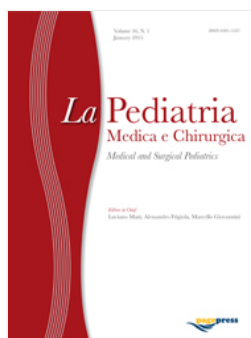


## Vol. 45 No. 1 (2023)

Published: 22-02-2023



### ABSTRACT BOOK



#### 52° Congresso Nazionale della Società Italiana di Chirurgia Pediatrica | Ancona, 20-22 ottobre 2022

The Editors

<https://doi.org/10.4081/pmc.2023.319>

0 0 0 0

274 PDF: 152

PDF

### ARTICLES



#### Protein tyrosine phosphatase non-receptor type 22 C1858T gene polymorphism in children with Down syndrome and autoimmune thyroid diseases

Muhammad Faizi, Nur Rochmah, Soetjipto Soetjipto, Anang Endaryanto, Sukmawati Basuki, Yuni Hisbiyah, Rayi Kurnia Perwitasari

<https://doi.org/10.4081/pmc.2023.283>

0 0 0 0

236 PDF: 73 HTML: 3

PDF

HTML



#### GERD surgery in non-neurologic patients: Modified Laparoscopic Hill-Snow Repair is a valid alternative to

## Nissen fundoplication. Results of a 20 years of follow-up

Salvatore Fabio Chiarenza, Lorenzo Costa, Maria Luisa Conighi, Elisa Zolpi, Lorella Fasoli, Giulia Brooks, Enrico La Pergola, Cosimo Bleve

<https://doi.org/10.4081/pmc.2023.310>

0 0 0 0

338 PDF: 157 HTML: 3

PDF

HTML



## Pediatric primary spontaneous pneumothorax: a comparison of treatment at pediatric surgery vs. thoracic surgery departments

Maria Enrica Miscia, Maria Castellano, Stella Chiarini, Giuseppe Lauriti, Marco Casaccia, Pierluigi Lelli Chiesa, Gabriele Lisi

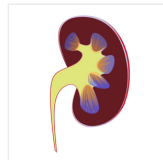
<https://doi.org/10.4081/pmc.2023.303>

0 0 0 0

324 PDF: 55 HTML: 1

PDF

HTML



## Uretero-pelvic junction obstruction in children: Is vascular hitch an effective and safe solutions in very long term outcome? Report of 25 years follow-up

Salvatore Fabio Chiarenza, Elena Carretto, Valeria Bucci, Samuele Ave, Giuseppe Pulin, Cosimo Bleve

<https://doi.org/10.4081/pmc.2023.309>

0 0 0 0

395 PDF: 87 HTML: 3

PDF

HTML

FOR AUTHORS

**SUBMIT YOUR PAPER**

# Editorial Board

## Editors in Chief

### Salvatore Fabio Chiarenza

Director of Pediatric Surgery Unit, Regional Center of Pediatric Urologic and Minimally Invasive Surgery and New Technologies, AULSS 8, *S. Bortolo Hospital*, Vicenza, Italy

### Alessandro Frigiola

Department of Pediatric Cardiology, *San Donato Hospital*, Milan, Italy

### Luca Rosti

Sant'Anna Clinic, *Sorengo*, Switzerland

### Andrew Balas

Biomedical Research Innovation Laboratory, *Augusta University*, GA, USA

## Associate Editors

Massimo Agosti, Neonatology, *Neonatal Intensive Care, and Pediatric Unit of Verbano, Filippo Del Ponte Hospital, University of Insubria, Varese, Italy*

Magd Ahmed Kotb, *Department of Pediatrics, Pediatric Hepatology, Cairo University, Egypt*

Nargis Albert Labib, *Department of Public Health and Community Medicine, Cairo University, Egypt*

Enrico La Pergola, *Paediatric Surgery Unit, Ospedale San Bortolo, Vicenza, Italy*

Fabio Mosca, *Department of Clinical and Community Sciences, IRCCS Foundation Ca' Granda Hospital, Milan, Italy*

Sameh Shehata, *Department of Pediatric Surgery, University of Alexandria, Alexandria, Egypt*

Youssef Tammam, *Department of Pediatric Cardiology and Cardiac Surgery, San Donato Hospital, Milan, Italy*

Francesca Vinci, *Doctor in specialist training in Paediatric Surgery, University "Federico II" of Naples, c/o U.O.C. Paediatric Surgery San Bortolo Hospital, Italy*

## Editorial Board

Raul Abella, *Department of Pediatric Cardiothoracic Surgery, Hospital Universitari Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain*

Aldo Agnetti, *Department of Maternal and Child Health, University Hospital of Parma, Parma, Italy*

Carlo Agostoni, *Department of Pediatrics, San Paolo Hospital, Milan, Italy*

Giuseppe Banfi, *Department of Biomedical Sciences for Health, University of Milan, Milan, Italy*

Mario Barbarini, *Neonatal Intensive Care and Neonatology Unit, Sant'Anna Hospital, Como, Italy*

Graziano Barera, *Laboratory of Pediatric Endocrinology and Department of Pediatrics, Scientific Institute H San Raffaele, University of Milan, Milan, Italy*

Roberto Bellò, *Neonatal Intensive Care Unit, Lecco Hospital, Lecco, Italy*

Enrico Bertino, *Department of Pediatric and Adolescent Sciences, University of Turin, Turin, Italy*

Sergio Bernasconi, *Department of Maternal and Child Health, University Hospital of Parma, Parma, Italy*

Cosimo Bleve, *Department of Pediatric Surgery, Vicenza Hospital, Vicenza, Italy*

Gianfranco Butera, *Pediatric Cardiology, GUCH Unit and Cardiac Surgery, San Donato Hospital, Milan, Italy*

Raffaele Calabrò, *Fetal Cardiology Unit, Department of Gynecology and Obstetrics, University Federico II of Naples, and Pediatric Cardiology, Second University of Naples-Monaldi Hospital, Naples, Italy*

Luciano Cavallo, *Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy*

Emma Cerini, *Department of Pediatric Ecocardiography, Carlo Poma Hospital, Mantua, Italy*

Massimo Chessa, *Department of Pediatric Cardiology and Congenital Cardiopathies in Adults, San Donato Hospital, Milan, Italy*

Mariarosa Colnaghi, *Mangiagalli e Regina Elena Hospital, Milan, Italy*

Giovanni Corsello, *Department of Maternal and Child Health, University Hospital P. Giaccone-University of Palermo, Palermo, Italy*

Carlo Dani, *Department of Neurosciences, Drugs and Child Health, University of Florence, Italy*

Bruno De Bernardi, *Department of Paediatric Haematology and Oncology, Giannina Gaslini Children's Hospital, Genoa, Italy*

Marc R. De Leval, *Cardiothoracic Surgery, Great Ormond Street Hospital for Children NHS Trust, London, UK*

Filippo de Luca, *Pediatric Unit, G.Martino Hospital, University of Messina, Messina, Italy*

Ciro Esposito, *Pediatric Surgery School, University Federico II of Naples, Naples, Italy*

Vassilios Fanos, *Pathology and Neonatal Intensive Care, Infant Care and Nursery Unit, University Hospital of Cagliari, Cagliari, Italy*

Pietro Ferrara, *Catholic University of the Sacred Heart, Bio-Medical Campus, Rome, Italy*

Anna Fesslova, *Pediatric and Neonatology School, University of Milan, Milan, Italy*

Monica Fumagalli, *Pediatric Nursery School, Mangiagalli e Regina Elena Hospital, Milan, Italy*

Alessandro Giamberti, *Congenital Diseases from Infants to Adults School, San Donato Hospital, Milan, Italy*

Maria Lorella Giannà, *Department of Clinical and Community Sciences, IRCCS Foundation Ca' Granda Hospital, Milan, Italy*

Mario Lima, *Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy*

Gianluca Lista, *Clinical Institutions of Improvement, Milan, Italy*

Guy Magalon, *Plastic Surgery Service, de la Conception Hospital, Marseille, France*

Giovanna Mangili, *Department of Neonatal Pathology, Ospedali Riuniti di Bergamo, Bergamo, Italy*

Gianantonio Manzoni, *Pediatric Urology Unit, IRCCS Foundation Ca' Granda Hospital, Milan, Italy*

Maurizio Marasini, *Cardiology Unit, , Giannina Gaslini Children's Hospital, Genoa, Italy*

Carlo Mazza, *Neurosurgeon private practitioner, Verona, Italy*

Emilio Merlini, *Pediatric Urology Unit, Regina Margherita Hospital, Turin, Italy*

Lorenzo Mirabile, *Anesthesia and Intensive Care Unit, Meyer Pediatric Hospital, Florence, Italy*

Halkawt Nuri, *Duhok Hospital, Duhok, Iraq*

Luigi Orfeo, *Neonatology and Neonatal Intensive Care Unit, Gaetano Rummo Hospital, Benevento, Italy*

Ezio Maria Padovani, *Pathology and Neonatal Intensive Care Unit, University Hospital of Verona, Verona, Italy*

Fernando Maria Picchio, *Pediatric Cardiology Unit, University of Bologna-Sant'Orsola Malpighi Hospital, Bologna, Italy*

Giuseppe Pomà, *Cardiovascular Center E. Malan, San Donato Hospital, Milan, Italy*

Lorenza Pugni, *Department of Clinical and Community Sciences, IRCCS Foundation Ca' Granda Hospital, Milan, Italy*

Luca Antonio Ramenghi, *Neonatal Pathology Unit, Giannina Gaslini Children's Hospital, Genoa, Italy*

Giovanna Riccipetitoni, *Pediatric, Surgical Pediatric and General Surgery School, University of Milan, Milan, Italy*

Enrica Riva, *Department of Pediatrics, San Paolo Hospital-University of Milan, Milan, Italy*

Paola Roggero, *Faculty of Medicine and Surgery, University of Milan, Milan, Italy*

Mauro Stronati, *Neonatology Unit, Department of Maternal and Child Health, University of Pavia, Pavia, Italy*

Alberto Giovanni Ugazio, *Italian Society of Pediatrics, Rome, Italy*

Luca Vaianti, *Department of Biomedical Sciences for Health, University of Milan, Milan, Italy*

Alessandro Ventura, *Clinical Pediatric Unit, Maternal-Child Burlo Garofolo Hospital of Trieste, Trieste, Italy*

Lucio Zannini, *Cardiovascular Surgery Unit, Giannina Gaslini Children's Hospital, Genoa, Italy*

anni Franco Zanon, *Department of Maternal and Child Health, University of Padua, Padua,*

Italy

Gian Vincenzo Zuccotti, *Clinical Pediatric Unit, Children's Hospital V. Buzzi, Milan, Italy*

## FOR AUTHORS

### SUBMIT YOUR PAPER

---

[Guide for Authors](#)

---

[Benefits for Authors](#)

---

[How to write a scientific paper](#)

---

[How to write a Review article](#)

---

[Article Processing Charge](#)

---

## FOR REVIEWERS

[Benefits for Reviewers](#)

---

[How to review](#)

---

[Thanks to Reviewers](#)

---

## INDEXING

[PubMed](#)

---

[Scopus](#)

---

[DOAJ](#)

---

## MOST READ LAST MONTH

[Ibuprofen versus steroids: risk and benefit, efficacy and safety](#)

 389

---

[Human milk: composition and health benefits](#)

 268

---

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/368714280>

# Protein tyrosine phosphatase non-receptor type 22 C1858T gene polymorphism in children with down syndrome and autoimmune thyroid diseases

Article in *La Pediatria medica e chirurgica: Medical and surgical pediatrics* - February 2023

DOI: 10.4081/pmc.2023.283

CITATIONS

0

READS

3

5 authors, including:



**Rayi Kurnia Perwitasari**

Dr Soetomo General Hospital

8 PUBLICATIONS 0 CITATIONS

[SEE PROFILE](#)



**Sukmawati Basuki**

Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

24 PUBLICATIONS 53 CITATIONS

[SEE PROFILE](#)



**Yuni Hisbiyah**

Dr Soetomo General Hospital

18 PUBLICATIONS 16 CITATIONS

[SEE PROFILE](#)



**Soetjipto Soetjipto**

Airlangga University

67 PUBLICATIONS 483 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



diabetes mellitus, thyroid [View project](#)



Tuberculosis (TB) in Indonesia [View project](#)

# Protein tyrosine phosphatase non-receptor type 22 C1858T gene polymorphism in children with down syndrome and autoimmune thyroid diseases

Correspondence: Soetjipto Soetjipto, Mayjend Prof. Dr. Moestopo No. 6-8, Surabaya, East Java, Indonesia, 60286.  
Tel.: +6281331340518.  
E-mail: Soetjipto1950@gmail.com

Key words: PTPN-22 C1858T polymorphism, hypothyroidism, down syndrome, autoimmunity.

Acknowledgments: The authors would like to express their gratitude to the patients, family patients, tropical disease team of Universitas Airlangga and endocrine staff at the Faculty of Medicine, Universitas Airlangga - Dr. Soetomo Hospital in Surabaya, Indonesia.

Contributions: All authors have read and approved the manuscript. MF: the study's conception, design, and supervision; NR: study's design, drafting, data collection, and analysis of data; SS: evaluation of ethical aspects, literature analysis; AE: approved the final draft, analysis of data and literature; SB: analysis and interpretation of data; YH: analysis of data and literature; RKP: revision critically for important intellectual content.

Conflict of interest: There are no conflicts of interest declared by the authors.

Funding: This research was funded by internal grant of doctoral dissertation research Faculty of Medicine University of Airlangga.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate: The Ethics Committee of Dr. Soetomo General Hospital approved this study (Ref. No. 1960/KEKP/IV/2020). The study is conformed with the Helsinki Declaration of 1964, as revised in 2013, concerning human and animal rights. All patients participating in this study signed a written informed consent form for participating in this study.

Informed consent: Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Received for publication: 19 January 2022.  
Revision received: 28 November 2022.  
Accepted for publication: 28 December 2022.

Publisher's note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

©Copyright: the Author(s), 2023  
Licensee PAGEPress, Italy  
La Pediatria Medica e Chirurgica 2023; 45:283  
doi:10.4081/pmc.2023.283

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

Muhammad Faizi,<sup>1,3</sup> Nur Rochmah,<sup>1,3</sup>  
Soetjipto Soetjipto,<sup>2,3</sup> Anang Endaryanto,<sup>1,3</sup>  
Sukmawati Basuki,<sup>3,4</sup> Yuni Hisbiyah,<sup>1,3</sup>  
Rai Kurnia Perwitasari<sup>1</sup>

<sup>1</sup>Department of Child Health, Faculty of Medicine, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, East Java, Indonesia; <sup>2</sup>Department of Medical Biochemistry, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia; <sup>3</sup>Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia; <sup>4</sup>Department of Parasitology, Faculty of Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia

## Abstract

Autoimmune Thyroid Disease (AIT) is a frequent comorbidity in Down Syndrome (DS). Protein Tyrosine Phosphatase Non-Receptor Type 22 C1858T (PTPN-22 C1858T) gene polymorphisms have a role in the progression of AIT. The study on PTPN-22 C1858T gene polymorphism as the risk factor of AIT in DS children is still limited. This study aims to evaluate PTPN-22 C1858T polymorphism in Indonesian DS children. A cross-sectional study involving 31 DS children with hypothyroidism (19 boys/12 girls) was conducted for ten months from February to November 2020 at Dr. Soetomo General Hospital Surabaya. The PTPN-22 C1858T gene polymorphism was analyzed using Polymerase Chain Reaction-Restriction-Fragment-Length Polymorphism (PCR-RFLP). Anti-Thyroid Peroxidase (Anti-TPO) and Anti-Thyroglobulin (Anti-TG), FT4, T3, and TSH levels were analyzed using Enzyme-Linked-Immunosorbent-Assay (ELISA). The mean age of the subjects was 19.45±17.3 months. The CT variant of PTPN-22 C1858T was observed in all subjects. The mean level of T3, FT4, and TSH were 1.59±0.45 ng/mL, 0.81±0.57 ng/mL, 0.22±0.21 µU/mL, respectively. Around 83.9% of patients suffered from central hypothyroidism, 12.9% from primary hypothyroidism, and 3.2% from subclinical hypothyroidism. The positive anti-TG and anti-TPO were observed in 96.8% and 58.1%, respectively. CT variant was observed in Indonesian DS children who suffered from hypothyroidism.

## Introduction

Down syndrome is the most common chromosomal abnormality reported. According to WHO, the global DS incidence is 1-10 per 1000 live births.<sup>1</sup> Data from the Indonesian Down Syndrome Association shows that there are 300.000 DS cases in



Indonesia.<sup>2</sup> Children with DS tend to have many comorbidities, including thyroid dysfunction. It is estimated that 4-19% of children with DS have thyroid dysfunction, and the prevalence increases by 54% in childhood due to genetic and environmental causes.<sup>3</sup> Immune dysregulation in DS children is considered to be the cause of the increased prevalence of many autoimmune diseases, such as Autoimmune Thyroid Diseases (AIT), as proven by the presence of thyroid antibodies such as Anti-Thyroid Peroxidase (Anti-TPO) and Anti-Thyroglobulin (Anti-TG).<sup>4</sup>

Protein Tyrosine Phosphatase Non-receptor-22 (PTPN-22 C1858T) is located on chromosome 1p13.2 and influences the progress of AIT. The PTPN-22 C1858T is found mostly in lymphoid tissue and helps to modulate immune system activity in response to negative signals.<sup>5,6</sup> Single nucleotide polymorphism at position 1858 (rs2476601) in the PTPN-22 C1858T gene's coding sequence results in a change of arginine (R) to tryptophan (W) at codon 620 of the Lyp protein, causing damage to the binding Lyp with Csk on the C-terminal domain of PTPN-22 C1858T. The self-expression of the T cell receptor (TCR) avoids negative selection, leading to autoreactivity in the T cell. Polymorphism of PTPN-22 C1858T correlates to many autoimmune diseases, such as AIT.<sup>7,8</sup> The PTPN-22 C1858T polymorphism study in DS children with AIT has not been widely researched. Therefore, this study was designed to evaluate PTPN-22 C1858T gene polymorphisms in Indonesian DS children with AIT.

## Materials and Methods

### Participants

This cross-sectional study involved 31 children with DS with hypothyroidism confirmed by karyotyping attending Dr. Soetomo General Hospital Surabaya from February and November 2020 who met the inclusion and exclusion criteria (Figure 1). The sampling technique was consecutive sampling. The inclusion criteria for the subjects were as follows: i) Children with newly diagnosed DS with hypothyroidism an outpatient at Dr. Soetomo General Hospital prior to starting levothyroxine; ii) Age range: 1 month to 18 years; iii) Parents consented to participate in the study.

Patients who met the following exclusion criteria were excluded from this study: i) Children with DS who are severely ill and require PICU care; ii) DS children with neurological illnesses (meningitis, meningoencephalitis, hydrocephalus).

This study was approved by the Ethics Committee of Dr. Soetomo General Hospital (Ref. No. 1960/KEKP/IV/2020).

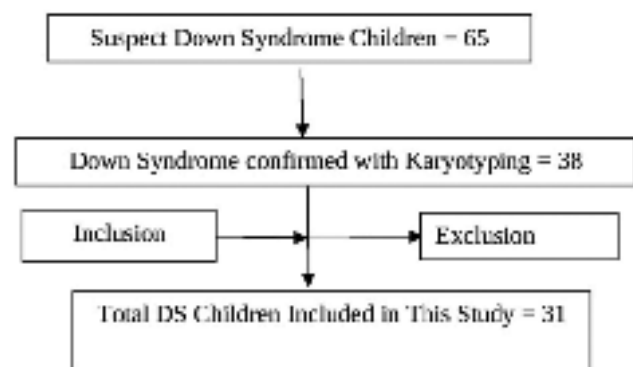


Figure 1. Flowchart for Selection Criteria.

All relevant national rules, institutional policies, and the tenets of the Helsinki Declaration were followed in the research for human use, which was authorized by the authors' institutional review board or equivalent body.<sup>9</sup>

### Methodology

The blood sample was withdrawn to analyze the thyroid function (FT4, TSH, antibody markers [antibody thyroid peroxidase (anti-TPO), antibody thyroglobulin (anti-TG)] and genetic polymorphism.

Anti-TPO examination used a Demeditec kit (Demeditec Diagnostics GmbH, catalog number: DE7580): Positive (>75 IU/mL), The TgAb values were classified as follows using a Demeditec kit (Demeditec Diagnostics GmbH, catalog number: DE7590): Positive ( $\geq 150$  IU/mL). The Triiodothyronine Total (T3) ELISA kit with catalog number CAN-T3-4220, Free Thyroxine (FT4) ELISA kit with catalog number CAN-FT4-4340, Thyroid Stimulating Hormone (TSH) with catalog number CAN-TSH-4080 by Diagnostic Biochem Canada in Canada (Table 1). The normal values of FT4 were 1.03 – 1.73 for cord blood and 1.0 – 2.1 for children age 2-7 years, normal values for T3 were 14 – 86 for

Table 1. Participant characteristics.

Characteristic	Value
Age (month), mean $\pm$ SD	19.45 $\pm$ 17.3
Sex, n (%)	
Boy	19 (61.3)
Girl	12 (38.7)
Maternal Ethnic, n (%)	
Javanese	26 (83.9)
Madura	2 (6.5)
Chinese	1 (3.2)
Bugis	1 (3.2)
Batak	1 (3.2)
Paternal Ethnic, n (%)	
Javanese	26 (83.9)
Madura	3 (9.7)
Chinese	2 (6.5)
Karyotyping, n (%)	
Free Trisomy (47XY+21)	14 (45)
Free Trisomy (47XX+21)	10 (32)
Mosaic (46XY;47XY+21)	5 (16)
Mosaic (46XX;47XX+21)	2 (7)
Autoimmune Marker, n (%)	
Positive Anti-TPO	18 (58.1)
Positive Anti-TG	30 (96.8)
Positive Both of Anti-TPO & Anti-TG	18 (58.1)
Cummulative Positive Autoimmune Marker	30 (96.8)
Cummulative Negative Autoimmune Marker	1 (3.2)
Diagnosis, n (%)	
Central hypothyroidism	26 (83.9)
Primary hypothyroidism	4 (12.9)
Subclinical hypothyroidism	1 (3.2)
Value, mean (ng/mL)	
T3	1.59 $\pm$ 0.45
FT4	0.81 $\pm$ 0.57
TSH, mean ( $\mu$ U/mL)	0.22 $\pm$ 0.21
TSH Subjects with Central Hypothyroidism, mean ( $\mu$ U/mL)	0.22 $\pm$ 0.22
Other Congenital Anomalies, n%	
Congenital Heart Diseases (CHD)	14 (45)
Hirschprung	1 (3.2)
No	17 (55)

cord blood and 105-269 for children age 1-5 years, and normal value for TSH for cord blood and children age 1-5 years were  $<2.5 - 17.4$  and  $0.6 - 6.3$ , respectively.<sup>10</sup>

The PTPN-22 C1858T polymorphism was analyzed from Peripheral Blood Mononuclear Cell (PBMC) using QIAamp®DNA Mini Kit. Protein Tyrosine Phosphatase Non-receptor-22 (PTPN-22 C1858T) genotyping was performed using Polymerization Chain Reaction-Restriction-Fragment-Length-Polymorphism (PCR-RFLP) technique with RsaI for a restriction enzyme with forward primer: 5'ACTGATAATGTTGCTTCAACCGG3', and the reverse primer: 5'TCACCAGCTTCCAAC-CAC3'. The result is divided into homozygous genotypes such as CC (176, 42 base pairs) and TT (218 base pairs) and also heterozygous genotypes such as CT (218, 176, 21 base pairs).

The PCR reactions were carried out at 95°C for 5 minutes, followed by 36 cycles at 95°C for 30 seconds, 64°C for 30 seconds, 72°C for 30 seconds, and a final incubation at 72°C for 7 minutes.

### Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 17 software (IBM Co., New York, USA). A simple descriptive analysis was conducted to explain the distribution and characteristics of the subjects and PTPN-22 C1858T polymorphisms.

## Results

Thirty-one subjects (19 boys and 12 girls) were included. The mean age was  $19.45 \pm 17.3$  months. DS children had free Trisomy 21 observed in 77% of subjects, while the others had mosaic Trisomy 21. The baseline characteristics are described in Table 1.

The mean level of T3, FT4, and TSH were  $1.59 \pm 0.45$  ng/mL,  $0.81 \pm 0.57$  ng/mL,  $0.22 \pm 0.21$   $\mu$ U/mL, respectively. Thyroid dysfunction was found in all subjects, with central hypothyroidism being the most common type of hypothyroidism (83.9%). The other types of hypothyroidism were primary hypothyroidism

(12.9%) and subclinical hypothyroidism (3.2%). Positive anti-TG was found in 96.8%, while anti-TPO was detected in 58.1% of subjects. The complete list of participants is presented in Table 1. Almost all of the subjects (96.8%) suffered from AIT.

The CT genotype was observed in all participants. The PTPN-22 C1858T genotypes were illustrated in Figure 2.

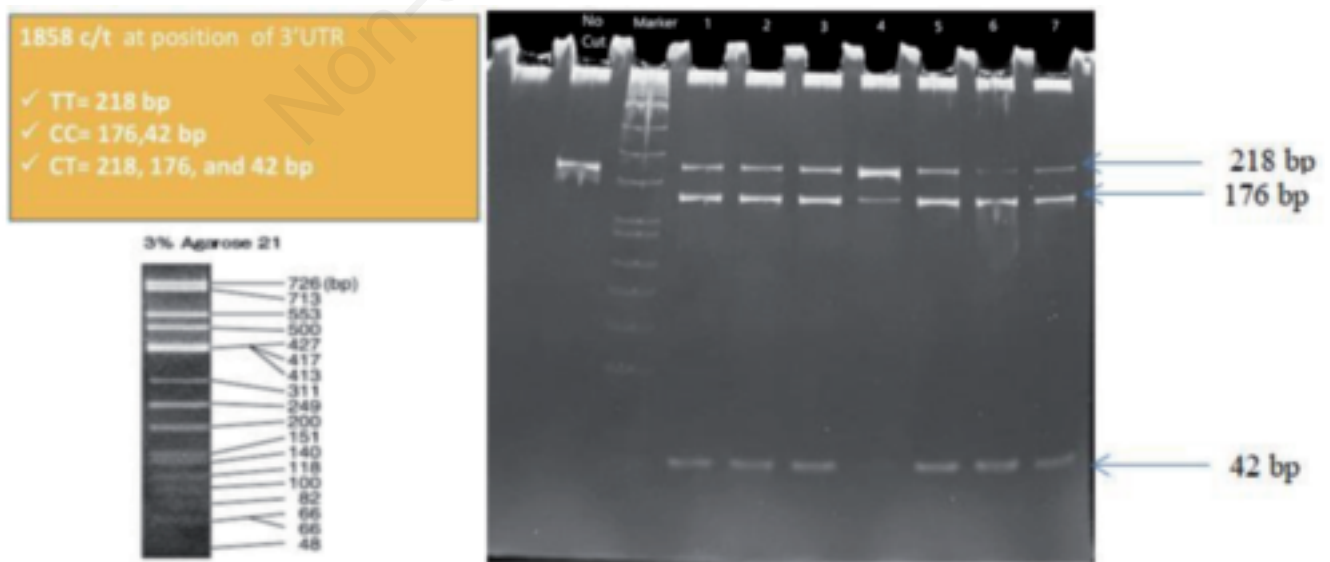
## Discussion

Our study showed that all children with DS complicated by AIT had heterozygous CT genotype variants of PTPN-22 C1858T. To the best of our knowledge, this is the first study about PTPN-22 C1858T in DS with AIT children. The CT genotype was reported more among Caucasians than in Asians with non-DS population with AIT, where the CC genotype was more prevalent, and no TT genotype was detected.<sup>11-17</sup> Yet, the CT genotype is not exclusive for AIT, it was reported in children with diabetes mellitus type 1 (T1DM), where it is more dominant followed by CC and TT, in vitiligo and immune skin diseases.<sup>18-20</sup>

Central hypothyroidism was observed in 83.9% of participants. According to Pierce *et al.* (2017), thyroid dysfunction in DS was more common than in non-DS children, but the disorder was mostly transient.<sup>21</sup> The exact cause of hypothyroidism in children with DS remains unclear. However, it was hypothesized that fetal development of the thyroid gland might have a significant role in causing hormonal dysregulation.<sup>22</sup>

In this study, positive anti-TG was dominantly observed compared to anti-TPO. This result is similar to previous studies where positive anti-TG was present in more than 80% of patients with Hashimoto Thyroiditis.<sup>23</sup> The positivity of autoimmune thyroid markers increases with age and usually becomes more prevalent after 8 years of age.<sup>24</sup> Another study also showed that anti-TPO in DS children was commonly observed at the age of  $>5$  years.<sup>25</sup> Subjects with positive anti-TPO were shown to have an increased risk of developing overt hypothyroidism in later years.<sup>25</sup>

The PTPN-22 C1858T polymorphism is associated with AIT



**Figure 2.** PCR-RFLP Electrophoresis result of PTPN-22 C1858T. The result of PCR-RFLP electrophoresis with enzyme restriction RsaI. The only genotype that was found in this study was CT, demonstrated in numbers one to seven. CT genotype was identified as three bands in 218, 176, and 42 base pairs.

risk, particularly in Caucasians ethnic compared to Asian and African American groups.<sup>26</sup> The mechanism of the PTPN-22 C1858T polymorphism in autoimmune disease was reported to be promotion of T cell autoreactivity, and increase inflammatory cytokines leading to immune cell dominance and the production of antibodies, such as anti-TPO and Anti-TG. Follicle destruction occurs as a result of local antibody production. As a result, thyroid hormone production decreases.<sup>7,27</sup>

The average age of DS children diagnosed with AIT was 19 months which support early regular screening for thyroid abnormalities in DS children at birth, six months, 12 months, and yearly.<sup>28</sup> It is beyond the premise of this study but we did not study factors associated with this early presentation contrary to the late DS who present by AIT at 6.5-7.5 years of age.<sup>21,29</sup>

Other congenital anomalies encountered among our studied DS cohort were congenital heart diseases, followed by Hirschsprung diseases. None of our studied cohort had other immune diseases such as diabetes or vitiligo, etc.

Children with Down syndrome have an increased risk of other disorders, such as acute myeloid and lymphoblastic leukemia. The characteristics and underlying factors were different when they occurred in non-DS children. In children with Down syndrome myeloid leukemia is preceded by a preleukemic clone (transient leukemia or transient myeloproliferative disorder), which may not need treatment, but myeloid leukemia develops in 20% of children with transitory leukemia.<sup>30</sup> None of our studied cohort suffered from leukemia.

Another gene associated with autoimmune disease is cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). It encodes a cell surface molecule expressed on the surface of activated T-lymphocytes and plays a role in the downregulation of the immune response.<sup>31</sup> Like PTPN22, CTLA-4 is a potent inhibitor of T-cell activation.<sup>32</sup>

This study can provide new insights for future research to establish the role of future CT mutation screening in DS to identify patients who are susceptible for AIT and their management.

There were some limitations to this study. We did not include the thyroiditis non-DS children as a control group, hence it is not clear if the CT mutation is related to the AIT in children or to AIT in DS. We also did not include DS without AIT, hence we do not know if the CT mutation is present in DS generally. We did not include older children with DS with established AIT on therapy, hence it is not clear if the CT mutation is related to the early DS presenters with AIT or not.

## Conclusions

To the best of our knowledge, this is the first study that analyzed the PTPN-22 C1858T gene polymorphism in children with DS and thyroid dysfunction in South East Asia. The CT genotype of PTPN-22 C1858T gene polymorphism was detected in all our studied DS children with AIT. It remains to be studied in Indonesian DS children without AIT, and in non-DS children with AIT.

## References

- Al-Biltagi M. Down syndrome from epidemiologic point of view. *EC Paediatrics* 2015;82-91.
- Ariani Y, Soeharso P, Sjarif DR. Genetic & genomic medicine in Indonesia. *Molecular Genetics & Genomic Medicine* 2017;5:103-9.
- Iughetti L, Predieri B, Buzzi P, et al. Ten-year longitudinal study of thyroid function in children with Down's syndrome. *Horm Res Paediatr* 2014; 82:113-21.
- Graber E, Chacko E, Regelmann MO, et al. Down syndrome & thyroid function. In Rapaport R (ed.), *Clinic review articles: endocrinology & metabolism clinics of North America: pediatric endocrinology*. Philadelphia USA: Elsevier; 2012.
- Iughetti L, Lucaccioni L, Fugetto F, et al. Thyroid function in down syndrome, *Expert Review of Endocrinol & Met* 2015;10:525-32.
- NCBI. PTPN-22 protein tyrosine phosphatase non-receptor type 22 [Homo sapiens (human)]. Accessed: 31 Dec 2021. Available from: <https://www.ncbi.nlm.nih.gov/gene/26191>
- Vang T, Miletic AV, Bottini N, Mustelin T. Protein tyrosin phosphatase PTPN-22 in human autoimmunity. *Autoimmunity* 2007;40: 453-61.
- Burn GL, Svensson L, Sanchez-Blanco C, et al. Why is PTPN22 a good candidate susceptibility gene for autoimmune disease? *FEBS Lett* 2011;585:3689-98.
- World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bull World Health Org* 2001;79:373-374.
- Soghier L. Reference range values for pediatric care. 2nd ed. American Academy of Pediatric; 2019.
- Wu H, Wan S, Qu M, et al. The Relationship between PTPN-22 R620W polymorphisms & the susceptibility to autoimmune thyroid diseases: an updated meta-analysis. *Imm Invest* 2020;00:1-14.
- Gu LQ, Zhu W, Zhao SX, et al. Clinical associations of the genetic variants of CTLA-4, Tg, TSHR, PTPN-22, PTPN12 & FCRL3 in patients with graves' disease. *Clin Endocrinol* 2010;72:248-55.
- Chabchoub G, Teixeira EP, Maalej A, et al. The R620W polymorphism of the protein tyrosine phosphatase 22 gene in autoimmune thyroid diseases & rheumatoid arthritis in the Tunisian population. *Ann Human Biol* 2009;36:342-9.
- Nikitin Y, Ymar O, Maksimov V, et al. Association of PTPN-22 haplotypes with Hashimoto's thyroiditis in population of Novosibirsk. *Klinicheskaâ I Èksperimental'naâ Tiroidologîâ* 2009;1:47-52.
- Kahles H, Amos-Lopez E, Lange B, et al. Sex-specific association of PTPN-22 1858T with type 1 diabetes but not with Hashimoto's thyroiditis or Addison's disease in the German population. *Eur J Endocrinol* 2005;153:895-9.
- Ban Y, Tozaki T, Taniyama M, et al. The codon 620 single nucleotide polymorphism of the protein tyrosine phosphatase-22 gene does not contribute to autoimmune thyroid disease susceptibility in the Japanese. *Thyroid* 2005;15: 1115-18.
- Smyth D, Cooper JD, Collins JE, et al. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN-22) with type 1 diabetes, & evidence for its role as a general autoimmunity locus. *Diabetes* 2004;53:3020-23.
- Abou El Ella, Soheir S, Mohammed ZS, et al. PTPN22 gene and IL2RA rs11594656, rs2104286 gene variants: additional insights of polygenic single-nucleotide polymorphisms' pattern among Egyptian children with type 1 diabetes. *Egyptian Pediatric Assoc Gazette* 2021;69:35.
- Huraib GB, Al Harthi F, Arfin M, et al. Association of Functional Polymorphism in Protein Tyrosine Phosphatase Nonreceptor 22 (PTPN22) Gene with Vitiligo. *Biomark Insights* 2020;31;15:1177271920903038.
- Rajendiran KS, Rajappa M, Chandrashekar L, Thappa DM.

Association of PTPN22 gene polymorphism with non-segmental vitiligo in South Indian Tamils. *Postepy Dermatol Alergol* 2018;35:280-85.

21. Pierce MJ, LaFranchi SH, Pinter JD. Characterization of thyroid abnormalities in a large cohort of children with down Syndrome. *Hormone Res Paediatrics* 2017;87:170-78.
22. Tuysuz B, Beker DB. Thyroid dysfunction in children with down's syndrome. *Acta Paediatr* 2001;90:1389-93.
23. Gentile F, Conte M, Formisano S. Thyroglobulin as an autoantigen: What can we learn about immunopathogenicity from the association of antigenic properties with protein structure?. *Immunology* 2004;112:3-25.
24. Karlsson B, Gustafsson J, Hedov G, et al. Thyroid dysfunction in down's syndrome: relation to age and thyroid autoimmunity. *Arch Dis Child* 1998;79:242-5.
25. Pascanu I, Banescu C, Benedek T, et al. Thyroid dysfunction in children with down's Syndrome. *Acta Endocrinol (Bucharest, Rom.)* 2009;5:85-92.
26. Luo L, Cai B, Liu F, et al. Association of protein tyrosine phosphatase nonreceptor 22 (PTPN22) C1858T gene polymorphism with susceptibility to autoimmune thyroid diseases: A meta-analysis. *Endocr J* 2012;59:439-45.
27. Sam-Yellowe Tobili Y. *Immunology: Overview and Laboratory*. Cleveland, OH, USA. Springer Nature; 2021.
28. Bull MJ; Committee on Genetics. Health supervision for children with Down syndrome. *Pediatrics* 2011;128:393-406.
29. Aversa T, Lombardo F, Valenzise M, et al. Peculiarities of autoimmune thyroid diseases in children with Turner or Down syndrome: an overview. *Ital J Ped* 2015;41:1-5.
30. Zwaan MC, Reinhardt D, Hitzler J, Vyas P. Acute leukemias in children with Down syndrome. *Pediatr Clin North Am* 2008;55:53-70, x.
31. Patel H, Mansuri M, Singh M, et al. Association of Cytotoxic T- Lymphocyte Antigen 4 (CTLA4) and Thyroglobulin (TG) genetic variants with autoimmune hypothyroidism. *PLoS One* 2016;11:e0149441.
32. Jacobson EM, Tomer Y. The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: Back to the future. *J Autoimm* 2007;28:85-98.

Non-commercial use only



SJR

Scimago Journal & Country Rank

Enter Journal Title, ISSN or Publisher Name

- Home
- Journal Rankings
- Country Rankings
- Viz Tools
- Help
- About Us

Psikolog Profesional Surabaya  
 Psikolog Profesional Surabaya  
 Berbagai Layanan Kesehatan Psikologi Tersedia Di Sini. Hubungi Kami untuk Detailnya.

Rute

Situs

# Pediatria Medica e Chirurgica

## COUNTRY

Italy



Universities and research institutions in Italy



Media Ranking in Italy

## SUBJECT AREA AND CATEGORY

Medicine

Pediatrics, Perinatology and Child Health Surgery

## PUBLISHER

Vicenza  
Pediatria Medica E Chirurgica

## H-INDEX

1

### Refereed Journal

#### Top Impact Factor Journal

Approved Nursing & Health Sciences International journal. Impact Factor

iosrjournals.org

OPEN

## PUBLICATION TYPE

Journals

## ISSN

03915387, 24207748

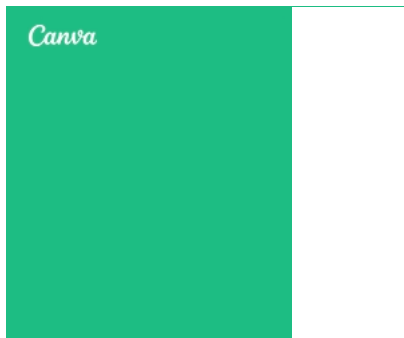
## COVERAGE

1979-2021

## INFO

How to publish this journal for free





SCOPE

La Pediatria Medica e Chirurgica publishes original papers in the field of basic science, clinical and laboratory research pertinent to and surgical pediatrics. In addition to Original Articles, La Pediatria Medica e Chirurgica welcomes Editorials (on invitation), Brief Reports, Letters to the Editor and Book Reviews as well. All manuscripts are critically assessed by external and/or in-house experts in accordance with the principles of peer review. Manuscripts must be written in English or Italian.

 Join the conversation about this journal


### Index Copernicus Indexed

Journal of nursing research

200 + Reviewer from 70 countries.

[iosrjournals.org](http://iosrjournals.org)

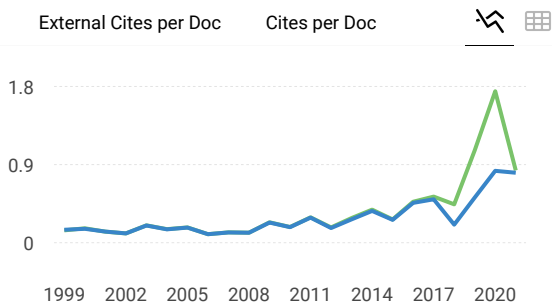
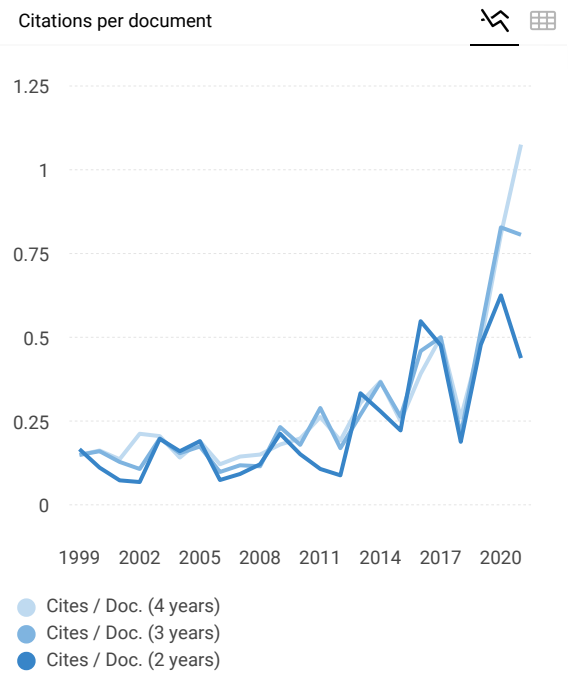
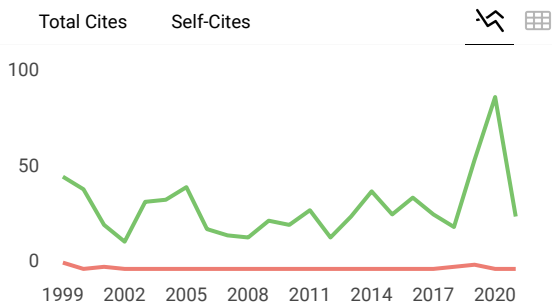
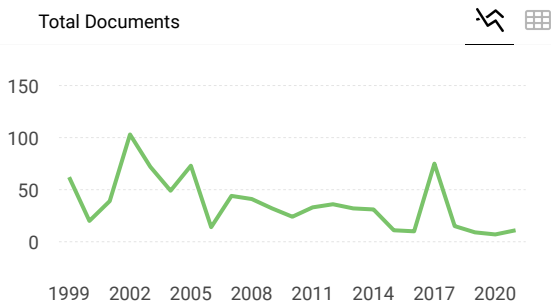
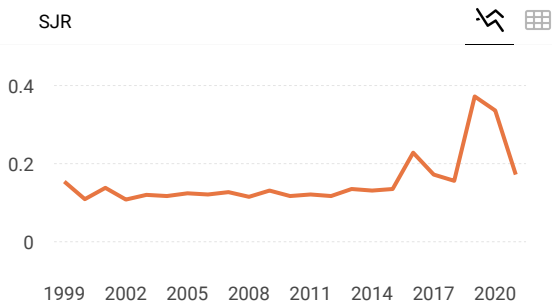
OPEN

 Quartiles

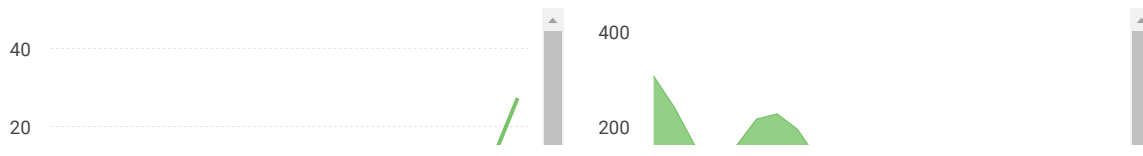


FIND SIMILAR JOURNALS 

<p>1 <b>Journal of Pediatrics</b> USA</p> <p><b>48%</b> similarity</p>	<p>2 <b>Journal of Neonatal-Perinatal Medicine</b> NLD</p> <p><b>45%</b> similarity</p>	<p>3 <b>Clinics in Perinatology</b> GBR</p> <p><b>43%</b> similarity</p>	<p>4 <b>Neonatal ne</b> USA</p> <p><b>4</b> s</p>
--	---	--	---

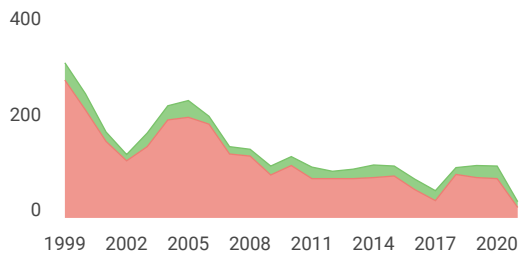


% International Collaboration   
  Citable documents   
  Non-citable documents



Cited documents

Uncited documents



**Pediatria Medica e Chirurgica**

**Q3** Pediatrics, Perinatology and Child Health  
best quartile

**SJR 2021**  
0.17

powered by scimagojr.com

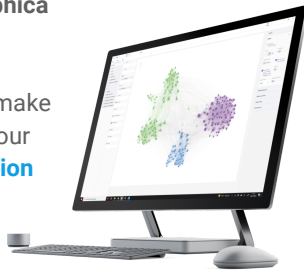
← Show this widget in your own website

Just copy the code below and paste within your html code:

```
<a href="https://www.scimaç
```

### SCImago Graphica

Explore, visually communicate and make sense of data with our [new data visualization tool](#).



Metrics based on Scopus® data as of April 2022



Loading comments...

Developed by:

Powered by:





EST MODUS IN REBUS  
Horatio (Satire 1, 1, 106)

[Cookie settings](#)

[Cookie policy](#)

---

