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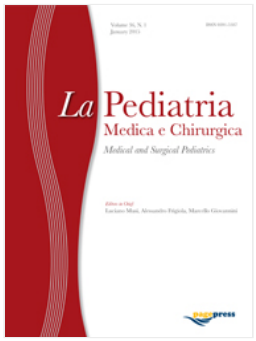

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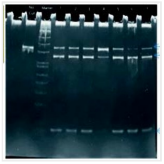

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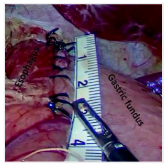

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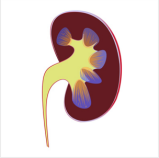

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Protein tyrosine phosphatase non-receptor type 22 C1858T gene polymorphism in children with down syndrome and autoimmune thyroid diseases

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

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

Muhammad Faizi,[1,3] Nur Rochmah,[1,3] Soetjipto Soetjipto,[2,3] Anang Endaryanto,[1,3] Sukmawati Basuki,[3,4] Yuni Hisbiyah,[1,3] Rayi Kurnia Perwitasari[1]

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

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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.

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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.

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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.[1] Data from the Indonesian Down Syndrome Association shows that there are 300.000 DS cases in

Indonesia.[2] 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.[3] 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).[4]

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.[5,6] 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.[7,8] 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).

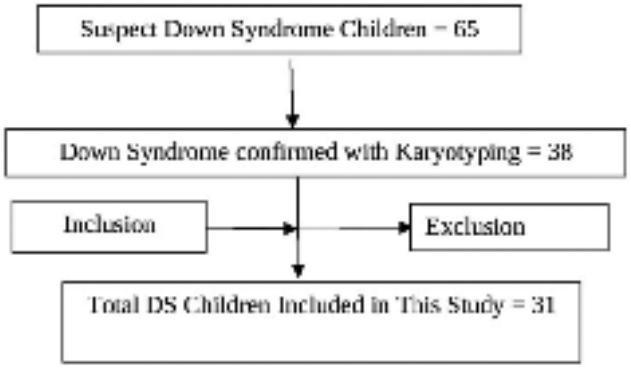

Figure 1. Flowchart for Selection Criteria.

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.[9]

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 (≥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±SD	19.45±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±0.45
FT4	0.81±0.57
TSH, mean (µU/mL)	0.22±0.21
TSH Subjects with Central Hypothyroidism, mean (µU/mL)	0.22±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.[10]

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'ACTGATAATGTTGCTTCAAC-CGG3', 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 95ºC for 5 minutes, followed by 36 cycles at 95ºC for 30 seconds, 64ºC for 30 seconds, 72ºC for 30 seconds, and a final incubation at 72ºC 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±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±0.45 ng/mL, 0.81±0.57 ng/mL, 0.22±0.21 µU/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.[11-17] 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.[18-20]

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.[21] 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.[22]

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.[23] The positivity of autoimmune thyroid markers increases with age and usually becomes more prevalent after 8 years of age.[24] Another study also showed that anti-TPO in DS children was commonly observed at the age of >5 years.[25] Subjects with positive anti-TPO were shown to have an increased risk of developing overt hypothyroidism in later years.[25]

The PTPN-22 C1858T polymorphism is associated with AIT

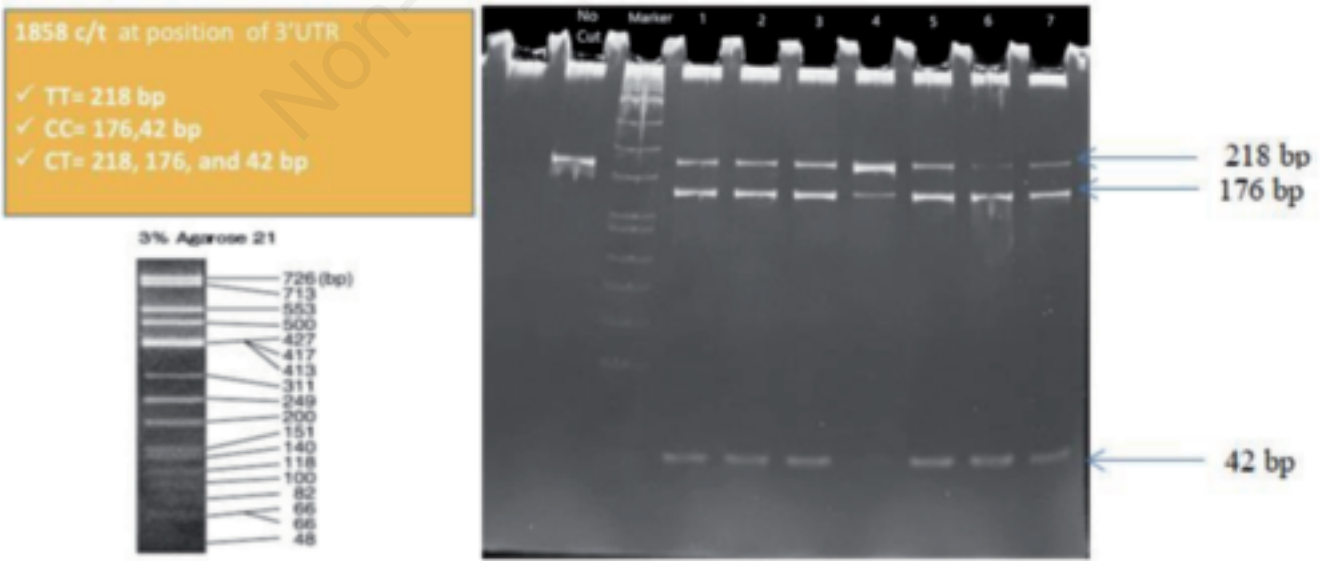

Figure 2. PCR-RFLP Electrophoresis result of PTPN-22 C1858T. The result of PCR-RFLP electrophoresis with enzyme restriction RsaI. The only genotype that was found in this study was CT, demonstrated in numbers one to seven. CT genotype was identified as three bands in 218, 176, and 42 base pairs.

risk, particularly in Caucasians ethnic compared to Asian and African American groups.[26] 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.[7,27]

The average age of DS children diagnosed with AIT was 19 months which support early regular screening for for thyroid abnormalities in DS children at birth, six months, 12 months, and yearly.[28] 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.[21,29]

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.[30] 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.[31] like PTPN22, CTLA-4 is a potent inhibitor of T-cell activation.[32]

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.

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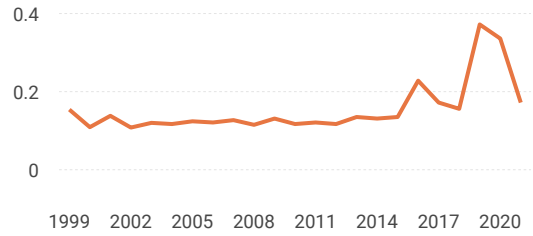

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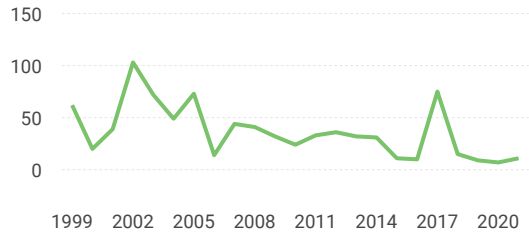

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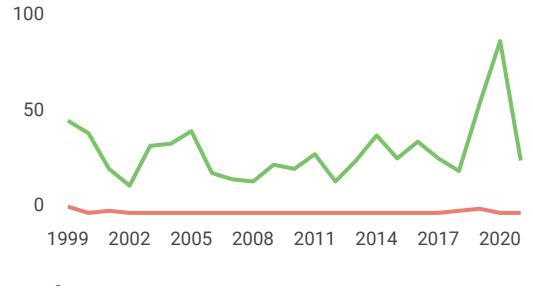

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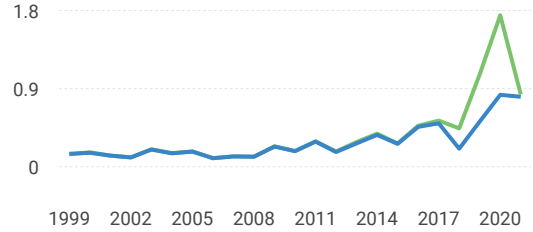

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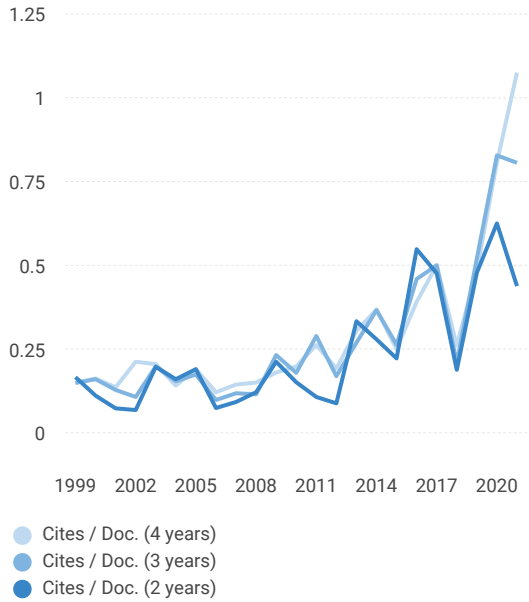

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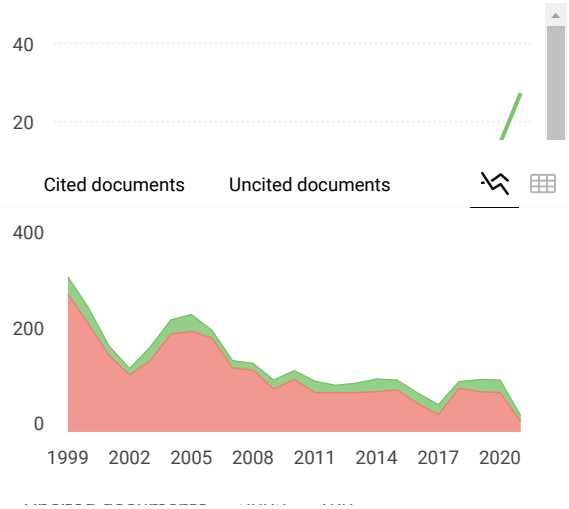

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