

## **A Novel Small Nuclear RNA-Activating Protein (SNPC4) Gene Mutation is Associated with Benign Recurrent Intrahepatic Cholestasis (BRIC)**

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### **Abstract**

Benign recurrent intrahepatic cholestasis (BRIC) is characterized by recurrent episodes of liver dysfunction called cholestasis. Such episodes last for weeks to months followed by a complete clinical, biochemical, and histologic normalization. BRIC is divided into two types based on the genetic cause of the condition. Mutations in the *ATP8B1* gene cause benign recurrent intrahepatic cholestasis type 1 (BRIC1), and mutations in the *ABCB11* gene cause benign recurrent intrahepatic cholestasis type 2 (BRIC2). However, the symptoms and signs are the same in both types. In a case with BRIC, we identified a novel homozygous missense mutation (chr9:139,278,072 G>A, p.R517W) in *SNAPC4* (small nuclear RNA activating complex polypeptide 4) gene. This variant segregates in the family, is predicted to be damaging and is absent in all control databases and from 500 healthy ancestry-matched control subjects. We report for the first time a mutation in the *SNAPC4* gene associated with benign recurrent intrahepatic cholestasis (BRIC).

**Keywords:** Small Nuclear RNA-Activating Protein (*SNPC4*); Benign Recurrent Intrahepatic Cholestasis (*BRIC*)

### **Introduction**

Benign recurrent intrahepatic cholestasis (BRIC) affects adolescence and adulthood, it represents benign forms of progressive familial intrahepatic cholestasis (PFIC) mainly caused by missense mutations in *ATP8B1* and *ABCB11* genes [1,2]. BRIC is characterized by acute episodes of cholestasis, jaundice and severe pruritus, caused by unknown factors which after weeks or months completely resolve to start again after an asymptomatic period of months to years.

BRIC1 like PFIC1 may be accompanied by pancreatitis, whereas BRIC2 may be accompanied by gallstone disease [1], Liver fibrosis has been described in cases of BRIC indicating a continuum between BRIC and PFIC in same cases [3]. There is no effective medical therapy of BRIC exists ursodeoxy-cholic acid (UDCA) and rifampicin have been anecdotally reported to affect the course of BRIC as has nasobiliary drainage [4].

A number of genes including *ATP8B1* and *ABCB11* are involved in autosomal recessive inheritance of BRIC, though some de novo mutations have been reported in these genes.

The study was approved by the IRB committee of the Istishari Arab Hospital, Ramallah. The control panel consisted of 500 unrelated of Palestinian origin ancestry. All samples used for this study were collected with informed consent.

**Case Report**

Our case is a 17-year-old male patient, presented to our institution with jaundice, dark urine and generalized itching of one month duration. His past medical history is significant for recurrent episodes of cholestatic jaundice with pruritus at the age of 15 and 15.5 years of life, first episode lasted one week, second episode lasted two weeks and the third lasted one month, first two episodes were managed conservatively by anti-histamine while the third episode treated by Ursodeoxy-cholic acid (UDCA) for one week in addition to anti-histamine.

On examination, he was jaundiced with multiple scratch markings. The liver function tests in the last two episodes ranged as depicted in the table 1.

Liver function test	2 <sup>nd</sup> episode at presentation	2 <sup>nd</sup> episode follow-up at 8 weeks	3 <sup>rd</sup> episode presentation	3 <sup>rd</sup> episode follow-up at 8 weeks
Total bilirubin (conjugated) mg/d (0 - 1.2)	3 (2)	1 (0.46)	4,7 (3)	1.2 (1)
SGOT U/L (0 - 40)	43	21	45	24
SGPT U/L (10 - 35)	79	37	65	28
ALP U/L (52 - 171)	787	230	810	142
GGT U/L (0 - 60)	38	30	39	30
Albumin g/dl (3.5 - 5.2)	4.3	4.4	4.1	4.2
INR (1 - 1.1)	0.9	0.8	1	0.9

**Table 1:** The liver function tests.

**Investigations**

Full laboratory testing was performed (Table 2) and this included testing for viral hepatitis, serological tests for immune, metabolic and genetic liver diseases and all tests were negative or in the normal range.

Test Name	Result	Test Name	Result	Test Name	Result
HB	13.3 g/dl	ESR	5	HbsAg	Negative
WBC	6800 K/uL	Creatinine	0.15 mg/dl	HbeAg	Negative
PLT	277 K/uL	BUN	12 mg/dl	HbcAb	Negative
ANTI TTG	Negative	LDH	120 U/L	HcvAb	Negative
ANTI IGA, IGG	Negative	Alpha-1anti-trypsin	130 (normal)	HAV	Negative
Ferritin	53 ng/dl (normal)	24 hour urine collection of copper	2 mic/24 hour (normal)	ASMA	Negative
IGG, IGA, IGM	All within Normal range	Bile acids (after episode)	2 umol/l normal	ANA	Negative
CRP	2	Ceruloplasmin	57 mg/dl	Anti LKM Antibody	Negative
AMA	Negative	c-ANCA	Negative	p-ANCA	Negative

**Table 2:** Detailed laboratory tests.

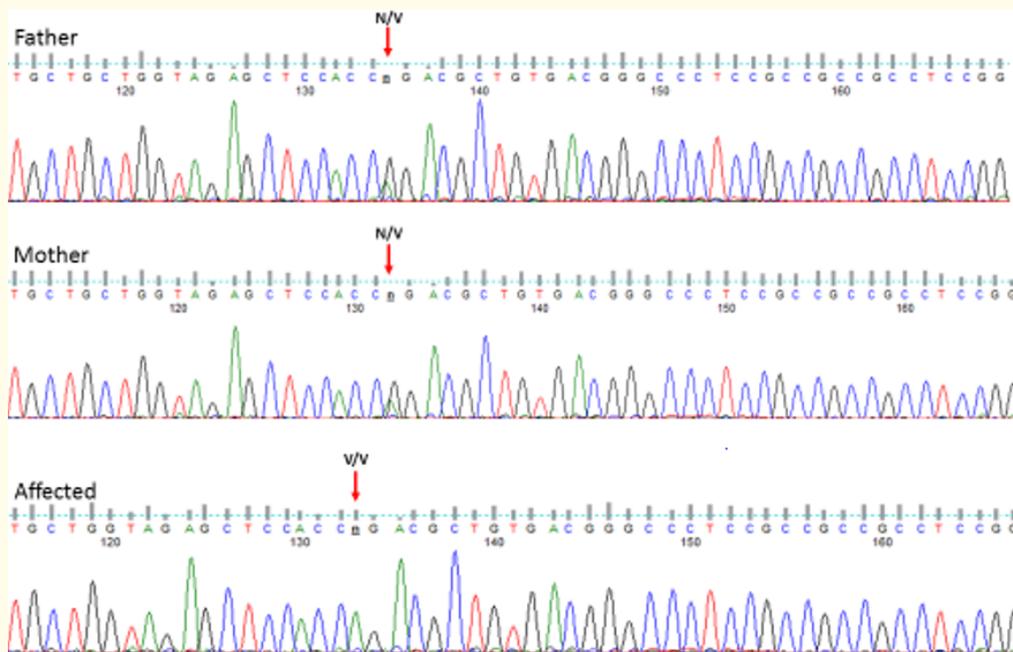
Besides, imaging were performed including abdominal U/S showing mild hepatomegaly with normal portal, hepatic, and splenic blood flow.

MRCP showed mild hepatomegaly with normal intrahepatic and extra hepatic biliary trees. So, liver biopsy was performed after the third episode and while the patient’s lab completely returned to normal levels and was reported to be normal. The patient was also genetically evaluated by direct sequencing for possible pathogenic variants in ATP8B1 and ABCB11 genes with normal finding (non-mutated genes).

**Whole exome sequencing (WES)**

We performed whole exome sequencing on genomic DNA collected from the patient white blood cells accordingly. In summary, the gDNA was quantified using Qubit v.3 and quality checked by gel electrophoresis. Library preparation was carried out using TruSeq Capture Exome Kit (Illumina). This kit provides coverage of 45 Mb of exonic content. The probe set was designed to enrich 214,405 exons. After sequencing on NextSeq 500, data was uploaded onto our server and 284,804,448 reads were aligned to the reference human genome (hg19) using BWA aligner. Prior to variant calling by GATK (Genome Analysis Toolkit), mapped reads (BAM format) went through preprocessing steps by removing PCR duplicates, realigning around indels, and recalibrating base quality. The final list of variants was annotated by Annovar using several databases of minor allele frequency such as 1000G as well as variant effect predictors such as SIFT, PolyPhen-2, and CADD. Variants with low coverage, synonymous, predicted benign (SIFT, PolyPhen-2, MutationTaster), MAF > 0.1% on ExAC and 1000G were filtered out. We identified a homozygous missense variant in SNAPC4 gene chr9:139,278,072 G>A, p.R517W. This variant is predicted to be damaging by PolyPhen-2, SIFT and MutationTaster. Mutation of zebrafish Snapc4 has been shown to be associated with loss of the intrahepatic biliary network [10].

This mutation was absent in all control databases and from 500 healthy ancestry-matched control subjects. The mutation was inherited in an autosomal recessive manner from both heterozygous carrier (Figure 1) parents. The predicted pathogenicity and the absence of this variant in control samples suggests that it is likely to be responsible for the BRIC like phenotype.



**Figure 1:** Representative chromatograms of the heterozygous chr9:139,278,072 G>A, p.R517W showing father (top), mother (middle), and affected (bottom). The mutation was absent in the ancestry-matched control cohort.

## Discussion

Summerskill and Walshe first described benign recurrent intrahepatic cholestasis in 1959 [5,6], as recurrent episode of jaundice and pruritus hence it's also called Summerskill - Tygstrup-De Groot disease.

There are two forms of BRIC, BRIC Type 1 and 2 are inherited as autosomal recessive and are related to mutation on chromosomes 18 and 2 respectively, Luketic and Shiffman (1999) gave diagnostic criteria for BRIC [7], which includes the following five criteria:

1. Episodes of jaundice separated by a symptom free interval lasting several month to years.
2. Laboratory value intrahepatic cholestasis.
3. Severe pruritus secondary to cholestasis.
4. Normal intra and extra hepatic bile ducts confirmed by cholangiography.
5. Absence of factors known to be associated with cholestasis.

Our patient has a clinical picture and typical criteria, but with novel genetic mutation, DNA from the patient was used for exome sequencing.

We identified a homozygous missense variant in SNPC4 gene chr9:139,278,072 G>A, p.R517W. This variant is predicted to be damaging by PolyPhen-2, SIFT and MutationTaster, segregated in the family, figure 1 and absent in 300 of an ancestry-matched control panel.

A mutation in this gene found to be associated with ankylosing spondylitis in human [8,9]. Mutation of zebrafish Snapc4 has been shown to be associated with loss of the intrahepatic biliary network [10].

## Conclusion

Our patient fulfills all five diagnostic criteria for BRIC as described by Luketic and Shiffman (1999), but with a novel genetic mutation (SNPC4 genetic mutation), which was never described in humans. Both the gene and the mutation detected needs to be further studied to show its biological and clinical association with BRIC.

## Conflict of Interest

The authors declare that there is no conflict of interest.

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