Association of TP53 Germline Variant and Choledochal Cyst among Clinically Diagnosed Filipino Pediatric Patients

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ABSTRACT

Background and Objective. Choledochal cysts (CC) are rare congenital, cystic dilations of the biliary tree occurring predominantly in Asian populations and in females. Patients are usually children presenting with any of the following: abdominal pain, palpable abdominal mass, and jaundice. Its congenital nature hints at a potential genetic cause. A possible causal gene is TP53, a tumor suppressor with a germline variant called rs201753350 (c.91G>A) that changed from a G allele to an A allele, decreasing the cell proliferation suppressing activity of its functional protein. Currently, there is no information on the TP53 rs201753350 germline variant available for the Filipino population. This study determined the prevalence of rs201753350 and the association between the functional G allele, the rs201753350 germline variant A allele, and the occurrence of CCs in Filipino pediatric patients in a tertiary government hospital.

Methods. Genomic DNA was extracted from blood samples of pediatric patients clinically diagnosed with CC. Controls were DNA samples collected from a previous study. The samples underwent PCR, electrophoresis, and sequencing.

Results. A total of 109 participants (22 cases and 87 controls) were included in the study. The A allele (22.94%) occurs at a lower frequency than the G allele (77.06%) among both cases and controls. More individuals have a homozygous G/G genotype (54.13%) than a heterozygous A/G genotype (45.87%) while the homozygous A/A genotype was not observed. The estimated risk of choledochal cyst occurrence is significantly lower in individuals with the A allele (PR: 0.08, 95% CI: 0.01 – 0.55) and the A/G genotype (PR: 0.06, 95% CI: 0.01 – 0.40).

Conclusion. There is no significant evidence to suggest an association between the TP53 rs201753350 germline variant and the occurrence of choledochal cysts in Filipinos. It is recommended that other mutations within and beyond the TP53 gene be investigated for possible associations with choledochal cyst occurrence.

Keywords: cystic bile duct dilatation, jaundice, rs201753350, germline, molecular

INTRODUCTION

Choledochal cysts (CC) are rare congenital, cystic dilations of the biliary tree that occurs predominantly in Asian populations. It has an estimated incidence of 1 in 1,000 livebirths compared to the estimated incidence of 1 in 150,000 livebirths in Western populations.1–5 CC is usually suspected in children presenting with any of the following signs or symptoms – abdominal pain, palpable abdominal mass, and jaundice.1–4 Its prevalence in the Philippines has not been recorded, but latest studies reported 100 CC cases in newborns and children below 18 years of age in the Philippine General Hospital (PGH) from 2004 to 2013 while 77 CC pediatric patients of the same age were recorded in
the Philippine Children’s Medical Center.5-7 Choledochal cysts have been associated with increased risk of malignancy that increases with age, ultimately leading to cirrhosis, portal hypertension, postoperative complications, or death, making early diagnosis and surgical intervention essential for a good prognosis. However, mortality rate in CC is relatively low.1,7-9

The classification of different CC types is based on the Todani classification, which has identified five main CC types (Table 1) whose development can generally be explained by two hypotheses.4,10,11 The pancreatic reflux hypothesis attributes the dilation of the biliary duct to the formation of an abnormal pancreaticobiliary duct junction (APBDJ), which is a long common duct and common bile duct, allowing the mixing of pancreatic and biliary juices that weaken the walls of the ducts. The congenital obstructing segment hypothesis, on the other hand, attributes biliary duct dilation to the improper formation of bile ducts during early development that causes an obstruction that slows down biliary stasis, leading to increased pressure in the duct and eventually dilation.1,4 Both hypotheses are congenital in nature, which point towards a possible genetic cause.

Several putative causal gene variants have been identified among pediatric CC patients in Hong Kong to have an association with CC development, including twelve (12) damaging genes variants that physically or functionally interact with each other. These include M4P2K1, PIK3CA, TLN1, PPP2R2B, SDC3, BYS1, EPS15, DNMI1, COL7A1, THBS1, TP53, and SETDB8. Among these genes, only TP53 has been previously associated with APBDJ and/or CC. TP53 gene codes for a tumor suppressor transcription factor that is activated in response to cellular stresses. The protein functions to regulate the cell cycle, facilitate DNA repair, and control apoptosis.12-16 A previous study on Chinese patients has shown that a TP53 germline single nucleotide variant (SNV) in rs201753350 (c.91G>A) in exon 2d may be a potential genetic basis of predisposition to choledochal cyst development. The shift from the G allele to the A allele in codon 91 causes as a missense mutation (p.Val31Ile) that decreases cell proliferation suppressing activity and transcriptional activation function of p53 on p21 and MDM2 promoters compared to the wild-type p53 protein. The decreased activity of the A allele can lead to the congenital malformation of biliary ducts, causing an obstruction in the distal bile duct according to the congenital obstructing segment hypothesis.14-18 While rs201753350 has been reported in other Asian populations, there are currently no reported occurrences of this variant in the Filipino population, whose ethnolinguistic groups have been found to be most genetically similar to Southeast Asian groups.19

Hence, the objectives of this study are to determine the prevalence of the TP53 rs201753350 germline variant, as well as its association with the occurrence of choledochal cysts in clinically diagnosed Filipino pediatric patients in a tertiary government hospital.

METHODS

Study Design

This cross-sectional study was conducted over a period of 22 months (May 2020 to March 2022). Approval by the University of the Philippines Manila Research Ethics Board (UPMREB 2020-0013-01) was obtained prior.

Sample Size Estimate

The sample size for determining the prevalence of TP53 rs201753350 germline variant among pediatric CC patients was computed using the equation for determining sample size for frequency in a population:20

\[
n = \frac{N\hat{p}(1-\hat{p})}{\left[\frac{d^2}{Z_{1-\alpha/2}^2}(N-1) \right] + \hat{p}(1-\hat{p})}
\]

where \(n\) is the sample size; \(N\) is the size of the population to be surveyed; \(N = 20\) based on the current population of pediatric CC patients in the PGH; \(Z\) is the level of confidence, which is typically \(Z = 1.96\) at 5% type I error (p-value < 0.05); \(\hat{p}\) is the expected % frequency of the TP53 rs201753350 germline variant in the population, \(p^\prime = 0.13\%\) based on the gnomAD-Exomes database; \(d\) is the desired absolute level of precision or the confidence limit, \(d = 5\%\); \(deff\) is the design effect, which measures the variation of prevalence estimates from the true population value given the sampling design.20,21

On the other hand, the sample size needed to determine the association between TP53 rs201753350 germline variant genotypes and the occurrence of CC among pediatric patients was computed using the equation for cross-sectional studies:22-24

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Table 1. The Todani Classification of Choledochal Cysts

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Dilatation of the extrahepatic bile duct</td>
<td>80-90</td>
</tr>
<tr>
<td>IA</td>
<td>Cystic dilation</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>Focal, segmental dilation</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>Fusiform dilation</td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>Discrete diverticuli malformation of the extrahepatic duct with a narrow stalk connection to the common bile duct</td>
<td>2</td>
</tr>
<tr>
<td>Type III</td>
<td>Intraduodenal (and occasionally intrapancreatic) dilated common bile duct</td>
<td>4-5</td>
</tr>
<tr>
<td>Type IV</td>
<td>Intra- and extrahepatic duct dilatation</td>
<td>10</td>
</tr>
<tr>
<td>IVA</td>
<td>Intrahepatic and extrahepatic bile duct dilatations</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>Multiple dilations in the extrahepatic biliary tree only</td>
<td></td>
</tr>
<tr>
<td>Type V (Caroli)</td>
<td>Multiple cystic dilations of the intrahepatic bile ducts</td>
<td>Rare</td>
</tr>
</tbody>
</table>
where \( n \) is the sample size; \( Z \) is the level of confidence, \( Z = 1.96 \); \( P \) is the expected prevalence of the TP53 rs201753350 germline variant in the population obtained from previous studies, which was 0.13% of 48,832 samples based on the gnomAD-Exomes database; and \( d \) is precision corresponding to effect size, which must be one-fourth or one-fifth of the expected prevalence if \( P \) is below 10% and is therefore \( d = 0.0325^{22,23} \).

Given these, the minimum required sample size to obtain a p-value of at least 0.05 is:

\[
\frac{(Z_{1-\alpha/2})^2 P(1-P)}{d^2} = \frac{(1.96)^2 \times 0.13(99.87)}{0.0325^2} = 47,219.76 \approx 47,220
\]

A minimum of 40 participants is required for determining the prevalence of the germline variant among pediatric CC patients while a minimum of 47,220 individuals is required for determining the association between the variant and the occurrence of choledochal cyst among pediatric patients. However, given the rarity of pediatric CC cases admitted and currently consulting at the study site, and time and budget constraints, only at least 20 patients were recruited as cases. The unexposed/exposed ratio used was 1:4 to increase sample size and consequently, the statistical power of the study, which is limited by the rarity of choledochal cyst in the population. This ratio is based on the law of diminishing returns.\(^ {24} \) Hence, the total number of controls for the study was four multiplied by the minimum number of cases.

**Study Participants**

Study participants were recruited from the clinical wards of the Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, PGH. Each participant (whether classified as case or control) required at least three generations of Filipino lineage.

Inclusion criteria for cases included Filipino patients aged 18 years and below, diagnosed with choledochal cyst using ultrasonography, CT scan, MRI, MRCP, or intraoperative cholangiography. Written informed consent forms (both consent and assent forms) were obtained from either the parents or legal guardians of study participants. For the controls, genomic DNA samples were collected from Filipino adult patients with no known bile duct disorders, biliary atresia, and polycystic liver disease or chronic illness (Figure 1).

**Polymorphism Analysis**

Genomic DNA was extracted from four (4) mL peripheral blood samples collected from the study participants. Extraction was performed using the Qiagen QIAamp DNA Blood Midi Kit (Qiagen, Santa Clara, CA, USA), according to the manufacturer’s recommendations. The concentration and purity of the DNA samples were quantified using the Thermo Scientific™ Nano-Drop Spectrophotometer (NanoDrop Technologies, Wilmington, DE). The region containing the \( TP53 \) gene was amplified using polymerase chain reaction (PCR) using the following primers: forward primer 5’–GAGACCTGTGGGAAGCGAAA–3’ and the reverse primer 5’–GGGGGACTGTAGATGGGTGA–3’. Primers were designed based on the published \( TP53 \) sequence (Genbank Accession No. NG_017013) using Primer-BLAST (https://www.ncbi.nlm.nih.gov/tools/primer-blast/).

The samples were amplified using the following PCR conditions: initial denaturation at 94°C for 5 minutes, 40 cycles of denaturation at 94°C for 30 seconds, annealing at 58-62°C for 30 seconds, and extension at 72°C for 30 seconds, final extension phase at 72°C for 10 minutes. Amplicon quality was checked by 2% agarose gel electrophoresis. Direct sequencing of PCR products was done using the ABI 3730xI system (Macrogen, Inc., South Korea). Sequencing results were analyzed by comparing the patient sample sequences with the published wild-type \( TP53 \) genomic DNA sequence (Genbank Accession No. NG_017013) using the Staden Package 2.0.0b11 and BioEdit Sequence Alignment Editor version 7.0.9.

**Data Processing and Analysis**

Student’s t-test was used to compare the demographic and clinical characteristics of the cases and controls while the Fischer’s exact test was used to compare allelic and genotypic frequencies. A p-value of less than 0.05 in both tests was considered statistically significant. The prevalence ratios
Table 2. Demographic and Clinical Characteristics of the Choledochal Cyst Cases (n=22)

<table>
<thead>
<tr>
<th>Age in years (mean ± SD)</th>
<th>5.14 ± 4.95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male:female)</td>
<td>1:1.75</td>
</tr>
<tr>
<td>Family history of hepatobiliary disease</td>
<td>0</td>
</tr>
<tr>
<td>Type of CC</td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>14 (63.64%)</td>
</tr>
<tr>
<td>Type II</td>
<td>0</td>
</tr>
<tr>
<td>Type III</td>
<td>1 (4.54%)</td>
</tr>
<tr>
<td>Type IV-A</td>
<td>7 (31.82%)</td>
</tr>
<tr>
<td>Type IV-B</td>
<td>0</td>
</tr>
<tr>
<td>Type V</td>
<td>0</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>18 (81.82%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (18.18%)</td>
</tr>
<tr>
<td>Palpable abdominal mass</td>
<td>6 (27.27%)</td>
</tr>
<tr>
<td>Acholic stool</td>
<td>10 (45.46%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (18.18%)</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>Cyst rupture</td>
<td>0</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>10 (45.46%)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>9 (40.91%)</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>14 (63.64%)</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>0</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (4.54%)</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>10 (45.46%)</td>
</tr>
</tbody>
</table>

Table 3. Distribution of TP53 Alleles among Choledochal Cyst Patients (n = 22) and controls (n = 87)

<table>
<thead>
<tr>
<th>Allele</th>
<th>Overall prevalence (% , n = 218)</th>
<th>CC (n = 44)</th>
<th>Controls (n = 174)</th>
<th>PR** (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G allele</td>
<td>77.06 (43)</td>
<td>97.73%</td>
<td>71.84 (49)</td>
<td>0.08 (0.01 – 0.55)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>A allele</td>
<td>22.94 (1)</td>
<td>2.27%</td>
<td>28.16 (49)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*AF - allele frequency ** PR - prevalence ratio

Table 4. Distribution of TP53 Genotypes among Choledochal Cyst Patients (n = 22) and Controls (n = 87)

<table>
<thead>
<tr>
<th>TP53 genotype</th>
<th>Overall prevalence (% , n = 109)</th>
<th>CC (n = 22)</th>
<th>Controls (n = 87)</th>
<th>PR** (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>G/G</td>
<td>54.13 (21)</td>
<td>95.45</td>
<td>43.68 (38)</td>
<td>0.06 (0.01 – 0.40)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>A/G</td>
<td>45.87 (1)</td>
<td>4.55</td>
<td>56.32 (49)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A/A</td>
<td>0 (0)</td>
<td>0</td>
<td>0 (0)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*GF - genotype frequency ** PR - prevalence ratio

(used to represent estimated risk of choledochal cyst among those with a certain allele and genotype) and 95% confidence intervals of each genotype was computed using conditional logistic regression. A likelihood-ratio p-value (two-tailed) of less than 0.05 was considered statistically significant. All statistical analyses were performed using Epi Info 7.2.0.1.

RESULTS

A total of 120 participants (24 CC cases and 96 controls) were recruited. However, 10 participants had inconclusive results while one rescinded consent; hence, data from these participants were excluded. Clinico-demographic characteristics of CC cases (n = 22) are summarized in Table 2. There is a significant difference between the mean age of the cases and controls, which are 5.14 and 30.49 years, respectively, since the cases are from the pediatric population (below 18 years) while the controls are adults. On the other hand, the male-to-female ratios of both groups are at comparable 1:1.75 and 1:1.35 for the CC cases and controls, respectively.

Only three CC types (Types I, III, and IVA) were reported in the study, with Type I as the most common type (63.64%) followed by Type IVA (31.82%). Most of the patients reported having jaundice (81.82%) and acholic stools (45.46%). The most commonly reported complications due to choledochal cyst are portal hypertension (63.64%), liver cirrhosis (45.46%), and cholangitis (40.91%). There was only one mortality and 10 out of 22 patients received a liver transplant for end-stage liver disease secondary to biliary cirrhosis (45.46%).

TP53 genotyping was done for all participants (Table 3). The overall prevalence of the A and G alleles among the study population were 22.94% and 77.06%, respectively. The allelic frequencies for the A and G alleles among cases were 0.02 and 0.98, respectively, and 0.28 and 0.72, respectively, among the controls. Therefore, the G allele has a significantly higher frequency among both cases and controls. There is a significantly lower estimated risk of choledochal cyst occurrence in individuals with the A allele than the G allele (PR: 0.08, 95% CI: 0.01 – 0.55).

Among the study population, 59 individuals (54.13%) have the homozygous G/G genotype while 50 individuals (45.87%) have the heterozygous A/G genotype (Table 4). The genotypic frequency of G/G is 0.91 and 0.44 among CC cases and controls, respectively, while that of A/G is 0.09 and 0.56, respectively. Hence, the homozygous G/G genotype is more frequent among CC cases while the heterozygous A/G genotype is more frequent among controls. Similar to
the TP53 alleles, there is a significantly lower estimated risk of choledochal cyst occurrence in individuals with the A/G genotype compared to the G/G genotype (PR: 0.06, 95% CI: 0.01 – 0.40).

DISCUSSION

Frequency of TP53 rs201753350 allelic variants and genotypes

This is the first study to document the allelic and genotypic frequencies and overall prevalence of the TP53 single nucleotide variants in codon 91 in a Filipino population. The results demonstrate that the A allele occurs less frequently than the G allele, which is in agreement with the observed trend in Asian populations. Its frequency on a global scale is approximately 1%, with Asian populations (especially East Asian) reporting the highest frequency (0.95%) according to the Allele Frequency Aggregator (ALFA) Project. The reported frequency in non-Asian populations is only 0.06% (https://www.ncbi.nlm.nih.gov/snp/rs201753350#frequency_tab). In addition, the A allele appears less frequently among choledochal cyst cases in the study population than the G allele, similar to the trend observed in pathogenic mutation studies done in other Asian populations, such as Chinese, Thai, Taiwanese, Japanese, and Korean.

The current study showed the prevalence ratios of TP53 alleles and genotypes among Filipino pediatric choledochal cyst patients. There is a significantly lower risk of choledochal cyst occurring among those with the A allele compared to those with the G allele, which is also the pattern seen with the heterozygous genotype. The ClinVar database showed conflicting reports on the clinical significance and pathogenicity of the rs201753350 germline mutation (c. 91G>A), with some papers associating this mutation with the hereditary cancer-predisposing syndrome and Li-Fraumeni syndrome while others annotated it as benign. However, it is more likely that the pathogenicity of this variant is overestimated because it has only been identified within Asian populations and is infrequent in other populations. The frequency of the variant within the study population, as well as the PolyPhen-2 online predictive tool for SNP pathogenicity (http://genetics.bwh.harvard.edu/pph2/), may suggest that it is more benign than pathogenic.

TP53 rs201753350 germline variant is more likely benign

In the study, there were more controls with a heterozygous A/G genotype than the homozygous G/G genotype while there was only one choledochal cyst patient with the mutation. This implies that the TP53 rs201753350 germline variant is more likely to be benign than pathogenic, corresponding to the low estimated risk of choledochal cyst occurrence based on the calculated prevalence ratios in the study.

Large-scale studies evaluating the activity of the TP53 rs201753350 protein show reduced but functional transcriptional activity with no dominant negative effects observed, further supporting the benignity of the variant. This may be because the affected residue (p.V31I) does not directly interact with p53 target proteins. The TP53 gene encodes for p53, a transcription factor that contains a highly acidic amino terminus with two transcriptional activation domains (TADs) – TAD1 and TAD2 – that function as important binding sites for many proteins including the RNA synthesis machinery (i.e., TATA-box binding protein), chromatin modifiers (i.e., p300), and p53 inhibitors (i.e., MDM2). While the tumor suppressive function of p53 is facilitated by the DNA-binding domain, its TADs are equally important to recruit transcriptional machinery for RNA synthesis, open adjacent chromatin, and facilitate the ubiquitin-mediated proteolysis of p53.

The V31I residue is located in TAD1, specifically in the long loop or linker region between the TAD1 residues that form helices when bound to their target proteins. Hence, a mutation in this residue would not significantly affect the transactivation potential of TAD1 unless it occurs with other mutations, leading to premature incapacitation of p53 activity. Particularly, there is truncated activity if V31I occurs with mutations and post-translational modifications (i.e., protein phosphorylation) in the key residues that directly interact with proteins, namely, F19, L22, W23, L25, L26. Therefore, it is possible that there are other mutations within the TP53 gene that predisposed the development of choledochal cyst among the patients in this study.

TP53 rs201753350 germline variant and CC clinical manifestations

There is no clear association between the choledochal cyst type and the TP53 rs201753350 genotype since only one patient had the mutation. This patient had a Type IVA cyst type, which is the second most common type of cyst among the patients in the study and in other populations. Type I cysts are the most common type, occurring in 80–90% of cases, while Type IVA cysts have been reported in 15–20%. These two types have the highest risk of developing into malignancy in adults, but have low incidence below 18 years. Cholangiocarcinoma is the most common cancer associated with these cysts, with TP53 being one of the most mutated genes reported. Other genetic abnormalities that may have led to the development of the cysts include chromosomal anomalies and other SNPs.

There is also no clear association between the symptoms observed among the study population and the TP53 rs201753350 genotype. The only heterozygote was a 16-year-old female who complained of abdominal pain and vomiting, which was also observed in other patients but were not common in this population. According to the study, the most common complaint related to choledochal cysts is jaundice, which has been reported in all pediatric age groups from other populations. Jaundice is caused by high bilirubin levels in the blood which is not properly excreted into the bile ducts.
In choledochal cyst, there is a stricture at the distal part of the duct due to chronic inflammation, causing biliary stasis that will eventually lead to obstructive jaundice. While all symptoms of the classic choledochal cyst triad of abdominal pain, palpable abdominal mass, and jaundice were present in the study population, none of the cases complained of having all three despite being commonly reported in Asians. Acholic stools, on the other hand, are reported to be more commonly seen in neonates and young infants. This was not necessarily seen in the study, with a 2- to 18-year age range of those presenting with acholic stools. Similar to jaundice, acholic stools are also indicative of abnormal levels of bilirubin in the body, particularly lower levels present in the gut and excreted through feces as urobilins.

There is also no clear association between the reported complications and the mutation despite the only heterozygote being the only one without reported complications. However, complications associated with choledochal cysts must be monitored given that the risk for postoperative complications, hepatolithiasis, and strictures increase as more complications are observed. Portal hypertension is the most common complication among the cases in this study but is rare in other populations. It occurs secondary to biliary cirrhosis, as seen in 8 out of 14 patients (57.14%) with portal hypertension who also had liver cirrhosis. Other possible etiologies for portal hypertension include compression or obstruction of the portal vein and extrahepatic portal vein thrombosis.

Cholangitis is another common complication found in the study population that is also seen in 30% of cases in other populations. Several studies observed cholangitis to be predominant in Type I and Type IVA cysts, which are the most common types in the study population. Cholestasis is characteristic of choledochal cysts, increasing intraluminal pressure within the bile duct, and leading to dilation and chronic inflammation. Recurrent cholangitis is a primary indication for liver transplantation, as is liver cirrhosis that is commonly associated with Type IVA cysts; however, majority of the current patients who received a liver transplant had Type I cysts instead (70%). Liver cirrhosis may be due to the pancreatic reflux that causes enzymatic destruction of the walls of the bile ducts of either cyst type. In this study, those who underwent liver transplantation had either cholangitis (30%), liver cirrhosis (40%), or both (50%).

Limitations of the Study

The present study used availability or convenience sampling due to the small number of patients currently following up in the Division of Pediatric Gastroenterology, Hepatology and Nutrition of the PGH, a tertiary government hospital that receives referrals from all over the country. This is more likely to produce biased estimates due to sampling bias compared to simple random sampling methods. In addition, only the prevalence of TP53 rs201753350 germline variant, which was previously found to be significant in populations genetically similar to Filipinos, and its association with CCs were investigated due to time and budget constraints.

CONCLUSION

This study showed that the frequency of the TP53 c.91G>A rs201753350 germline mutation (A allele) is lower than the G allele among clinically diagnosed Filipino pediatric choledochal cyst patients, which is similar to the observed trend in other Asian populations. The significant low estimated risk of choledochal cyst among those with the A allele and with a heterozygous A/G genotype implies that this mutation is more likely to be benign within the Filipino population. There is no clear association between the choledochal cyst type, symptoms, and complications observed among the cases and the TP53 rs201753350 germline mutation. Hence, there is no significant evidence to suggest an association between the TP53 rs201753350 germline variant and the occurrence of choledochal cysts in Filipinos.

Due to the possibility of other mutations occurring with the TP53 rs201753350 variant, further studies must be done to investigate other mutations within and beyond the TP53 gene to look for other mutations that may be associated with choledochal cyst development. Analysis of the whole TP53 gene for mutation hotspots and gene expression may help narrow down other possible mutations.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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Association of TP53 Variant and Choledochal Cyst among Filipinos


