SASLT
الجمعية السعودية لأمراض وزراعة الكبد
Saudi Society for the Study of Liver Disease and Transplantion

الجمعية تحت إشراف
الهيئة السعودية للتخصصات الصحية
Saudi Commission for Health Specialties

SASLT
NEWSLETTER

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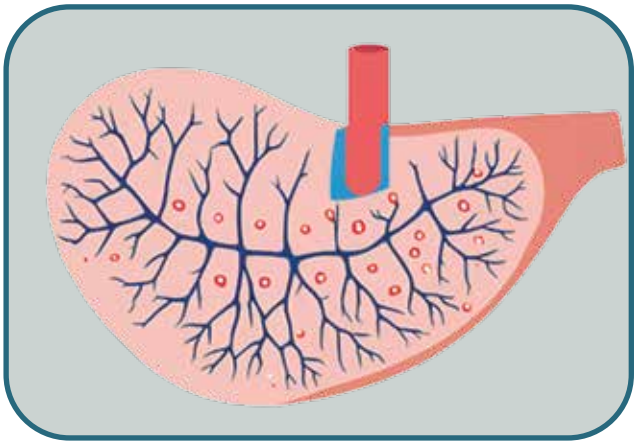
Sateesh Maddirevula,
PhD-Biography

Sateesh Is Working As A Scientist In Center For Genomic Medicine (Cgm), King Faisal Hospital Research Center, Riyadh, Saudi Arabia. He Is A Trained Molecular Geneticist (By Dr. Fowzan Alkurya) With Extensive Experience In Decoding Mendelian Form For Rare Diseases. He Possesses Nine Years' Experience In Ngs Based Data Analysis (Panels, Exome, Genome And Rnaseq) And Optical Genome Mapping (Ogm) (Bionano's Saphyr® System For Structural Variation Detection). He Published More Than 70 Peer Reviewed Articles And Discovered More Than 100 Candidate Genes For Rare Disease Including Intellectual Disability, Brain Malformations, Ciliopathies, Infertility, Liver Disease Etc. 80% Of The Proposed Candidate Genes Got Additional Confirmations And Established On Omim. Few Of The Genes Are Considered For Saudi Arabia Premarital Screening Program. He Identified 100s Of Founder Variants In The Local Population. He Is Working As A Head Of The Genotyping Unit And Running Array Based Clinical Test Like Whole Genome Snp Array And Pharmacogenomics (Pgx). He Discovered Various Novel Genes (Kif12, Ppm1f, Usp53, Lsr, Wdr830s, Znf808) And Hundreds Of Novel And Founder Variants In Known Genes For Liver Disease. A Large Study Of Pediatric Cholestasis Is Under Review With Around 60% Diagnostic Yield From Local Population. All These Achievements Made Him A Member Of Gencc Consortium And Natural Course And Prognosis Of Pfic And Effect Of Biliary Diversion.
(Napped) Consortium (Napped Created A Global Network Focused On Rare Genetic Liver Diseases In The Progressive Familial Intrahepatic Cholestasis (Pfic) Spectrum). He Is Interested In Rare Disease Research, Positional Mapping, Haplotypes, Ngs Based Pipelines, Long Read Sequencing, Pharmacogenomics, Druggable Genome And Molecular Diagnostic Kits.

Saudi Arabia's Physicians And Researchers Discover New Genetic Disease "Hepatorenal Ciliopathy"



To the extension of novel disease discovery (PFIC7 (USP53), PFIC8 (KIF12), Biliary, renal, neurologic, and skeletal syndrome (TTC26), Novel Type of Infantile Intrahepatic Cholestasis (LSR)) KFSH&RC discover another new genetic disease, "Hepatorenal Ciliopathy". Also discovered variants spanning 37 genes with established or tentative links to cholestasis'

An incredible achievement by the King Fasal Specialist Hospital & Research Center (KFSHRC) in Riyadh, Saudi Arabia marks a significant leap forward in the field of pediatric cholestasis and medical genetics. Pioneering research, published in Genetics in Medicine, sheds light on a new genetic disease with profound implications for families worldwide.

The discovery came after Chairman of the translation genomics, Center for Genomic Medicine, KFSH&RC Dr. Fowzan Alkuraya along with consultant Dr. Mohammad Shagrani (Transplantation Organ Transplant Centre Of Excellence, KFSH&RC, Riyadh) and their team conducted comprehensive molecular testing on 299 pediatric participants (279 families) with intrahepatic cholestasis. By utilising

in house exome sequencing techniques, they identified acandidate gene PSKH1. This critical finding led to the recognition of a new ciliopathy disease. International collaborators from Canada, Australia and Netherlands are also contributed to PSKH1- related hepatorenal ciliopathy.

Pediatric cholestasis is the phenotypic expression of clinically and genetically heterogeneous disorders of bile acid synthesis and flow. Although a growing number of monogenic causes of pediatric cholestasis have been identified, the majority of cases remain undiagnosed molecularly. Primary (cholic acid and chenodeoxycholic acid) and secondary (deoxycholic acid and lithocholic acid) bile acids are conjugated in the liver to form bile salts, which together with phospholipids, cholesterol, conjugated bilirubin, electrolytes, and water constitute bile and ensure its normal flow. Their role in facilitating fat absorption through emulsification has long been recognized and, more recently,

they have been implicated in a wide range of physiological functions as major signaling molecules. Impaired formation or flow of bile manifests clinically as cholestasis and can trigger an adverse inflammatory cascade culminating in liver failure. Intrahepatic cholestasis, in particular, can be the first manifestation of numerous genetic disordersthat typically manifest in the pediatric age group. In recognition of this, the updated guidelines on the management of pediatric cholestasis call for a broader utilization of genetic testing. Most genetic studies on pediatric cholestasis have been based on a panel of predetermined set of genes with known links to the disease. An inherent limitation of these studies is their inability to expand the genetic heterogeneity of pediatric cholestasis, which is clearly not fully captured considering that the diagnostic yield of these panels is typically <%30. Ciliopathies, disorders of the primary cilium, are highly heterogeneous clinically with remarkable pleiotropy, although predilection toward certain organs is noteworthy. Liver is one of the most affected organs in ciliopathies and congenital hepatic fibrosis is considered a classical ciliopathy phenotype. Although infantile cholestasis is the typical presentation of hepatic ciliopathy, only a fraction of patients with infantile cholestasis has an underlying ciliopathy, which poses a diagnostic challenge.

A novel hepatorenal ciliopathy caused by PSKH1 mutations

A novel candidate gene (PSKH1) is discovered in 4 families. PSKH1 was particularly compelling because of strong linkage in 3 consanguineous families who shared a novel hepatorenal ciliopathy phenotype. PSKH1 encodes a putative protein serine kinase of unknown function. Patient fibroblasts displayed abnormal cilia that are long and show abnormal transport. A homozygous Pskh1 mutant mouse faithfully recapitulated the human phenotype and displayed abnormally long cilia. The phenotype could be rationalized by the loss of catalytic activity observed for each recombinant PSKH1 variant using in vitro kinase assays

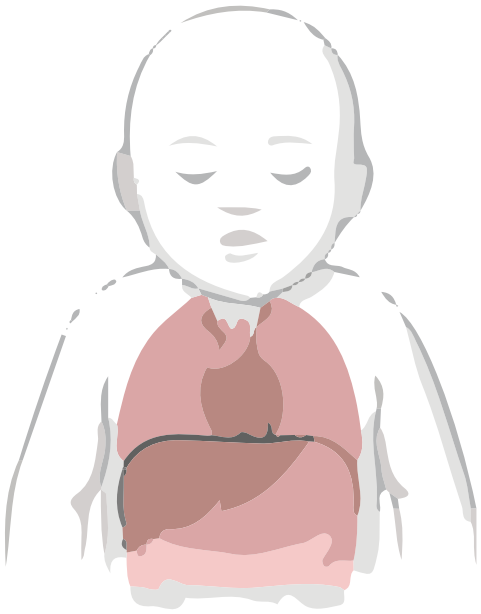
Exome sequencing as a first tier and noninvasive approach in pediatric cholestasis.

In a cohort of 299 pediatric participants (279 families) with intrahepatic cholestasis, a likely causal variant was identified in 135 families. These comprise 135 families that harbor variants spanning 37 genes with established or tentative links to cholestasis. This is the largest exome-based study on pediatric cholestasis, and it suggests that monogenic diseases account for at least %48.56.

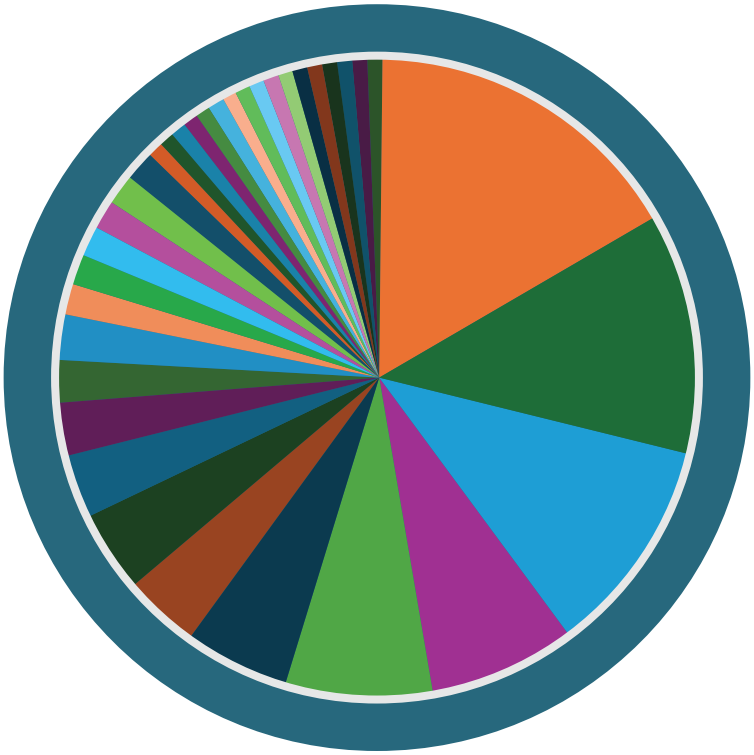
We show that these forms range from relatively common, eg, ABCB4, ABCB11, ATP7B, DCDC2, KIF12, and TALDO1, to extremely rare, eg, LSR, ONECUT1, BCS1L, IGFBP7, and SI. Also acknowledged that the relative contribution of genes to this phenotype may vary between populations. In addition, in a large number of families who received a molecular diagnosis by our exome-first approach, the clinical team decided not to pursue a liver biopsy.
This is consistent with a trend seen in other clinical specialties where there is a drop in the use of invasive diagnostic procedures concomitant with the growing use of diagnostic genomics.

Also highlighted the fact in many instances in which the liver biopsy was erroneously pointing the clinical team in the direction of biliary atresia, although the actual diagnosis as revealed by exome sequencing was different. In summary, exome sequencing as an effective and high yield first-tier diagnostic noninvasive test for pediatric cholestasis, that can obviate the need for invasive and costly diagnostic tests. A novel autosomal recessive hepatorenal ciliopathy linked to PSKH1. The latter finding increases the repertoire of genes that should be targeted in the clinical sequencing of patients with hepatorenal ciliopathy and suggests a potential mechanism.

Large-scale genomic investigation of pediatric cholestasis



Number of families per gene



ABCB4 (22)
ABCB11 (16)
KIF12 (15)
ATP8B1 (5)
IFT56 (TTC26) (5)
MPV17 (4)
TJP2 (4)
HSD3B7 (3)
BCS1L (2)
PKHD1 (2)
SKIV2L (2)
TALDO1 (2)
ADK (1)
GALT (1)
GBE1 (1)
GJC2 (1)
IGFBP7 (1)
MYO5B (1)
SI (1)
SLC25A15 (1)
SLC37A4 (1)
SULT1A2 (1)
TRMU (1)
ATP7B (10)
DCDC2 (10)
JAG1 (7)
USP53 (3)
ABCC2 (2)
AKR1D1 (2)
AIRE (1)
BAAT (1)
DYNC2I 1 (1)
NPC1 (1)
NR1H4 (1)
PEX1 (1)

Reference

Maddirevula S, Shagrani M, Ji AR, Horne CR, Young SN, Mather LJ, Alqahtani M, McKerlie C, Wood G, Potter PK, Abdulwahab F,AlSheddi T, van der Woerd WL, van Gassen KLI, AlBogami D, Kumar K, Muhammad Akhtar AS, Binomar H, Almanea H, Faqeih E, Fuchs SA, Scott JW, Murphy JM, Alkuraya FS.Large Scale Genomic Investigation of Pediatric Cholestasis Reveals a Novel Hepatorenal Ciliopathy Caused by PSKH1 Mutations. Genet Med. 2024 Aug 9:101231. doi: 10.1016/j.gim.2024.101231. Epub ahead of print. PMID: 39132680.

Extracorporeal Albuumin Dialysis In The Treatment Of Liver Dysfunction : Promising Insights And Ongoing Debates

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Liver dysfunction affects millions of people globally; it can be caused by alcohol abuse, viral infections and genetic predisposition. Liver transplants are in short supply, and demand is soaring for alternative therapies.

Different therapies including Extracorporeal albumin dialysis have proven to be effective in prolonging liver function.

Exploring ECAD Therapies

ECAD (extracorporeal albumin dialysis) treatments, including molecular adsorbent recycling system (MARS), single-pass albumin dialysis (SPAD) and Prometheus are in development to remove toxins from the blood stream while at the same time boosting liver function. Although these treatments reduce bilirubin levels and ameliorate hepatic encephalopathy (HE), their efficacy and safety are still highly debated. A documented systemic review of multiple studies appraised the safety and efficacy status quo between ECAD therapies versus special medical treatments. The authors searched all available electronic databases for randomized trials of interventions targeting liver disorders. The results were stratified according to: (i) safety endpoints; and, (ii) efficacy endpoints including changes in bilirubin levels, bile acids decreasing rate, ammonia concentration variations during the study period vs baseline values, mental improvement assessing as reduction of overt HE stages downgrades along time scales throughout treatment sites outcomes for only survived patients. Safety endpoints included post-treatment adverse events and an improvement in HE, defined as a two-grade improvement on the West Haven scale.

Selection and Quality Appraisal of Studies

A strict selection criteria were followed, including only studies published in English Grey literature or duplicates removed. The methodological quality of studies was evaluated including risk ratios (RRs) and mean differences (MDs). From this search , 4,359 initial articles were identified; following reference lists of the included studies and two hand-searched bibliographies. But the road from literally thousands of articles to a few studies considered really "on topic" was paved with difficulties. The first step was to remove duplication, a time-consuming process that finally reduced the number of articles from 4425 duplicates down to only 2742 records. From these, 1,801 were removed due to not meeting screening criteria and 886 of those excluded because they could not be accessed (conference abstracts or case reports among others). Finally, 12 papers were selected for review. Methodological quality was assessed in terms of bias within selection, attrition, performance and reporting domains amongst others. The final analyses used the DerSimonian and Laird random effects model. This last review looked at 12 trials that recruited 653 patients with liver etiology.

These trials were distributed across one or several countries and were conducted over 21 years, testing different ECAD interventions.

Exploring ECAD Therapies

Both MARS & Prometheus reduced total bilirubin compared to Standard Medical Therapy (SMT). It shows that the therapies can effectively control bilirubin, a key marker of liver health. The adverse effects seen following therapy with MARS and Prometheus are equivalent to those after SMT, thereby ratifying them as safe alternatives in the field of liver dialysis. For example, in a trial that included patients with alcoholic cirrhosis complicated by alcoholic hepatitis, Prometheus showed a greater decrease of total bilirubin levels compared to MARS. This difference might be due higher dialysate flow rate in prometheus treatment (300 ml/l) compared to MARS (200 ml). Pre-treatment bilirubin levels also differed significantly between the patient groups, which could limit generalization of these findings.

A Step Forward

This comprehensive review represents significant progress towards recognizing the therapeutic opportunity of ECADs in liver disease. As we search for better and safer treatments to help patients with liver failure, we can build upon these findings later on. While encouraging, these findings emphasise the importance of further well-designed and blinded trials in order to more firmly establish whether or not any observed improvements are due to
efficacy

SASLT
World Hepatitis Day Celebration 2024

On28th of July 2024 , the Saudi Society for the Study of Liver Disease and Transplantation (SASLT) headed by Dr. Faisal Abaalkhail, the president of SASLT joined the effort of the Ministry of Health in celebrating the World Hepatitis Day this 28th of July 2024.

Every 28th of July each year, World Hepatitis Day is celebrated by people around the globe in honor of Dr. Baruch Blumberg's. He discovered the hepatitis B virus in 1967 and eventually developed the vaccine after 2 years.

These years' theme is "It's Time for Action," to highlight the urgent need for swift and decisive measures to tackle hepatitis on a global scale.

The guidelines also emphasis providing high-quality services, identifying hepatitis D through established testing protocols, and improving diagnostics with providing high-quality services.

On this date the time to take action to realize a hepatitis free world. Now is the time to prioritize testing, treatment and vaccination to realize a hepatitis-free world and meet our 2030 targets.

There are several booths where the SASLT participated as our contribution for the celebration of this year in the office Ministry of Health building at the digital city in Riyadh, KSA.


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اليوم العالمي
لالتهاب الكبد
World Hepatitis Day
28
July


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Global Fatty Liver Day

What is Global Fatty Liver Day?

Global Fatty Liver Day, formerly known as International NASH Day, is a public education campaign that was inaugurated in June 2018 to enhance awareness and emphasize the pressing nature of fatty liver disease, particularly its advanced stages, which impacts a staggering 115 million individuals worldwide.

Fatty liver disease, and its more advanced form, remains a concealed global epidemic. An estimated 357 million people will be affected by 2030. Because symptoms of fatty liver disease are often not overt, it is often underdiagnosed and underreported. Fatty liver disease is considered a major risk factor for concurrent conditions: more than 70% of patients are living with obesity, up to 75% have type 2 diabetes, and anywhere from 20-80% have hyperlipidemia. Unchecked, fatty liver disease may lead to cirrhosis, liver cancer, and liver transplant.

Against this backdrop, the inaugural International NASH Day was launched on June 12, 2018, with the primary aim of heightening consciousness regarding NASH and promoting preventative actions against the disease. Spearheaded by GLI, #NASHday 2023 was commemorated on June 8, garnering participation from more than 100 partners spanning across 55 countries. This event secured endorsements from over 30 international societies and effectively inaugurated a multitude of activities including liver health screenings, briefings, media outreach, and global social media campaigns. As the campaign enters its seventh year, we cordially invite you to rally behind patients, advocate for early detection, and fervently champion the movement. (https://globalfattyliverday.com/)

With this, last June 13, 2024 the Saudi Society for the Study of Liver Disease and Transplantation (SASLT) with the support of the members joined hand to participate and celebrate the Global Fatty Liver Day.

We aim to influence everybody including patients, families, health care leaders, health workers and patient organizations to work collaboratively towards promoting health care preventions and safety interventions that truly reflect the needs and preferences of patients, ultimately enhancing healthcare safety globally. We encourage participation to spread awareness and education related to fatty liver.

SASLT Activities:

Dr. Faisal Abaalkhail – SASLT president deliver Lecture about Fatty Liver .

TWITTER POST:

https://twitter.com/sasltksa/status/1801152814581711185?s=46&t=2XO4jl4RVUAADUg_uc06Hw

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