-11 / 2016-11-11 - Boston, United States

**Non-alcoholic fatty liver disease (NAFLD)** **Relevant**

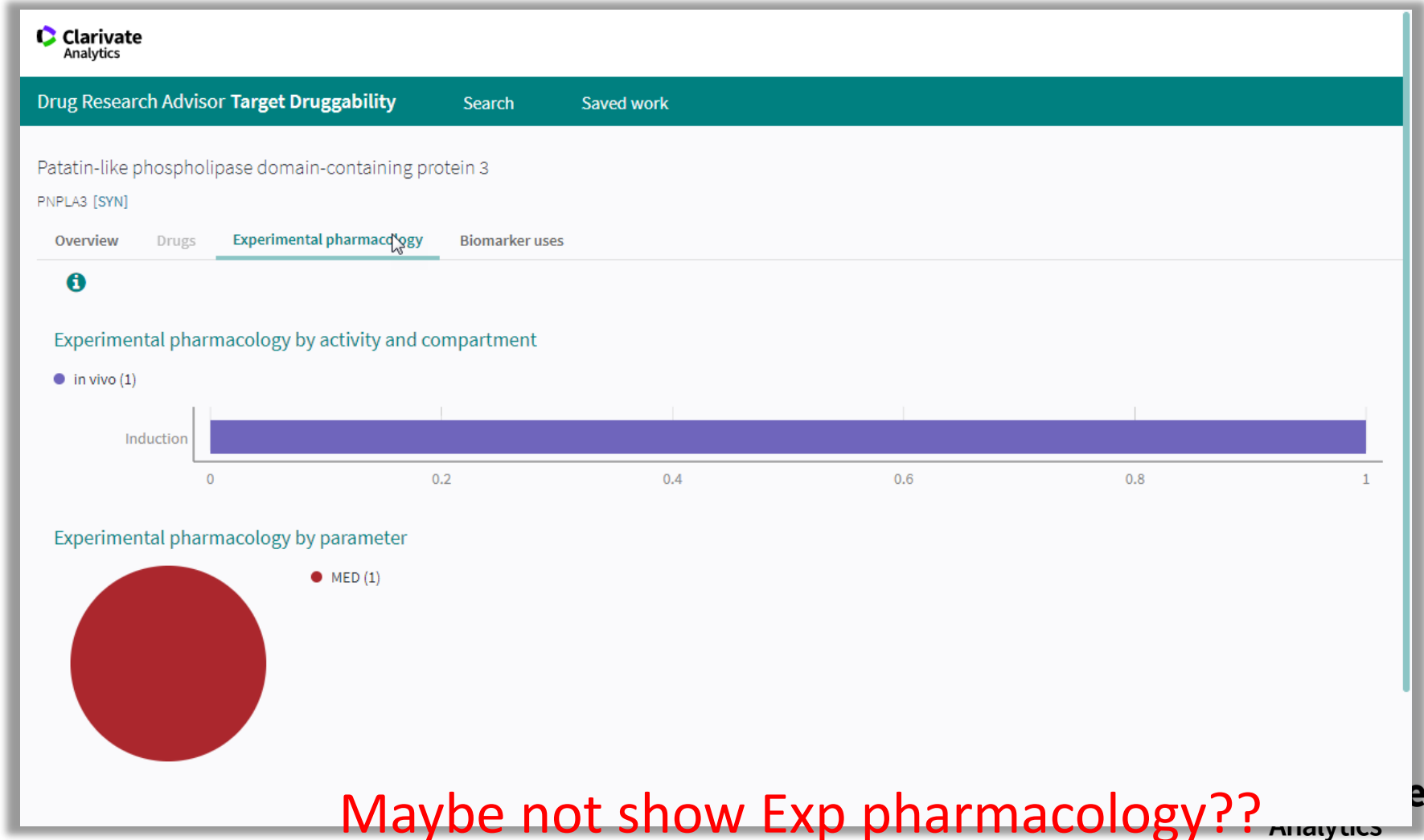
##### CONFERENCE

#### Analysis of 26K multiethnic whole-exomes to identify novel T2D risk variants

Author: Udler, M. | Mahajan, A. | Flannick, J.A.

## Patatin-like phospholipase domain-containing protein 3 as a suitable novel target for NASH Experimental Pharmacology

Examination of Experimental Pharmacology data associated with Patatin-like phospholipase domain-containing protein 3 and NASH suggests that Patatin-like phospholipase domain-containing protein 3 could be a valid target for the treatment of NASH.



## Patatin-like phospholipase domain-containing protein 3 Biomarkers

