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OPINION REVIEW

### Repurposing drugs to target nonalcoholic steatohepatitis

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### Abstract

Nonalcoholic fatty liver disease (NAFLD) is a complex disorder that has evolved in recent years as the leading global cause of chronic liver damage. The main obstacle to better disease management pertains to the lack of approved pharmacological interventions for the treatment of nonalcoholic steatohepatitis (NASH) and NASH-fibrosis-the severe histological forms. Over the past decade, tremendous advances have been made in NAFLD research, resulting in the discovery of disease mechanisms and novel therapeutic targets. Hence, a large number of pharmacological agents are currently being tested for safety and efficacy. These drugs are in the initial pharmacological phases (phase 1 and 2), which involve testing tolerability, therapeutic action, and pharmacological issues. It is thus reasonable to assume that the next generation of NASH drugs will not be available for clinical use for foreseeable future. The expected delay can be mitigated by drug repurposing or repositioning, which essentially relies on identifying and developing new uses for existing drugs. Here, we propose a drug candidate selection method based on the integration of molecular pathways of disease pathogenesis into network analysis tools that use OMICs data as well as multiples sources, including text mining from the medical literature.

Key words: Drug discovery; Drug repositioning; Fibrosis; Genetics; Treatment; Systems biology

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Core tip: As a proof-of-concept of the advantages that can be yielded by applying multi-



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omics systems-based approaches to the analysis of potential candidates to the treatment of nonalcoholic steatohepatitis (NASH) we selected the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway map of nonalcoholic fatty liver disease (NAFLD), which illustrates a stage-dependent progression of the disease. After generating a protein-chemical interaction network, we predicted remarkable examples of potential drug repurposing for the treatment of NASH based on the NAFLD-KEGG connectivity map.

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#### INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a complex disorder that has emerged as the leading global cause of chronic liver damage in recent years<sup>[1]</sup>. The disease course progresses through highly dynamic histological stages, ranging from simple steatosis or nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), NASHfibrosis and cirrhosis<sup>[1,2]</sup>. NASH-fibrosis and its complications, including cirrhosis and hepatocellular carcinoma, not only significantly reduce life expectancy by increasing liver-related mortality<sup>[3]</sup> but also represent a challenge for the healthcare system because much of the affected population is also affected by NAFLD-associated comorbidities, including obesity, type 2 diabetes (T2D), and cardiovascular disease<sup>[1,4+6]</sup>. Absence of reliable noninvasive biomarkers that allow identification of patients at a high risk of fibrosis and /or disease progression is one of the obstacles facing disease management<sup>[7,8]</sup>. Similarly, while a large number of drugs against NASH are currently being tested for efficacy and safety, no pharmacological interventions are presently approved for treating NASH<sup>[2,5,9,10]</sup>.

Information retrieved from public domain data sources and clinical ClinicalTrials.gov (updated December 2018), a resource provided by the U.S. National Library of Medicine, indicates that approximately 47 different drugs that target NASH and NASH-fibrosis are currently being tested in different pharmacological stages, including 188 drugs in phase 1 and 162 in phase 2 studies (Figure 1). A significant proportion of these drugs are small molecules or proteins that either antagonize or act as exogenous agonists of one or more targets of interest; the 47 aforementioned NASH drugs are in fact predicted to be linked to 151 molecular targets (Figure 1). Considering that a large majority of these drugs are in the earliest pharmacological phases that involve testing tolerability, therapeutic action, and pharmacological issues, it is reasonable to conclude that there will be a significant time lag before the next generation of NASH drugs is available for clinical use.

One potential solution to this expected delay is drug repurposing or repositioning, which relies on identifying and developing new uses for existing drugs<sup>[11]</sup>. The advantage of drug repurposing is not limited to the fact that drugs selected for a novel indication have already passed the time-consuming pharmacokinetics, pharmacodynamics, and toxicity profiling evaluation, but are also already approved by major regulatory agencies, including the United States Food and Drug Administration and/or the European Medicines Agency.

Drug repurposing can be addressed by different approaches. Most common ones involve the selection of drug candidate/s based on known targets involved in the pathogenesis of the disease of interest. More recently, system biology strategies based on a broad search into genomic resources, as well as large-scale gene expression libraries, have been proposed as an attractive and innovative solution, particularly for the treatment of complex diseases like NAFLD that shares disease mechanisms with diseases of the metabolic syndrome<sup>[12-14]</sup>. Hence, we propose a drug candidate selection method based on the integration of molecular pathways of disease pathogenesis into network analysis tools that use OMICs data as well as multiples sources, including text mining from pertinent medical literature.

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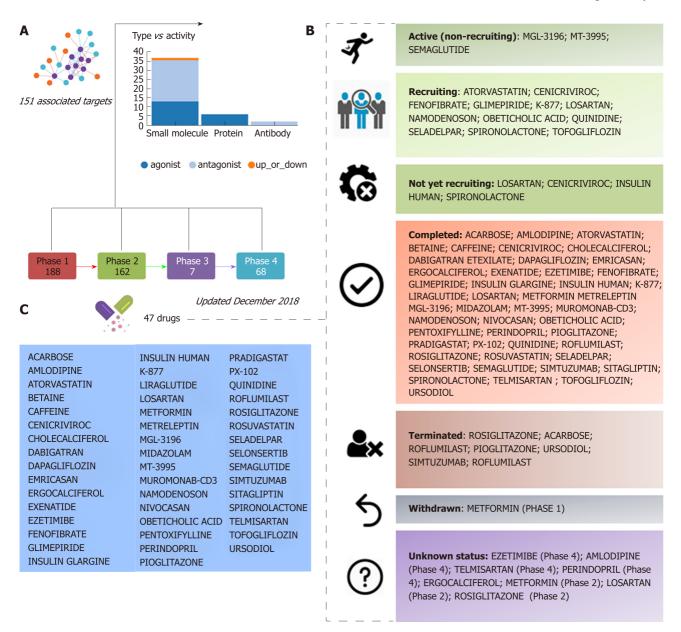


Figure 1 Clinical trials for the treatment of nonalcoholic steatohepatitis. A and B: Figure highlights 47 drugs that are currently under investigation for the treatment of nonalcoholic steatohepatitis in different pharmacological phases (from phase 1 to phase 4): Information on clinical trial status (recruitment status) as well as prediction of potential associated targets were retrieved from the Target Validation Platform available at https://www.targetvalidation.org; C: Drugs listed in the most advanced pharmacological phase updated December 2018 concerning to privately and publicly funded clinical studies. Not yet recruiting: The study has not started recruiting participants; Recruiting: The study is currently recruiting participants; Active, not recruiting: The study is ongoing, and participants are receiving an intervention or being examined, but potential participants are not currently being recruited or enrolled; Terminated: The study has stopped early and will not start again; participants are no longer being examined or treated; Completed: The study has ended normally, and participants are no longer being examined or treated (that is, the last participant's last visit has occurred); Withdrawn: The study stopped early, before enrolling its first participant; Unknown: A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been last verified within the past 2 years).

### DRUG REPURPOSING FOR THE TREATMENT OF NASH BASED ON THE NAFLD-KEGG CONNECTIVITY MAP

As a proof-of-concept of the advantages of using multi-omics systems-based approaches for the analysis of potential NASH treatment candidates, we selected the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway map of NAFLD (pathway ID: hsa04932), which illustrates a stage-dependent progression of the disease (Figure 2). This pathway is composed of 149 genes/proteins involved not only in the progression of NAFL to NASH and to cirrhosis, but also genes/proteins shared with obesity and T2D (Table 1). Significant disease-related pathogenic processes, including *de novo* fatty acid biosynthesis, lipid peroxidation, endoplasmic reticulum stress and mitochondrial dysfunction<sup>[15-17]</sup>, as well as apoptosis and cell death related mechanisms are represented in the NAFLD-KEGG pathway (Figure 2). Thus, we

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generated a protein-chemical interaction network by mapping the significant genes/proteins that are represented in the pathway to chemicals/drugs that are annotated in the Comparative Toxicogenomics Database. The 149 genes (seeds) yielded by our analysis were then mapped to the corresponding molecular interaction database; this procedure produced an extensive network comprising of approximately 2000 nodes. One of the largest subnetworks included 3212 smaller nodes (that represent the number of gene/protein-chemical interactions in this subnetwork), with 13314 interactions among node members. For simplicity, we manually curated some chemical-drug interactions focusing specifically on certain genes/proteins of potential interest, including members of the caspase family (CASP3 and CASP7), interleukins (IL1A, IL1B, and IL6), tumor necrosis factor a (TNFa), nuclear factor kappa B subunit 1 (NFKB1) and inhibitor of nuclear factor kappa B kinase subunit beta, Jun proto-oncogene (JUN), transcription factor subunit, and AKT serine/threonine kinase 1 (Figure 3). Remarkably, several drugs were predicted to have a significant interaction with the highlighted targets. For example, minocycline that is a broad spectrum long-acting derivative of the antibiotic tetracycline was mapped in the pathway of caspases, whereas IL1B (Figure 3) or pomalidomide that is a derivative of thalidomide with immuno-modulating, antiangiogenic and antineoplastic activities was mapped in the network of TNF, NFKB1, and interleukins (Figure 3).

Additional targets predicted in the minoclycline interaction network are arachidonate 5-lipoxygenase (which is involved in the synthesis of leukotrienes from arachidonic acid), cytochrome C (a central component of the electron transport chain in mitochondria), matrix metallopeptidase 9 (involved in the breakdown of extracellular matrix), vascular endothelial growth factor A (which induces proliferation and migration of vascular endothelial cells, particularly during pathological angiogenesis) and Poly(ADP-ribose) polymerase 1 (which is involved in the regulation of a myriad of cellular processes, such as differentiation, proliferation, and tumor transformation, as well as in the regulation of the molecular events implicit in the cell recovery from DNA damage). Further two candidate targets predicted in the network of pomalidomide are prostaglandin-endoperoxide synthase 2 (also known as cyclooxygenase, which is the key enzyme in prostaglandin biosynthesis) and CRBN (a calcium channel membrane protein, thought to play a role in brain development).

Additional examples of drugs that could be potentially tested for the treatment of NASH based on the concept of drug repositioning are illustrated in Figure 3. Drugs in the category of angiotensin II receptor type 1 (AGTR1) antagonists that were predicted in the network of JUN, for instance irbersartan-a nonpeptide AGTR1 antagonist with antihypertensive activity-might indeed be regarded as an indication expansion rather than drug repositioning because, as mentioned above, NAFLD and components of the Metabolic Syndrome, including arterial hypertension, present shared disease mechanisms (12-14). Therefore, given the pleiotropic effects of AGTR1 blockers<sup>[18]</sup> it is plausible to suggest that drugs in this pharmacological group-sartanswould synergize or potentiate the benefits of blocking the renin angiotensin system in the liver<sup>[19-22]</sup>. Remarkably, the pharmacological properties and toxicity profiles of some of the drugs presently undergoing NASH clinical trials are already known, such as atorvastatin, ezetimibe, fenofribrate, losartan, and pioglotazone, just to mention a few (Figure 1).

### PLEIOTROPY: CHALLENGES AND OPPORTUNITIES FOR THE TREATMENT OF NASH

It is also important to acknowledge the possibility that some of the novel pharmacotherapy options for the treatment of NASH might eventually present pleiotropic effect/s. This point represents the paradox of a drug covering multiple pathways and cell types, which could be either harmful or beneficial for patients. Remarkable examples of the advantages of pleiotropic effects of pharmacological targets for the treatment of complex traits are, as already mentioned, agents that modulate or interfere with the rennin–angiotensin system, which not only reduce cardiovascular risk but also improve systemic inflammation, oxidative stress, and even present anti-fibrogenic properties in the liver. Similar effects have also been demonstrated for statins<sup>[23,24]</sup>.

When focusing on the new generation of NASH targets, obeticholic acid (OCA), a synthetically-modified bile acid (a dihydroxy-5beta-cholanic acid), is a remarkable example of the potential systemic effects of a drug targeting nuclear receptors. OCA exhibits a potent agonist effect on the farnesoid X nuclear receptor (FXR). More

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# Table 1 Non-alcoholic fatty liver disease-Kyoto Encyclopedia of Genes and Genomes pathway (hsa04932)

#### Gene symbol; description

IL6; interleukin 6
IL6R; interleukin 6 receptor
SOCS3; suppressor of cytokine signaling 3
TNF; tumor necrosis factor
TNFRSF1A; TNF receptor superfamily member 1A
NFKB1; nuclear factor kappa B subunit 1
RELA; RELA proto-oncogene, NF-kB subunit
INS; insulin
INSR; insulin receptor
IRS1; insulin receptor substrate 1
IRS2; insulin receptor substrate 2
PIK3CA; phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PIK3CD; phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
PIK3CB; phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
PIK3R1; phosphoinositide-3-kinase regulatory subunit 1
PIK3R2; phosphoinositide-3-kinase regulatory subunit 2
PIK3R3; phosphoinositide-3-kinase regulatory subunit 3
AKT1; AKT serine/threonine kinase 1
AKT2; AKT serine/threonine kinase 2
AKT3; AKT serine/threonine kinase 3
GSK3A; glycogen synthase kinase 3 alpha
GSK3B; glycogen synthase kinase 3 beta
NR1H3; nuclear receptor subfamily 1 group H member 3
RXRA; retinoid X receptor alpha
SREBF1; sterol regulatory element binding transcription factor 1
MLX; MLX, MAX dimerization protein
MLXIP; MLX interacting protein
MLXIPL; MLX interacting protein like
PKLR; pyruvate kinase L/R
LEP; leptin
LEPR; leptin receptor
ADIPOQ; adiponectin, C1Q and collagen domain containing
ADIPOR1; adiponectin receptor 1
ADIPOR2; adiponectin receptor 2
PRKAA1; protein kinase AMP-activated catalytic subunit alpha 1
PRKAA2; protein kinase AMP-activated catalytic subunit alpha 2
PRKAB1; protein kinase AMP-activated non-catalytic subunit beta 1
PRKAB2; protein kinase AMP-activated non-catalytic subunit beta 2
PRKAG1; protein kinase AMP-activated non-catalytic subunit gamma 1
PRKAG3; protein kinase AMP-activated non-catalytic subunit gamma 3
PRKAG2; protein kinase AMP-activated non-catalytic subunit gamma 2
PPARA; peroxisome proliferator activated receptor alpha
CDC42; cell division cycle 42
RAC1; Rac family small GTPase 1
MAP3K11; mitogen-activated protein kinase kinase kinase 11
MAPK8; mitogen-activated protein kinase 8
MAPK10; mitogen-activated protein kinase 10
MAPK9; mitogen-activated protein kinase 9
ITCH; itchy E3 ubiquitin protein ligase
ERN1; endoplasmic reticulum to nucleus signaling 1
TRAF2; TNF receptor associated factor 2
MAP3K5; mitogen-activated protein kinase kinase kinase 5



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JUN; Jun proto-oncogene, AP-1 transcription factor subunit IL1A; interleukin 1 alpha IL1B; interleukin 1 beta IKBKB; inhibitor of nuclear factor kappa B kinase subunit beta XBP1; X-box binding protein 1 CEBPA; CCAAT enhancer binding protein alpha CYP2E1; cytochrome P450 family 2 subfamily E member 1 FASLG; Fas ligand CXCL8; C-X-C motif chemokine ligand 8 TGFB1; transforming growth factor beta 1 EIF2AK3; eukaryotic translation initiation factor 2 alpha kinase 3 EIF2S1; eukaryotic translation initiation factor 2 subunit alpha ATF4; activating transcription factor 4 DDIT3; DNA damage inducible transcript 3 BCL2L11; BCL2 like 11 BAX; BCL2 associated X, apoptosis regulator FAS; Fas cell surface death receptor CASP8; caspase 8 BID; BH3 interacting domain death agonist CYCS; cytochrome c, somatic CASP3; caspase 3 CASP7; caspase 7 NDUFV1-3; NADH:ubiquinone oxidoreductase core subunit V1 -V3 NDUFA1-3; NADH:ubiquinone oxidoreductase subunit A1-3 NDUFA4; NDUFA4, mitochondrial complex associated NDUFA4L2; NDUFA4, mitochondrial complex associated like 2 NDUFA5-13; NADH:ubiquinone oxidoreductase subunit A5-A13 NDUFAB1; NADH: ubiquinone oxidoreductase subunit AB1 NDUFB1-11; NADH:ubiquinone oxidoreductase subunit B1-B11 NDUFS1-S8; NADH:ubiquinone oxidoreductase core subunit S1 -S8 NDUFC1; NADH:ubiquinone oxidoreductase subunit C1 NDUFC2; NADH:ubiquinone oxidoreductase subunit C2 NDUFC2-KCTD14; NDUFC2-KCTD14 readthrough SDHA; succinate dehydrogenase complex flavoprotein subunit A SDHB; succinate dehydrogenase complex iron sulfur subunit B SDHC; succinate dehydrogenase complex subunit C SDHD; succinate dehydrogenase complex subunit D UQCRFS1; ubiquinol-cytochrome c reductase, Rieske iron-sulfur polypeptide 1 CYTB; cytochrome b CYC1; cytochrome c1 UQCRC1; ubiquinol-cytochrome c reductase core protein 1 UQCRC2; ubiquinol-cytochrome c reductase core protein 2 UQCRH; ubiquinol-cytochrome c reductase hinge protein UQCRHL; ubiquinol-cytochrome c reductase hinge protein like UQCRB; ubiquinol-cytochrome c reductase binding protein UQCRQ; ubiquinol-cytochrome c reductase complex III subunit VII UQCR10; ubiquinol-cytochrome c reductase, complex III subunit X UQCR11; ubiquinol-cytochrome c reductase, complex III subunit XI COX3; cytochrome c oxidase III COX1; cytochrome c oxidase subunit I COX2; cytochrome c oxidase subunit II COX4I2; cytochrome c oxidase subunit 4I2 COX4I1; cytochrome c oxidase subunit 4I1 COX5A; cytochrome c oxidase subunit 5A COX5B; cytochrome c oxidase subunit 5B COX6A1; cytochrome c oxidase subunit 6A1



COX6A2; cytochrome c oxidase subunit 6A2
COX6B1; cytochrome c oxidase subunit 6B1
COX6B2; cytochrome c oxidase subunit 6B2
COX6C; cytochrome c oxidase subunit 6C
COX7A1; cytochrome c oxidase subunit 7A1
COX7A2; cytochrome c oxidase subunit 7A2
COX7A2L; cytochrome c oxidase subunit 7A2 like
COX7B; cytochrome c oxidase subunit 7B
COX7B2; cytochrome c oxidase subunit 7B2
COX7C; cytochrome c oxidase subunit 7C
COX8C; cytochrome c oxidase subunit 8C
COX8A; cytochrome c oxidase subunit 8A

https://www.genome.jp/kegg-bin/show\_pathway? hsa04932.

importantly, its target-FXR (formally Nuclear hormone receptor subfamily 1 group H member 4, NR1H4, also known as BAR) is predicted to be involved in the pathogenesis of multiple phenotypes that practically cover the full range of human diseases and traits (Figure 4). It is well known that OCA is currently used to treat not only NASH but other chronic liver diseases as well, including primary biliary cholangitis<sup>[25]</sup>. However, there are at least 65 registered clinical trials in various pharmacological phases for ~50 different diseases (Figure 4).

Based on this evidence, one may presume that the pleiotropic effects, and thus the clinical consequences, of the novel NASH drugs that are predicted to concurrently modulate a broad range of molecular pathways could be surprisingly extensive and therefore largely beneficial for treating multiple phenotypes. However, potential pleiotropic effects of the novel anti-NASH drugs could produce undesirable effects that we need to understand in order to anticipate their management. Some of these potential pleiotropic effects are indeed related to the primary biological and molecular network associated with the drug target itself. To illustrate the importance of this issue, we randomly selected five molecular targets (MAP3K5 or ASK1, FXR, PPAR $\alpha/\delta$ , THR $\beta$ , and MPC1) against which five drugs are currently being tested in patients with NASH (selonsertib<sup>[26]</sup>, OCA<sup>[27]</sup>, elafibranor<sup>[28]</sup>, MGL-3196 (https://clinicaltrials.gov/ct2/show/NCT02912260), and MSDC-0602K<sup>[29]</sup> https://clinicaltrials.gov/ct2/show/NCT02784444). Next, we explored the potential pleiotropic effect/s of modulating these targets in humans by searching for associations of genetic variants in the aforementioned targets with different phenotypes and traits, known as PheWAS (Phenome-wide association studies). We specifically retrieved publically available information from the United Kindom Biobank that explored genetic variations in 452264 United Kindom Biobank White British individuals (http://geneatlas.roslin.ed.ac.uk/)<sup>[30]</sup>.

As shown in Figure 5 and Table 2, *MAP3K5/ASK1*, *FXR*, *PPARa/δ*, *THRβ*, and *MPC1* variants are involved in multiple pleiotropic effects, including modulation of blood cell count, body mass index, and general body adiposity, along with complex systemic disorders, such as asthma, acute pancreatitis, migraine, intestinal malabsortium, thyroid disease, and malignant neoplasm. Hence, understanding the pleiotropic effects of the novel NASH drugs is the key to optimizing their use as well as preventing emergent-yet poorly understood-undesirable systemic complications that could potentially jeopardize their short- or long-term use.

#### CONCLUSION

We provide new strategies and approaches by which known drugs can be repurposed for the treatment of NASH. Although we explored and mapped NAFLD-chemical interaction networks, it will be necessary to perform clinical trials not only to assess therapeutic response and optimize dosage and delivery routes, but also to explore the possibility that new uses of existing (old) drugs could act on novel or unanticipated targets. The presence of potential "off target"-pleiotropic-effects raises the mandatory necessity of pharmacological optimization, including the assessment of drug interactions and adjustment according to liver function tests.

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# Table 2 Associations between variants in locus that are targets of novel drugs for the treatment of nonalcoholic steatohepatitis and multiple traits from individuals of the United Kindom Biobank

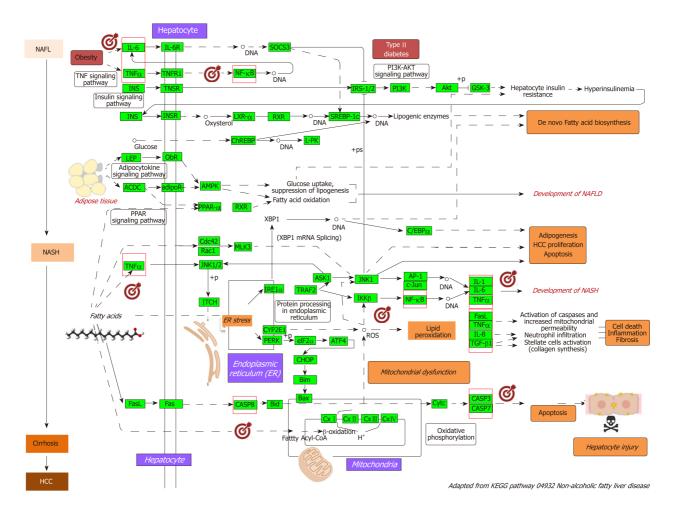
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migraineent237440100960714.43929011high chockred0.00853724.43949722high chockred0.00853724.4394722180 Dondres of vestibut functionn.9490463100923394.6092361PAR5 (Persoisone Poliferator Activated Receptor Dela)0.009233959.74553212High circumferancen.8001887338887242.087564Which koly farbres massn.8001887338887220.452544Body fait percentagen.8001887332673443.864025Body fait percentagen.80008326623121.5456677Hacker entn.998000326623117.122462Which koly fait percentagen.998000326623117.122462Backer entn.998000326623117.8226160Which koly fait percentagen.9980003326623117.122462Backer entn.9980003326623117.122462Backer entn.9980003326623117.122462Backer entn.9980003326623117.122462Backer entn.9980003326623117.122462Backer entn.9980003326623117.122462Backer entn.9980003326623117.122462Backer entn.9980003326623117.122462Backer ent and malaborytionn.968079333267317.807186Backer ent and malaborytionn.96807916.973183.2982718Backer ent and anaborytionn.96807916.973184.2929718Backer ent and anaborytionn.9649731	Impedance of arm (right)	rs1409791	100851307	5.152661824
normno	Impedance of whole body	rs1409791	100851307	4.772216099
NoNO1093047044202005B31 Decodes of veshbal functionns1404631092047010970407PA85 (Peocures Poliziant Activated Recepto Polizi10920470Whele body fair free massns30118873538872974052121B47 circumferencens30118873538872472007664Whele body fair free massns3011887353887220137941B504 fair percentagens3011887353887220137941B504 fair percentagens3011887353687220137941B504 fair percentagens309228352979721.426151B504 coll (leckocyte) courtns958500352623117.1825018Destrophill percentagens958500352623117.1825018Destrophill percentagens958500352623117.1825018Destrophill percentagens958500352623117.1825018Destrophill percentagens958500352623117.1825018Destrophill percentagens958500352673718.1897150Destrophill percentagens95850035277718.1897150Destrophill percentagens9595116.6757182.5857755B4 bod coll (leckocyte) courtns951216.6757182.5857755B4 bod coll (leghtocyte) courtns9712157685354867Destrophill percentagens97128168778792.5857755B4 bod coll (leghtocyte) courtns972517.8974814.8957105Destrophill percentagens9712815778515.399024Destrophil	migraine	rs12579460	100966714	4.639293011
HSI Disorders of vestibular functionrs104640510023394.08976447PAL8PMBe body fare massrs.504118875338487242.057154Hip circumferencers.504118875338487220.353444Moles body far massrs.504118875338487220.353444Moncybe preentagers.504118875338487220.353444Moncybe preentagers.40469623320534845.8540625Platele cirilrs.3098203332623121.555677Platele coll (ledocybe) courtrs.908500352662121.515677Platele coll (ledocybe) courtrs.908500352662117.182462Cosinophil preentagers.908500352662117.182462Sonophil preentagers.908500352662117.182462Lymphocybe preentagers.908500352662117.182462Lymphocybe preentagers.908500352662111.182462Lymphocybe preentagers.908500352662111.182462Lymphocybe preentagers.908500352662111.869743Lymphocybe preentagers.9771463352057712.869745MCI (Mitechondrial Prevate Carrier )11.86974187.3781215Platele courtrs.978162166779187.3781215Platele courtrs.97817137824814.895109Cosinophil roomrs.978267137824814.9992605Appenda Call (rythrocyb) courtrs.97287137824814.997105Mari Labele (thrombocyb) courtrs.97287137824814.997105 <td>high cholesterol</td> <td>rs7967468</td> <td>100853792</td> <td>4.543497322</td>	high cholesterol	rs7967468	100853792	4.543497322
PARS (Perokisene Poliferitor Activated Receptor Deta)Whole body factore massn500188753086872507.485212Hip circumforeven5001897333887237.0011994Body fat pacentagen5001897333887220.452346Body fat pacentagen5018987333887220.452346Patalet critn33992883525939721.6726615White body cell (ealcocyte) countn908000525623121.5156677Patalet critn59080035262317.1125462Patalet critn59080035262317.1125462Patalet critn59080035262317.1125462Patalet critn59080035260309.18412016Nattrophill pecentagen29585535206309.18412016Statisma maleborptionn57578435206309.18412016Statisma maleborptionn57578435206309.18412016Statisma maleborptionn575784166778187.3751215Patalet critinombocyte volumen6016416166778187.3751215Patalet critinombocyte volumen601248716778181.34992016Statisma maleborptionn692187166778181.3658673Patalet critinombocyte volumen602487137082481.3658673Statisma maleborptionn692187137082481.3658673Statisma maleborptionn692187137082481.3658673Statisma maleborptionn692187137082481.3658673Statisma maleborptionn692187137082481.3658673<	N30-N39 Other diseases of urinary system	rs79306023	100938470	4.420628035
Whole body fat-free massns/860183733888729274853212Hip crounferencens/8018873386872320011994Body fat massns/801837338687220432444Body fat precentagens/801837338687220432444Body fat precentagens/801837338687220453244Body fat precentagens/801837338687220453244Body fat precentagens/801807352623121545567Balede critns/80500352663117132462White blood cell (leukoyte) countns/981810336453417.8827486Body tapecentagens/9808073350453117.132462Beinophill precentagens/98080733504579.4146051Steninophil precentagens/98080733504579.4146051Beinophil precentagens/98080735304471.8097451Steninophil precentagens/98080735304471.8097451Beinophil precentagens/98080735304471.8097451Beinophil precentagens/980807165758182.3525773Ablo cell (eythrocyte) countns/9816101667786792.3525773Ablo cell (eythrocyte) countns/9816101667786792.3525773Ablo cell (eythrocyte) countns/991811.667786793.2852773Ablo cell (eythrocyte) countns/991871.37082481.44857110Ablo cell (eythrocyte) countns/992871.37082481.9379026Ablo cell (eythrocyte) countns/992871.37082481.9379126	H81 Disorders of vestibular function	rs140644635	100923359	4.069764347
Hip circumfenencens/801837353807242.0207564Whole body fat masesns/801837353807232.0011394Body fat percentagens/8018373526073445.804025Bodte crittns/309528352693921.672661Platelet crittns/9892083526623121.555667White blood cell (leukocyte) countns/9818003526623121.125462Platelet crittns/9818003526623121.125462Destrophill countns/9818003526623121.125462Layder countns/9818003526623121.125462Layder countns/9818003526623121.4125402Lownphill countns/9818003526623121.4125402Lownphill percentagens/9818003526623121.4125402Lownphill countns/9818013526623121.4125402Lownphill percentagens/9818013526623121.4125402Lownphill countns/97184352044713.63404201KPC1 (Micrott Carier 1)10.000016.6778182.37512135Platelet countns/971816.6778182.37512135Platelet countns/9718116.6778184.3991105Lownphile countns/972816.6778494.69921502Platelet countns/9728116.67784916.87981813.955687Lownphile countns/9728116.77842816.87981813.955687Lownphile countns/9728113.70824810.89781213.955687Lownphile countns/9728113.9	<i>PPARδ</i> (Peroxisome Proliferator Activated Receptor Delta)			
Whele bedy fat massns6018387353868727.0011934Body fat preventagens600183873538687224.5524464Momocyte protentagens60183873526524145.8644662Plaelet critns3959228352593721.6726615Mite blood cell (teukocyte) countn9080003526623117.1825462Baleele countn9080003526623117.1825462Exemptific countn9080003526623117.1825462Evandpuil preventagen295625350054115.000201Lymphocyte percentagen905807035267319.1413016K90 Insettinal malabsorptionn97714743532047711.8007145MPCI (Mitcohomital Provate Carrel )m1005761837.78512135Matelet countn977281667780737.8521235Patelet countn974281667781842.992050D13 Other necrotising vascuopathiesn74199511667781943.992705D31 Other necrotising vascuopathiesn69909511667781843.9947026Mari Lotted (Intrombocyte) volumen6924871570824813.995687D400 pelcet (Intrombocyte) volumen6924871570824810.991781D400 pelcet (Intrombocyte) volumen6924871570824810.9918981D500 pelcet (Intrombocyte) volumen6924871570824810.991898D500 pelcet (Intrombocyte) volumen6924871570824810.9918918D500 pelcet (Intrombocyte) volumen6924871570824810.9918918D500 pelcet (Intrombocyte) volume <td>Whole body fat-free mass</td> <td>rs36018387</td> <td>35386872</td> <td>59.74853212</td>	Whole body fat-free mass	rs36018387	35386872	59.74853212
Body fat percentagenS6011837S3386872Q4582464Monocyte percentager39469982S32673445.8640455Platelet critr3959238S325939721.6726615Mihe Islood cell (leukocyte) countr3980500S326623121.5435667Platelet countr3980500S3266231C1.53896121Coisnophill percentager2958255S408461C3.390121Lymphocyte percentager2958257S408461C3.390121Lymphocyte percentager3957861S3203047P14126151Ashmar357586S320437P14126151Ashmar357586S320437P14126151Ashmar357586S320437P14126151Ashmar35758S320437P14126151Ashmar35758S320437P14126151Ashmar35758S320437P14126151Ashmar35728166778679S28527735Adel local (leythrocyte) countr6916128166778613425911155Male lacted (leythrocyte) countr6914287166774533425921155Mark (JAKC) (Mitogen-Activated Protein Kinase	Hip circumference	rs36018387	35386872	49.20670564
Body far percentagens6018387353808720.24528464Monocyte percentagens400982352673445.8540452Placket critns3998500352662312.1545677Placket critns980500352662317.8717147Balect countns980500352662317.8717147Disorbpill percentagens29850735327779.741626151Lymphocyte percentagens29565135302477.971426151Solon Institutional mabbsorptionns77147435320477.971426151More placet (frombocyte) volumens707147435320477.18697455More placket (frombocyte) volumens70460401667786792.52552775Placket (frombocyte) volumens70460401667786792.52552775Placket (frombocyte) volumens7040541667745314.5992105More placket (frombocyte) volumens7028941667745394.5992105More placket (frombocyte) volumens72851570824881.39956873Mark Starket (More bocyte) volumens92589157082481.039986473More placket (frombocyte) volumens92587157082481.03996473Natrik (frombocyte) volumens92587157082481.03996473Natrik (frombocyte) volumens92587157082481.03996473Natrik (frombocyte) volumens92587157082481.03996473Natrik (frombocyte) volumens92587157082481.03997693Natrik (frombocyte) volumens92587157082481.03997162Natrik (frombocyte)	-	rs36018387	35386872	37.00113934
Platelet critrs.33959228352993721.672.6615White blood cell (kukocyto) countn.9398000352.6623121.5455.6677Platelet countn.9398000352.6623117.1125342Exinophill perentagen.239582534.0546115.3490.021Lymphocyte percentagen.9658079353.27779.7416.26151asshman.8757568352.06330.91411301.04K90 Intestinal malabsorptionn.87771474353.204730.186071.45K90 Intestinal malabsorptionn.87771474353.204730.186071.45K40 platelet (thrombocyte) volumen.87971.61281.66778187.378512135Platelet countn.877281.66778197.378512135Badel bood cell (erythrocyte) countn.869161.281.667391334.82991105M31 Other necrotising vasculopathiesn.86921871.5781894.54470026M473K5 (ASK-1) (Mitogen-Activated Protein Kinase Kina	Body fat percentage	rs36018387	35386872	20.45328464
Mile blod cell (leukocyte) countrs93800035262312.1.545667Fladet countrs968111333453417.88276186Neutrophill countrs93805003526233541541Lisymphocyte percentagers95805735325777.7.41626151ashnars155756835205039.14130164KND cyte percentagers96807935325777.7.41626151ashnars155756835205039.14130164KND chronichal Pyruxet Carier 1)rs77274735324771.8.607145MAC1 (Miccohadrial Pyruxet Carier 1)rs72781.667757187.37851215Badele countrs72781.667786792.82527735Red blood cell (erythrocyte) countrs4099411.66778182.38527735M3 Other necrotising vasculopathiesrs4099411.667781934.829911105M47357 (ASK-1) (Minger-Activated Poten Kinase Kinase Kinaserr1.3052687M47357 (ASK-1) (Minger-Activated Poten Kinase	Monocyte percentage	rs9469982	35267548	45.86340625
Platelet countn94881113534453417.8276186Neutrophill countn93805003526251354054117.1123442Eosinophill percentagen9680579332257774.142611Jurphocyte percentagen9680579332257774.142611Athman8155768352605309.184130164K00 Intestinal malabsorptionn7.0774743352605309.184130164MPC1 (Mitcohordrial Provise Carrier J)1667578187.37851213Mean platelet (thrombocyte) volumen5019611281667784792.88522735Red bod cell (erythocyte) countn50495341667744294.6992605MJ1 Other necroitising vasculopathiesn54949541667744294.6992605MJ2 Other necroitising vasculopathiesn569493713708218813.9356673Losinophill countn5923891370813813.9356673Login platelet (thrombocyte) volumen5923871370824810.9371522Login platelet (thrombocyte) volumen5923871370824810.9371522Login platelet (thrombocyte) volumen5923871370824810.9371522Login platelet (thrombocyte) volumen5923871370824810.9371522Mean platelet (thrombocyte) volumen5923871370824810.937152Login platelet (thrombocyte) volumen5923871370824810.937163Mean reticuloy the volumen5923871370824810.937163Mean reticuloy the volumen598755137144208.1172716Mite blood cell (eydocyte) countn	Platelet crit	rs33959228	35259397	21.6726615
Instruction         Instruction         Instruction         Instruction           Neutrophill count         ps980500         35366211         15.34904201           Lymphocyte percentage         ps980507         35366231         15.34904201           Lymphocyte percentage         ps9658079         3526737         9.714626151           Abbinotion         ps771474         35320457         9.1841904           MCCI (Mitochondrial Pyruvate Carrier 1)           7.378512135           Method platelet (thrombocyte) volume         ps0916128         166779819         7.378512135           Platelet count         ps0916128         166779819         4.699926505           MSD Other necordising vasculopathies         ps7445954         166778198         4.699926505           MAPSKI GAK-(Mitogen-Activated Protein Kinase Kinase Sinase Sinappill         10198248         16.499924505           Marski GAK-(Mitogen-Activated Protein Kinase Kinase Sinappill         ps092389         17082448         10.84396601           Lymphocyte percentage         ps092487         137082448         10.84396601           Lymphocyte percentage         ps092437         137082448         10.84396601           Lymphocyte percentage         ps0924387         137082448         0.847970562           P	White blood cell (leukocyte) count	rs9380500	35266231	21.54556677
non-optimization         rs239525         3540540         15.4904201           Lymphocyte percentage         rs0658079         3322757         9.741626151           asthm         rs155756         3320303         0.184130164           K90 Intestinal malabsorption         rs155756         3320307         0.184030164           K90 Intestinal malabsorption         rs157764         332047         0.186071657           Mach platelet (thrombocyte) volume         rs10946160         16677878         7.37851215           Red lood cell (erythrocyte) count         rs6916128         16677867         5.28552735           Red lood cell (erythrocyte) count         rs6916128         16677867         5.28552735           Red lood cell (erythrocyte) count         rs6916128         16677867         4.825911165           M31 Other necroinsing vasculopathies         rs690951         16678189         4.84591080           M31 Other necroinsing vasculopathies         rs690932         157082948         14.4885109           Disnophill count         rs902387         137082948         16.4399611           Numbrocyte percentage         rs6924387         137082948         16.3490621           Numbrocyte percentage         rs9325807         137082948         16.3490621           Numbrocyte pe		rs9658111	35364534	17.88276186
Ension bill percentagers2395253540540115.4904201Lymphocyte percentagers%6807935327779.74162.6151astmars155756835200309.18413014K90 Intestinal malabsorptionrs.155756835204079.1843014K90 Intestinal malabsorptionrs.0771474353204073520577Maen platelet (thrombocyte) volumers.07147435205775.2555277.55Red blood cell (erythrocyte) countrs.6714281667786795.255527.75Red blood cell (erythrocyte) countrs.6714294166774294.69920505M31 Other necroising vasculopathiesrs.691428166778184.324992050M31 Other necroising vasculopathiesrs.6943871370829484.5494902050M478X5 (MSCI) (Migen-Activated Protein Kinase K	Neutrophill count	rs9380500	35266231	17.11253462
Lymphory percentagers968807935327579/21626151ashmars1557568352605309.184130164K90 Inestinal malbsorptionrs1557568352605309.184130164MPC1 (Micehondrial Prywate Carrier 1)malon platelet (thrombocyte) volumers10946160166778187.378512135Platelet (thrombocyte) volumers109461601667781934.82591116M31 Other necrotising vasculopathiesrs69161281667781934.82991105M31 Other necrotising vasculopathiesrs74495941667781934.82991086M429K5 (ASK-1) (Mitogen-Activated Protein Kinase	-	rs2395625	35405461	15.34904201
ashima         rs1557568         3520437         9,184130164           K90 Intestinal malabsorption         rs771474         33320447         11,86097145           MPCT (Mitochondrial Pruvate Carrier J)               Mean platelet (thrombocyte) volume         rs107146         rs5728         166778678         5,285527755           Red blood cell (erythrocyte) count         rs6916128         166758198         4,825911105           M31 Other necrotising vasculopathies         rs7449594         166778678         2,85527755           MAP3K5 (ASK-1) (Mitogen-Activated Protein Kinase Kinase Kinase Sinase		rs9658079	35327577	
MPCI (Mitchondrial Pynate Carrier 1)       ns10946160       166757818       7.375512135         Mean platelet (thrombocyte) volume       ns5728       166778679       5.28552775         Red bood cell (erythrocyte) count       ns6916128       166779813       4.6992610         M30 Other necrotising vasculopathies       ns690991       16675913       4.6992630         dyspepsia / indigestion       ns690991       16675918       4.6992630         MAPUKS (ASK-1) (Mitogen-Activated Protein Kinase Kina		rs1557568	35260530	9.184130164
MPCI (Mitchondrial Pynate Carrier 1)       ns10946160       166757818       7.375512135         Mean platelet (thrombocyte) volume       ns5728       166778679       5.28552775         Red bood cell (erythrocyte) count       ns6916128       166779813       4.6992610         M30 Other necrotising vasculopathies       ns690991       16675913       4.6992630         dyspepsia / indigestion       ns690991       16675918       4.6992630         MAPUKS (ASK-1) (Mitogen-Activated Protein Kinase Kina	K90 Intestinal malabsorption	rs7771474	35320447	11.86097145
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		rs189397255	24389732	
		rs13100197	24491484	8.731024419



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Trunk predicted mass	rs13100197	24491484	8.614769205
Leg fat percentage (left)	rs1349265	24159387	8.323233252

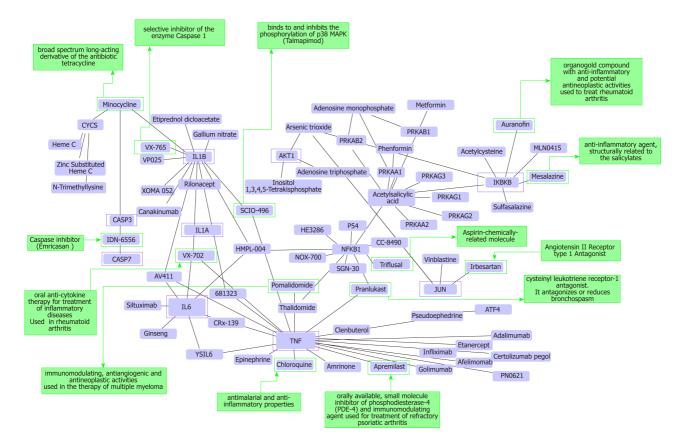
The associations have been computed using 452264 United Kindom Biobank White British individuals. http://geneatlas.roslin.ed.ac.uk/.



**Figure 2** Nonalcoholic fatty liver disease-Kyoto Encyclopedia of Genes and Genomes pathway and mechanisms of disease pathogenesis. Pathway was retrieved from https://www.genome.jp/dbget-bin/www\_bget?pathway+hsa04932; figure was modified to highlight key molecular processes. This map shows a stage-dependent progression of nonalcoholic fatty liver disease (NAFLD). In the first stage of NAFLD, pathway highlights excess lipid accumulation associated with the induction of insulin resistance, which leads to a defect in insulin suppression of free fatty acids (FAAs) disposal. In addition, two transcription factors, SREBP-1c and PPARα, activate key enzymes of lipogenesis and increase the synthesis of FAAs in liver. In the second stage, pathway is presented as a consequence of the progression to nonalcoholic steatohepatitis (NASH); the production of reactive oxygen species is enhanced due to oxidation stress through mitochondrial beta-oxidation of fatty acids and endoplasmic reticulum (ER) stress, leading to lipid peroxidation. The lipid peroxidation can further cause the production of cytokines [Fas ligand, tumor necrosis factor α (TNF-α), IL-8 and transforming growth factor], promoting cell death, inflammation and fibrosis. The activation of JNK, which is induced by ER stress, TNF-α and FAAs, is also associated with NAFLD progression. Increased JNK promotes cytokine production and initiation of hepatocellular carcinoma. Major organelles involved in the pathogenesis of NASH are also highlighted in the NAFLD-pathway, including mitochondria dysfunction. In the figure, molecular targets that were further selected to explore protein-chemical interactions are highlighted by red squares. NAFLD: Nonalcoholic fatty liver; FAAs: Free fatty acids; TNFα: tumor necrosis factor α.

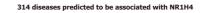


Sookoian S et al. NASH drug discovery



**Figure 3 Protein-chemical interactions and potential repurposing drugs to target nonalcoholic steatohepatitis.** We generated a protein-chemical interaction network by mapping the significant genes/proteins that are represented in the nonalcoholic fatty liver disease-Kyoto Encyclopedia of Genes and Genomes pathway to chemicals/drugs that are annotated in the Comparative Toxicogenomics Database. The 149 genes (seeds) from our analysis were mapped to the corresponding molecular interaction database; full list of seed genes is listed in Table 1. This analysis generated a huge network composed of approximately 2000 nodes. Current figure shows chemical-drug-interactions specifically focused on selected genes/proteins of potential interest, including members of the caspase family (CASP3 and CASP7), interleukins (IL1B, IL1A, and IL6), tumor necrosis factor α (TNF-α), NFKB1 (Nuclear factor kappa B subunit 1) and IKBKB (inhibitor of nuclear factor kappa B kinase subunit beta), JUN (Jun proto-oncogene, AP-1 transcription factor subunit), AKT1 (AKT serine/threonine kinase 1). In green charts we summarized information on current use and known action of selected drugs. Interaction network was predicted by the Networkanalyst resource available at https://www.networkanalyst.ca/faces/home.xhtml. The network is shown as a Cytoscape graph.





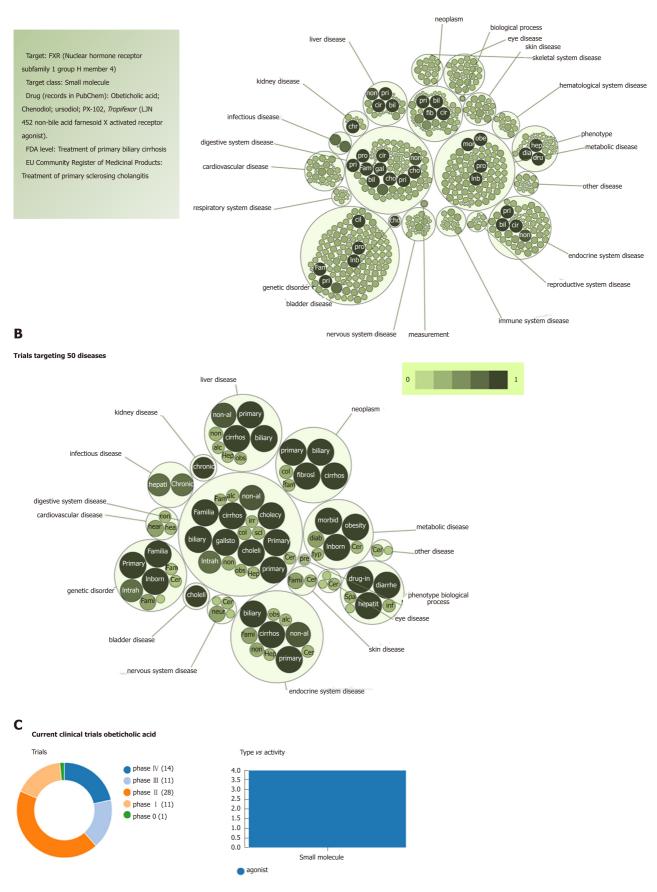
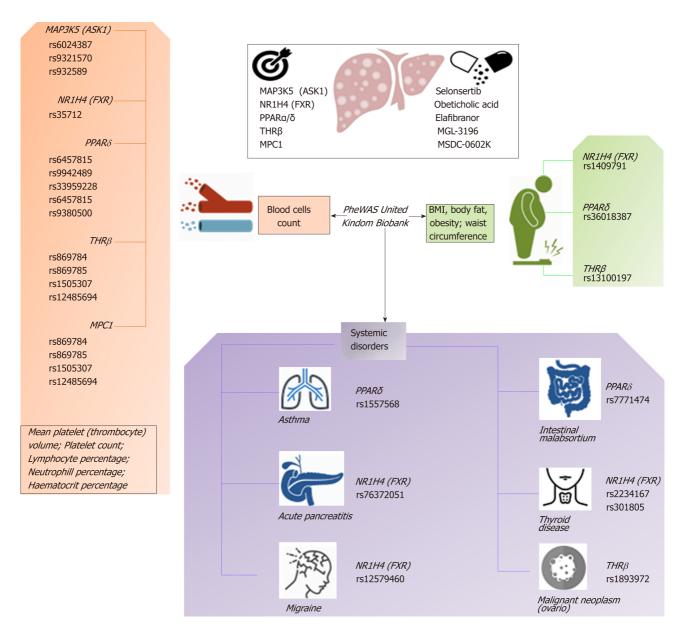


Figure 4 Farnesoid X nuclear receptor (nuclear hormone receptor subfamily 1 group H member 4): Analysis of pleiotropy. A: Graph shows all predicted diseases associated with farnesoid X nuclear receptor; B: Clinical trials of drugs that target farnesoid X nuclear receptor. Predictions were explored in The Open Targets Platform that allows prioritisation of drug targets based on the strength of their association with a disease (https://www.targetvalidation.org/); C: Evidence curated from ClinicalTrials.gov, a database of privately and publicly funded clinical studies conducted around the world. https://clinicaltrials.gov/. Diseases are

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presented as bubbles grouped into therapeutic areas using their Experimental Factor Ontology relationships. The size and shade of the color of each bubble is proportional to the strength of association between the disease and farnesoid X nuclear receptor. The concept of a target-disease association is based on the analysis of several resources, including genetic associations (GWAS Catalog, UniProt, European Variation Archive, Gene2Phenotype), somatic mutations (Cancer Gene Census, European Variation Archive somatic, IntOGen), RNA expression (expression atlas), drugs (ChEMBL), affected pathways (Reactome), animal models (PhenoDigm) and text mining (Europe PMC). The platform is available at https://www.targetvalidation.org. Data last updated December 2018.



**Figure 5** The complexity of molecular targets and novel nonalcoholic steatohepatitis drugs: Pleiotropy assessed in the PheWAS United Kindom Biobank. Figure shows associations between gene variants in five nonalcoholic steatohepatitis-related molecular targets (*MAP3K5/ASK1, FXR, PPARα/δ, THRβ*, and *MPC1*) with different traits and phenotypes in the UK-PheWAS (Phenome-wide association study). Information regarding single nucleotide polymorphisms and associations were retrieved from the United Kindom Biobank (http://geneatlas.roslin.ed.ac.uk/).

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