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Hirschsprung's Disease in Indonesia: Potential Contributing Factor and Pedigree Analysis

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Abstract: Hirschsprung's disease (HD) has a complex origin involving genetic factors. While HD cases have been documented in Indonesia, the genetic inheritance is unexplored. This study aims to update HD in Indonesia, determine the inheritance pattern through pedigree analysis, and identify the non-genetic factors contributing to HD, including parental demographics and maternal aspects. A cross-sectional survey was conducted with 87 respondents across Indonesia. The results revealed a male-to-female incidence ratio of 1.90:1, with the ultra-short segment being the most common type (75.86%), and familial cases accounted for 8%. Seventeen patients exhibited other congenital abnormalities, with pneumonia, redundant colon, and cardiac defect as the highest cases. Over 70% of the parents were aged 20-35 and had relatively high education and income levels. Notably, nearly half of the mothers experienced food aversion in the first trimester (n=38) and frequently consumed fast or instant food during pregnancy (n=33). The study confirmed that HD follows an autosomal recessive inheritance pattern. These findings emphasize the role of genetic inheritance in incidents of HD, which is valuable for developing early detection strategies and providing genetic counseling for at-risk families. Maternal lifestyle factors may play a role in the development of HD, which needs further investigation.

Keywords: Autosomal recessive; Congenital abnormalities; Hirschsprung's disease; Inheritance pattern; Maternal lifestyle

Introduction

Hirschsprung's disease (HD) is a congenital disorder of the hindgut characterized by the absence of ganglion cells in both the submucosal plexus (Meissner's plexus) and the myenteric plexus (Auerbach's plexus) (Klein & Varga, 2020). The incidence of HD ranges from 1.5 to 2.8 per 10,000 births, with a rate of 2.8 per 10,000 births in Asians (Tam, 2016) and 3.1 per 10,000 births in Indonesia (Gunadi et al., 2018b). HD typically manifests in one of three ways: neonatal distal intestinal obstruction, chronic constipation in an older child, or enterocolitis (Langer, 2013). A substantial risk associated with HD is Hirschsprung-associated enterocolitis (HAEC), a severe condition affecting approximately 16% of patients and responsible for 50% of HD-related mortality (Moore, 2016).

The combination of genetic and environmental factors impacts the development of HD (Granström et al., 2016). Extensive research has focused on HD-related mutations across various genes and loci (Amiel et al., 2008), with two genes primarily implicated in the disease: the tyrosine kinase receptor (RET) located at 10q11.2 and the endothelin receptor type B (EDNRB) located at 13q22.3 (Karim et al., 2021). However, some cases of HD occur without associated mutations (Heuckeroth, 2018; Heuckeroth & Schäfer, 2016; Tilghman et al., 2019), and 70% of cases are isolated (non-syndromic) (Amiel et al., 2008).

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HD has been reported in Indonesia (Corputty et al., 2015; Gunadi et al., 2018b; Isa et al., 2019; Palissei et al., 2021), with previous studies mainly focusing on treatment outcomes (Gunadi et al., 2018b; Gunadi et al., 2022; Isa et al., 2019) and genetic investigations (Gunadi et al., 2016; Gunadi et al., 2018a; Iskandar et al., 2019; Kalim et al., 2023; Saryono et al., 2010). However, the mechanisms underlying the inheritance patterns of HD remain poorly understood. This study provides an updated overview of HD cases in Indonesia and is the first to systematically analyze the genetic inheritance of HD through the construction and evaluation of pedigrees across three generations: grandparents, parents, and siblings. Additionally, we identify non-genetic factors contributing to HD, particularly those related to parental aspects. Understanding these factors is crucial for several reasons. First, identifying both genetic and non-genetic factors can enhance early detection and enable effective genetic counseling for at-risk families, ultimately reducing delays in diagnosis and intervention. Second, insights into parental characteristics, including lifestyle and health history, may uncover modifiable risk factors, opening avenues for prevention strategies. Lastly, this research lays the foundation for future studies on the interaction between genetic predisposition and environmental influences in HD development. This study significantly advances our understanding of HD's etiology by addressing these gaps and provides a basis for developing prevention and management strategies in Indonesia.

Method

Study Design and Subject

This research employed a cross-sectional survey method. Samples were collected using a non-probability sampling method with consecutive sampling. The subjects were drawn from two WhatsApp groups, consisting of individuals who have family relatives with HD (n = 87). The study protocol was reviewed and approved by the Committee of Dr. M. Djamil Central General Hospital, Padang, approval number (Ethical approval No. DP.04.03/D.XVI.XI/87/2024).

Samples Criteria

The inclusion criteria consisted of HD patients of both genders and all ages who had been diagnosed by a medical professional and were willing to participate as respondents. The exclusion criteria included HD patients who were unwilling to participate or those who were unaware of their family history.

Data Collection

Data were obtained through a questionnaire via Google Forms. The collected data in HD patients included gender, age, type of HD, family history of HD, parental demographics, maternal medical history, maternal lifestyle during pregnancy, and three-generation pedigree.

Data Analysis

The inheritance patterns were determined by examining the patient's pedigree to identify whether the inheritance was autosomal dominant or autosomal recessive. Pedigree was constructed using Quickped (Vigeland, 2022).

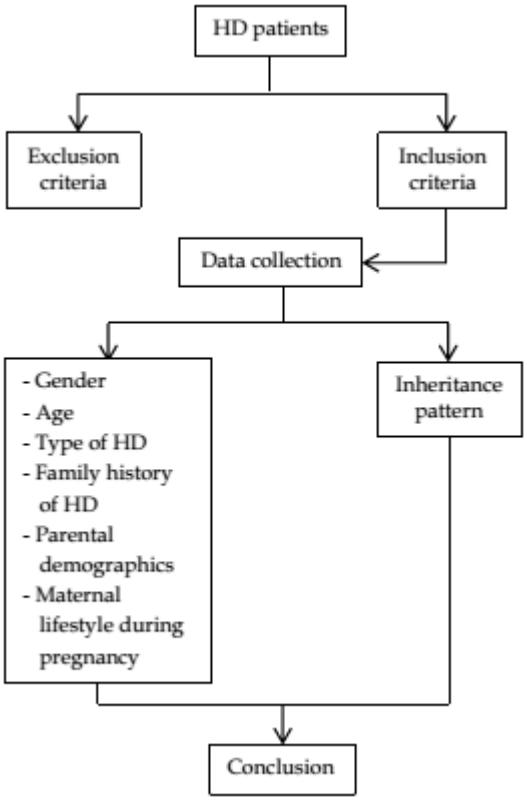

Figure 1. Study flowchart

Result and Discussion

The profiles of 87 patients with HD are summarized in Table 1, including their gender, age, type of HD, associated abnormalities, and family history of HD. The male-to-female ratio was 1.90:1, indicating a higher incidence in males, which is consistent with prior studies (Abbas et al., 2013; Anandasari & Margiani, 2023; Ishfaq et al., 2014; Izadi et al., 2009; Rahman et al., 2010).

Most HD diagnoses occur prenatally or within the first year of life. However, there were six cases where the diagnosis was made after the child was over one year old (Table 1). Delays in diagnosis often arise due to mild or

non-specific symptoms (Khare et al., 2022; Prato et al., 2024) and limited access to adequate healthcare services in certain regions (Khare et al., 2022). Misdiagnosis is also a concern, as approximately 10% of HD cases are asymptomatic (Martucciello, 2008), and the clinical presentation can vary depending on the extent of the affected colon segment (Khare et al., 2022).

Although ultra-short segment Hirschsprung disease (US-HD) is classified as a rare variant (Hong et al., 2014; Tjaden & Trainor, 2013), it had the highest prevalence in this study (Table 1). US-HD is characterized by the shortest aganglionic segment, measuring 1-2 cm in the distal rectum or colon (Friedmacher & Puri, 2013).

Table 1. Distribution of HD Patients by Gender, Age, Type of HD, Associated Congenital Abnormalities, and Family History of HD

Characteristics	*f*	%
Gender		
Male	57	65.52
Female	30	34.48
Age at diagnosis		
< 28 days	67	77.01
1 - 12 months	14	16.09
1 - 5 years	4	4.60
5 - 10 years	1	1.15
> 10 years	1	1.15
Type of HD		
Ultra-short segment	66	75.86
Long-segment	6	6.90
Total colonic	1	1.15
Rectosigmoid	1	1.15
Adult HD	3	3.45
Uncertain	10	11.49
Congenital anomalies		
Present	17	19.54
Absent	70	80.46
Family history of HD		
Present	7	8.05
Absent	80	91.95

The clinical symptoms and congenital diseases or abnormalities found in HD patients are summarized in Table 2. The most common symptom observed was abdominal distension, followed by delayed passage of meconium, chronic constipation, and vomiting. In the early stages of diagnosis, HD is typically identified based on symptoms such as a distended abdomen, delayed meconium passage (lasting more than 24 hours), and vomiting (Tjaden & Trainor, 2013). Chronic constipation is particularly noted in patients diagnosed at later stages.

Seventeen patients with HD were found to have congenital anomalies and associated diseases, with pneumonia being the most common, similar to findings in Hirschsprung-associated enterocolitis (HAEC) patients (Li et al., 2016). Various heart defects were identified, including atrial septal defect (ASD), patent ductus arteriosus (PDA), and patent foramen ovale (PFO). Central nervous system abnormalities, such as autism spectrum disorder (ASD), were also noted. Additionally, gastrointestinal malformations, including redundant intestines and imperforate anus, were observed. This study demonstrated that HD-related anomalies frequently affect the cardiac, gastrointestinal, central nervous, and genitourinary systems. Other abnormalities were also observed, including orofacial clefts, vaginal stenosis, and phimosis. Previous studies have reported congenital heart disease in patients with HD (Best et al., 2014; Hasserius et al., 2017; Wu et al., 2023), as well as the presence of cleft lips and imperforate anus (Mashuda et al., 2014).

Table 2. Distribution of HD Patients by Clinical Symptoms and Associated Congenital Anomalies

Criteria	*f*	%
Congenital anomalies and diseases		
Pneumonia	3	16.67
Redundant colon	2	11.11
Patent Ductus Arteriosus (PDA)	2	11.11
Atrial Septal Defect (ASD)	2	11.11
Patent Foramen Ovale (PFO)	1	5.56
Imperforate anus	1	5.56
Orofacial cleft	1	5.56
Hypothyroidism	1	5.56
Autism Spectrum Disorder (ASD)	1	5.56
Vaginal stenosis	1	5.56
Speech delay	1	5.56
Colitis	1	5.56
Phimosis	1	5.56
Clinical presentation		
Abdominal distension	72	34.12
Delayed meconium passage	50	23.70
Chronic constipation	45	21.33
Vomiting	44	20.85

Most parents of HD patients were between 20 and 35 years old (Table 3). While older or younger parents are often associated with a higher risk of birth defects and health issues in their children (Liu & Li, 2011), this study suggests that parental age may not be a contributing factor to HD. Previous research has also indicated that the incidence of HD is not correlated with maternal age (Best et al., 2014; Kapapa et al., 2022). Furthermore, the study found that the parents of HD patients generally had good socio-economic status, with over 50% having higher education and incomes above the city's minimum wage. Although socio-economic factors can influence the development of congenital malformations (Lee et al., 2021), this study found no

clear association between these factors and the incidence of HD.

A high prevalence of food aversion during early pregnancy and frequent fast food consumption were reported in maternal pregnancy period, which is closely linked to fetal nutrient intake. Although not scientifically proven, fetal malnutrition may play a role in the occurrence of HD (Heuckeroth & Schäfer, 2016), as maternal eating habits directly affect fetal growth (Blumfield et al., 2012) and may pose a risk for various reported malformations (Dean et al., 2014; Giordano et al., 2008; Moore et al., 2020). Furthermore, since the embryological development of HD occurs between the 5th and 12th weeks of pregnancy, it is crucial to identify external influences during early pregnancy (Zhang et al., 2017).

Table 3. Parental Demographics of HD Patients by Age, Education, Occupation, and Income

Parental characteristics	*f*	%
Age		
Mother		
< 20 years	1	1.15
20-35 years	77	88.51
> 35 years	9	10.34
Father		
< 20 years	1	1.15
20-35 years	67	77.01
> 35 years	19	21.84
Educational level		
Primary education	0	0.00
Lower secondary education	4	4.65
Upper secondary education	31	36.05
Higher education	51	59.30
Occupation		
Private sector employee	30	34.48
Public sector employee	20	22.99
Labor	6	6.90
Other	31	35.63
Income		
< District/City Minimum Wages	33	37.93
> District/City Minimum Wages	54	62.07

Table 4. Medical History and Lifestyle Factors of Mothers of Patients with HD

Criteria	*f*	%
Medical history		
Bleeding during pregnancy	8	8.79
Diabetes	0	0.00
High blood pressure	6	6.59
Low blood pressure	9	9.89
No reported medical conditions	68	74.73
Lifestyle factors		
Food aversion in the first trimester	38	29.92
Frequently consuming fast food or instant food	33	25.98
Consuming alcohol	0	0.00
Active smoking	0	0.00
Passive smoking	7	5.51
Exposed to air pollution	7	5.51
Taking drugs	12	9.45
No reported lifestyle factors	30	23.62

Table 5 displays the provinces in Indonesia where patients with HD were studied. Data regarding the province of origin were not available for six out of the 87 patients included in the study. Over 50% of the patients came from Java, with the highest numbers from East Java, West Java, and Central Java. These findings suggest that the incidence of HD is widespread across Indonesia. The representation of various provinces in the study indicates that HD is not limited to a specific region. The high number of patients from Java may suggest a greater prevalence of the disease in this area, potentially due to genetic or environmental factors. The absence of data from a small number of patients highlights the need for more comprehensive data collection in future studies to understand the distribution of HD in Indonesia.

Table 5. Distribution of HD Patients by Province of Origin

Provinces	*f*	%
Banten	6	6.90
Bengkulu	2	2.30
Central Java	11	12.64
Central Kalimantan	1	1.15
East Java	23	26.44
East Kalimantan	3	3.45
East Nusa Tenggara	1	1.15
Jambi	1	1.15
Lampung	1	1.15
North Kalimantan	1	1.15
Riau Islands	2	2.30
South Kalimantan	1	1.15
South Sumatra	1	1.15
Special Capital Region of Jakarta	5	5.75
Special Region of Yogyakarta	2	2.30
West Java	16	18.39
West Kalimantan	1	1.15
West Nusa Tenggara	1	1.15
West Sumatra	2	2.30
Data unavailable	6	6.90

Pedigree analysis was conducted on 3 out of 7 individuals with familial HD (as mentioned in Table 1). These families are identified as proband family 1, proband family 2, and proband family 3. In proband family 1, the proband (III-1) is a male diagnosed with short-segment HD at the age of four months (Figure 2). The proband and another affected family member, a maternal cousin (III-2), are part of the third generation. The inheritance pattern remains unclear; however, the disease's occurrence in the offspring of phenotypically

normal parents suggests it is unlikely to follow an autosomal dominant inheritance pattern.

In proband family 2, HD also manifested in the third generation, affecting both the proband (III-5) and her sibling (III-1), as shown in Figure 3. The proband (III-5), the youngest of five siblings, was diagnosed with HD before reaching one month of age. She was identified as having total colon aganglionosis. Since both parents (II-1 and II-2) exhibit normal phenotypes, the pedigree suggests an autosomal recessive inheritance pattern. This indicates that both parents are carriers of the recessive allele, which their affected children inherited from both sides.

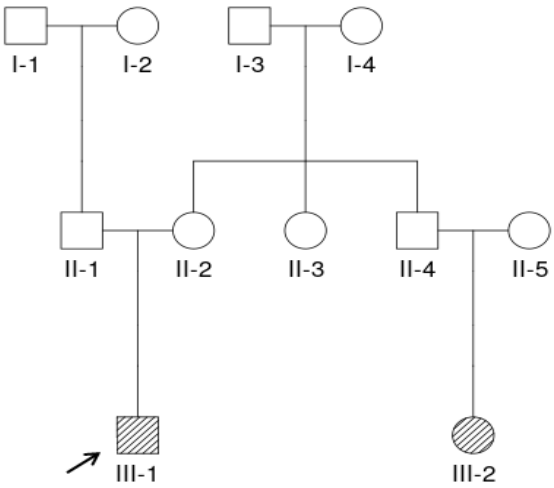

Figure 2. Pedigree of proband family 1. Males are represented by boxes and females by circles. Roman numerals indicate generations, while Arabic numerals represent individual family members. The arrow points to the proband, and shading denotes family members affected by Hirschsprung's disease

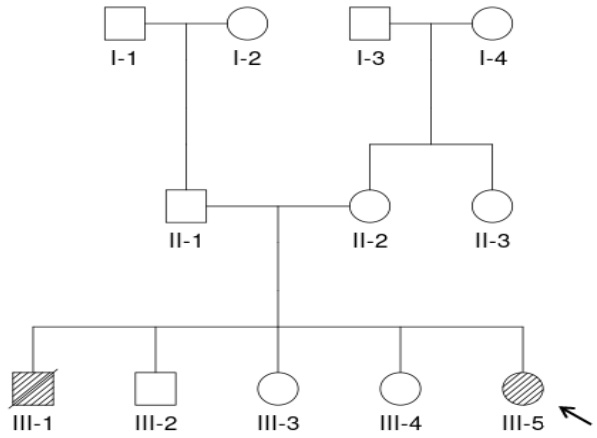

Figure 3. Pedigree of proband family 2. Males are represented by boxes and females by circles. Roman numerals indicate generations, while Arabic numerals represent individual family members. The arrow points to the proband, shading indicates family members with Hirschsprung's disease, and a diagonal line through the shape represents deceased family members

In proband family 3, the proband is the youngest of three siblings (Figure 4). The proband (III-3) is a female and was diagnosed with HD before one month old. The type of HD is an ultra-short segment. Other affected family members include the proband's father's sibling (II-3). The pedigree shows an autosomal recessive inheritance pattern, where the proband (III-3) is affected despite both parents (II-4, II-5) being clinically unaffected.

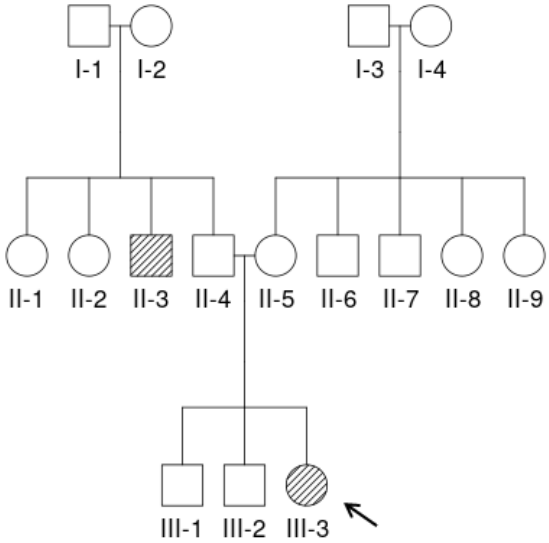

Figure 4. Pedigree of proband family 3. Males are represented by boxes and females by circles. Roman numerals indicate generations, while Arabic numerals represent individual family members. The arrow points to the proband, and shading indicates family members with Hirschsprung's disease

HD exhibits complex genetic patterns (Xiao et al., 2023), and its inheritance is not yet fully understood (Moore, 2016). Nevertheless, genetic factors are known to play a crucial role in its development (Granström et al., 2016). The inheritance patterns of HD can vary and include autosomal dominant, autosomal recessive, and multigenic traits (Moore, 2016).

There may be data bias in studying HD inheritance, as some family members might be unaware of their family history. Additionally, HD exhibits incomplete penetrance and variable expressivity (Martucciello et al., 2000). Consequently, some family members may have HD but remain undiagnosed due to mild symptoms, which can affect the conclusions drawn about inheritance patterns.

Our findings are limited by the relatively small number of HD cases, particularly those involving familial cases. More detailed pedigree information from HD families may provide a better understanding of inheritance patterns, especially within the Indonesian population. Moreover, there may be variations in HD expression and penetrance among different ethnic

groups in Indonesia, indicating the need for further research. Although this study did not address every possible cause of HD, more research on non-genetic factors may assist in developing preventive strategies for HD, particularly in sporadic cases.

Conclusion

Our study shows that the prevalence of HD in Indonesia is higher in males (1.90:1), with the majority of cases found in the ultra-short segment (75.86%). Sporadic cases account for 91.95%, while familial cases comprise only 8.05%. Congenital abnormalities were present in 19.54% of patients. Over 70% of parents are aged 20–35, exhibiting high education and income, indicating that socioeconomic status has an insignificant impact on HD. Notably, 74.73% of mothers had no history of certain diseases, but 29.92% experienced food aversion during early pregnancy, with 25.98% consuming fast food frequently. This observation suggests a potential link between maternal lifestyle and fetal development, warranting further investigation. Pedigree analysis confirmed an autosomal recessive inheritance pattern, emphasizing the role of genetic factors. These findings provide valuable insights for public health strategies, including promoting healthier maternal lifestyles and enhancing genetic counseling. Further research is required to understand the complex interplay between genetic and non-genetic factors contributing to the incidence of HD.

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Author Contributions
Conceptualization, Y.A., Z.T, and D.L.; methodology, resources, Y.A., K..; data curation, data analysis, Y.A., K.; writing—original draft preparation, Y.A., K., R.U.M.; writing—review and editing, Y.A.; project administration, K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest
The authors declare no conflict of interest.

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