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Genetic Studies On The GHSR and IGF1R and Their Relationship With Stunting: A Systematic Literature Review

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Abstract

Stunting, also known as short stature, is a condition that occurs in children where children grow too short for their age. It can be influenced by several external and internal factors. This study explored various databases including Pubmed, Science Direct, Sage Journal, Springer Link, with keywords: "stunting OR short stature AND GHSR AND IGF1R AND genetic". There are 114 articles that match the PICOTS elements to be further reviewed using the PRISMA diagram. In this review article, 10 research articles published in 2011-2024 were used as sources of information. This review article discusses that internal factors of stunting can be caused by genetic factors influenced by growth genes, one of which is GHSR and IGF1R. Whole genome sequencing revealed potential genes involved in the growth pathway that showed an association between genetic variation in GHSR and IGF with the risk of the body's production or response to growth hormone that causes delayed child growth. The evidence highlights the possibility that these putative genetic markers could offer more effective treatment by focusing on the pathophysiology associated with development stunting. Due to lack of genetic studies on stunting genes carried out in Asian nations, genetic testing has not been used in clinical practice as a routine evaluation in the current national implementation, especially in Indonesia.

Keywords: *Genetic; GHSR; IGF1R; Short stature; Stunting*

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INTRODUCTION

Stunting or short stature is a condition that occurs in children where children grow too short for their age due to growth failure caused by poor nutrition and child health before and after birth (Daracantika et al., 2021; Gabain et al., 2023; Supadmi et al., 2024). Stunting is one of the crucial problems faced by the whole world. According to WHO, stunting is a condition of shortness based on age which can be known based on the index value of height or length for age (TB/U or PB/U) less than -2 standard deviations (Siswati, 2018). A person affected by stunting is not only short, but can also be interpreted

as having a. linear growth disorder for a long period of time in a matter of years (Sutarto et al., 2018).

Stunting is still a major problem in developing countries such as Indonesia due to its high prevalence. Based on data from WHO, in 2022 the percentage of stunted children under 5 years old in Indonesia is 31.0%. This figure is higher than other Asian countries such as Myanmar (24.1%), Thailand (11.8%), Malaysia (21.9%) This number, causing Indonesia to be ranked 10th in the Southeast Asia region with the highest stunting rate (WHO, 2023). based Meanwhile, on data from the Ministry of Health, the stuting rate in Indonesia in 2022 was 21.6%, this figure is still quite high because the WHO standard regarding stunting prevalence must be below 20% (Ardiyah et al., 2015).

Toddlers who experience stunting have an impact on stunted growth and this is irreversible. The impact of stunting can last a lifetime and affect the next generation (Pelletier et al., 2013). Stunting is a complex problem that is not only influenced by poor nutrition, there are several factors, both internal and external. In internal factors, stunting can be caused by genetic factors. During growth, the process of human growth and development is a complex phenomenon (Rogol & Hayden, 2014).

In terms of human growth and development, the main hormone that controls human growth and development is growth hormone secretagogue receptor (GHSR) (Christesen et al., 2016). Growth hormone causes the release of insulin-like growth factor 1 (IGF-1) from the liver. IGF-1 directly affects skeletal muscle fibers and cartilage cells in long bones to increase the rate of amino acid absorption and incorporate them into new proteins, thus contributing to linear growth during infancy and childhood (Kjaer et al., 2021).

There is ample evidence from studies of children with abnormally short stature resulting from environmental factors that disrupt the endocrine system, causing a reduction in the release of growth hormone. However, other hormones are also affected, making the causes of growth disorders complex. In Indonesia, there has not been much research on the relationship between stunting and genetic factors. Therefore, the purpose of this research is to learn more about the genes that affect stunting, namely GHSR and IGF-1.

METHOD

A systematic search was conducted in February 2024 through Pubmed, Sage Journals, Science Direct, Semantic scholar, and Springer links. The search terms used were "Stunting and Short stature and GHSR and IGF1 and Genetics". The articles used were published from 2011 to 2024. From the search results, 1,236 articles were obtained, then the articles were selected based on duplication of the article title to 659, based on title identification to 114 articles, then the abstract to 38 articles, then 10 articles were taken. The articles were then briefly reviewed to ensure that the articles taken were in accordance with the elements of participants, intervention, comparator, outcome, timeframe, and setting (PICOTS) (Astuti & Sriwijayanti, 2016). The results of the review can be seen in the (Table 1).

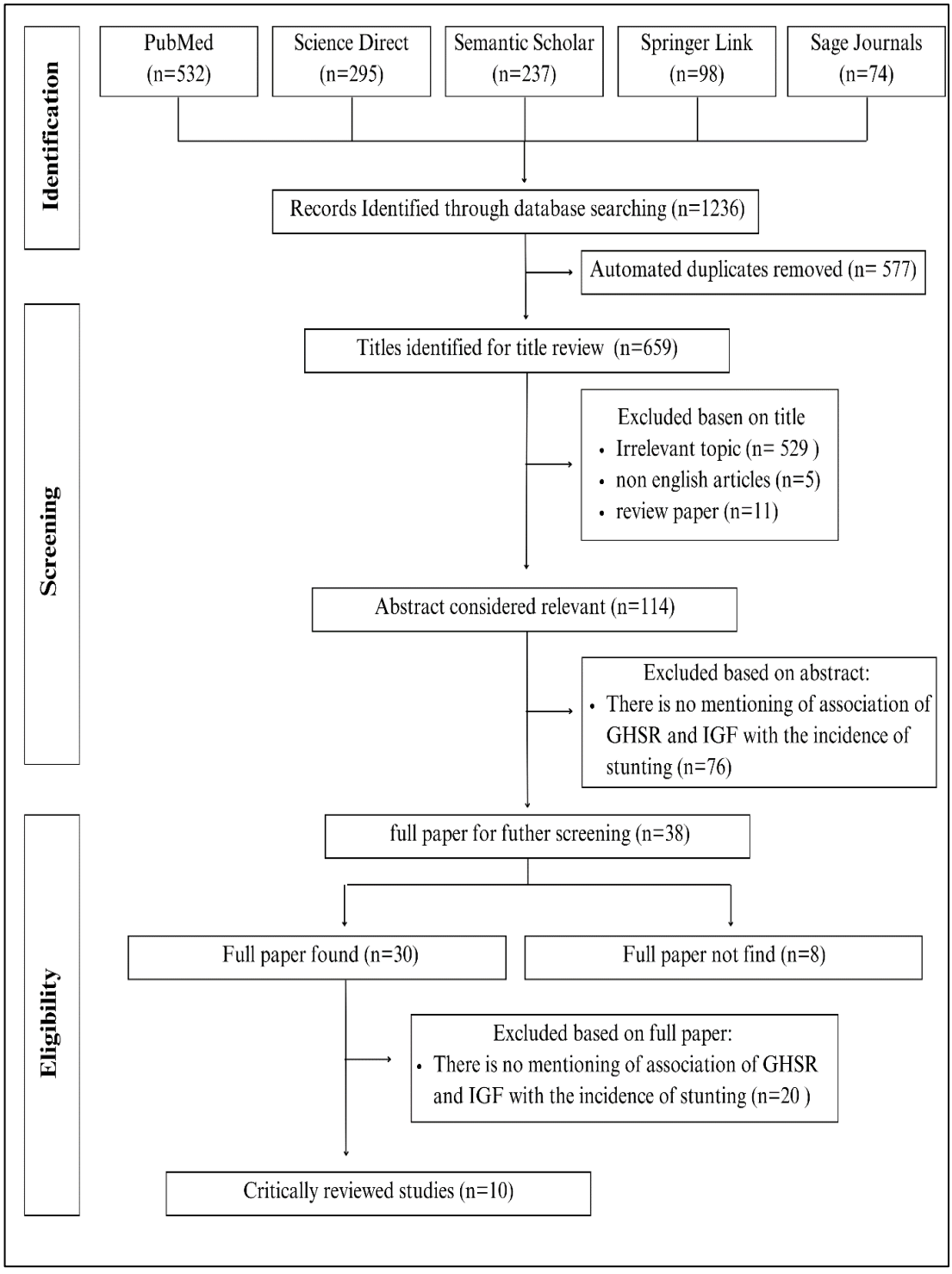

Figure 1. PRISMA diagram modified from (Wagey, 2020)

Tabel 1. Inclusion criteria based on PICOTS elements

PICOTS	Inclusion Criteria
Participants	Stunted children with normal growth
Intervention	Gene GHSR and IGF1R
Comparator	Child growth that happens between stunted children and normal children
Outcome	How the GHSR and IGF1R genes affect the incidence of stunting
Timeframe	Articles published in 2011 - 2024
Setting	All countries

After screening by inclusion, articles were then selected based on the eligibility test, the assessment carried out on the articles taken, and then analyzed according to the inclusion data. Article inclusion criteria are English articles, there is information about the topic of discussion, and full paper/text articles (Wagey, 2020). Exclusion criteria are duplication and cannot be accessed in full. The scheme of the article selection process can be seen in the prism diagram (Figure 1).

RESULTS AND DISCUSSION

Based on the results of data selection using the PRISMA method, 10 relevant journals were obtained regarding the relationship between GHSR and IGF1R on the incidence of stunting. The results of the review can be seen in Table 2.

Table 2. Review Result

No.	Reference	Location	Subjects and Methods	Results
1	Fadel et al., 2021	Massachusetts, USA	• The study subjects were pediatric ISS patients aged 2-8 years at Boston Hospital. • Data collection instruments were height and weight, blood samples from patients and parents. • Sample analysis using copy number variant (CNV) analysis with verified using qPCR analysis.	• The presence of homozygous IGF1R gene mutations results in abnormal length and birth weight and postnatal growth failure with low serum IGF1R.
2	Xiao et al., 2020	Japan	• The study subject was a 9-year-old girl from Japan, with a history of severe short stature (height: 137 cm). • Data collection instruments were	• A novel heterozygous missense mutation in the tyrosine kinase domain of IGF1R (D1105E) occurred in a 9-year-

No.	Reference	Location	Subjects and Methods	Results
			height and weight, blood samples from patients and parents. • Sample analysis using PCR method with verified by analysis using sanger sequencing	old girl and her mother who developed short stature. • The mutation at nucleotide position c.3405C>G results in a tyrosine phosphorylation deficiency in the IGF1R receptor and has a dominantly negative effect on the IGF1R receptor.
3	Fujimoto et al., 2015	Japan	• The study subjects were 55 patients with short stature in Japan, since 2004, focusing on 2 patients, an 8-year-old boy (Case 1) and a 3-year-old girl (Case 2). • Analysis using quantitative RT-PCR analysis of IGF1R mRNA expression in whole blood cells	• Two novel heterozygous nonsense mutations (case 1: p.Q1250X, case 2: p.W1249X) have been identified. • By affecting IGF1R's C-terminal region (p.Q1250X, p.W1249X), these mutations reduce IGF1R expression via the ERAD pathway.
4	Yang et al., 2019	China	• The subjects were children aged 5 years and 11 months with short stature. • Data collection instruments were height and weight, blood samples from patients and parents. • Sample analysis using next-generation sequencing (NGS) by reading through the AlignGVGD web portal (http://agvgd.iarc.fr/).	• Exon 3 (c.926C>T, p.S309L) of the type-IIGF1R gene included a new heterozygous missense mutation that the patient received from her mother. • The patient's grandpa and mother also carry the same mutation; their height standard deviations are -1.7 (moderate shortness) and -3.1 (short stature), respectively. This suggests a significant family history in this particular case.
5	Batey et al., 2014	Egypt	• The study subjects used 40 children aged 2-16 years with a diagnosis of short stature, with 5 boys and 35 girls.	• MLPA method can detect genetic CNVs underlying short stature.

No.	Reference	Location	Subjects and Methods	Results
			• Data collection instruments used a complete medical history up to three consecutive generations of pedigree, then blood samples from each subject. • Analysis looked through copy number variants (CNVs) of IGF1R using multiplex ligation-dependent probe amplification (MLPA).	• Heterozygous IGF1R deletions (exons 4 to 21) in familial short stature patients were identified out of 40 patients studied (2.5%).
6	Plachy et al., 2019	Czech	• The study subjects were 33 pediatric patients with severe short stature. • Data collection instruments through the blood of each subject • Analysis was performed using whole-exome sequencing (WES) confirmed by sanger sequencing.	• Gene variations are often the cause of short stature, one of which is GHSR and IGF1R. • In the GHSR gene, there is 1 subject who carries a genetic variant that affects the secretion of GHSR with a mutation at nucleotide position c.526G>A • In the IGF1R gene there are 6 subjects who have mutations in the nucleotide position c.158C.T
7	Ammar et al., 2024	Egypt	• The study subjects were 10 patients with an age range of 7-17 years, decreased height (<-2.5 SD), low growth hormone level response (≤10 ng/ml), and no associated congenital abnormalities. • Data collection instruments utilized comprehensive clinical examination results, and blood samples. • Analysis was performed by PCR confirmed using sanger sequencing	• The existence of 2 GHSR gene mutations with the discovery of one newly reported heterozygous frameshift variant in exon 2 (c.1043dup) and one previously reported rare variant also identified in exon 2 of the GHSR gene (c.1021G>A). • The presence of the same mutation between the patient and the patient's family who both experience short stature, this proves

No.	Reference	Location	Subjects and Methods	Results
				the inheritance of the GHSR gene mutation that causes short stature.
8	Toni et al., 2024	Czech	• The study subjects consisted of 176 children treated with GH between May 2008 and December 2018. • Data collection instruments used patient clinical examination results and blood samples • Analysis began with examination of patient SRS by MS-MLPA method, which was confirmed by sanger sequencing	• The analysis showed that 42% (74/176) of patients had short stature caused by genetics. • Of the 74 patients, 16 percent had confirmed genes impacting pituitary development or GH secretion, such as GHSR, the GH-IGF1R axis, and the IGF-2 axis, which includes IGF1R. • The GHSR gene was found in one patient and there was a mutation at the nucleotide position c.526G>A, while for the IGF1R gene there were 3 patients who had gene mutations with nucleotide locations (c.2215C>T; del15q26.3; c.807C>G).
9	Inoue et al., 2011	Japan	• The study subjects consisted of 127 undiagnosed short stature patients with isolated GH deficiency or idiopathic SS. • Data collection instruments used patients' clinical examination results and blood samples • Analysis was performed by PCR confirmed by sequencing	• Four new heterozygous GHSR1A mutations were identified (Q36, P108L, C173R, and D246A). • Mutations of this gene have different functional consequences that affect GHSR gene secretion which ultimately contributes to the onset of short stature.

No.	Reference	Location	Subjects and Methods	Results
10	Pugliese-Pires et al., 2011	Brazil	• The study subjects were 96 independent patients with a diagnosis of short stature who met the diagnostic criteria. • Data collection instruments were based on routine laboratory examinations including blood cell count, erythrocyte sedimentation rate, electrolytes, albumin levels, kidney and liver function tests. • Analysis was performed by PCR with PCR products were bi-directionally sequenced by the dideoxy chain termination method using a dye terminator kit and analyzed in an ABI Prism 3100 automated sequencer.	• Five different heterozygous point variations in GHSR were found (c.545 TOC (p.Val182Ala), c.K6 GOC, c.505GOA (p.Ala169Thr), c.251GOT (p.Ser84Ile), and c.1072GOA (p.Ala358Thr)) in all patients diagnosed with short stature. • A reduction in cell surface expression can account for at least some of the drop in basal GHSR activity. Decreased ghrelin potency is also linked to the p.Ser84Ile mutation.

DISCUSSION

Genetics play an important role in the development of human diseases. Genetic factors can influence a person's predisposition to certain diseases, and the interaction between genetic factors and the environment can play a key role in the onset of disease. In the last few decades, many genomic studies have been conducted with molecular biology approaches that can identify diseases genetically (Taib & Ismail, 2021). One of these techniques is SNP array, this technique is able to identify genes that are thought to be associated with human disease. This genome association study has successfully identified hundreds of genetic variations that are thought to be associated with several. Based on this technology, the data obtained successfully showed the existence of genetic variants responsible for human height described by polygenic traits (Lin et al., 2017).

DNA sequencing is one more method that is employed. The technique of figuring out the nucleic acid or nucleotide sequence in DNA is called DNA sequencing. Because it provides the instructions required for the construction of a living thing's body, he sequence is referred to as a DNA sequence that is used as the most basic information of a gene or genome because it contains the instructions needed for the formation of the body of living things (Bazyari et al., 2023). By comparing the sequences of genes or other DNA fragments with those of other known DNA sequences, DNA sequencing can be used to identify and determine the function of these entities (Blinova et al., 2022).

This test is often used for Single Nucleotide Polymorphism (SNP) analysis, which is a genetic variation that involves a change of a single nucleotide in DNA

(Ozhegov et al., 2020). SNP analysis can help in identifying specific locations in the genome that are associated with disease. SNPs can be identified and analyzed to determine if a particular allele is associated with a disease or phenotype (Blinova et al., 2022).

Sequencing has several methods. One of them is the sanger sequencing method, which is a method of extending or extending the DNA chain starting at a specific site on the printed DNA using short oligonucleotides called primers that are complementary to the DNA at that site (Ozhegov et al., 2020). This method is the most commonly used method, and has successfully identified many genetic variations (Ammar et al., 2024; Inoue et al., 2011; Plachy et al., 2019; Toni et al., 2024; Xiao et al., 2020). Another method is the NGS (next generation sequencing) method. Tests conducted in China using NGS successfully identified a new heterozygous missense mutation in exon3 (c.926C>T, p.S309L) of the type-I IGF1R gene (Yang et al., 2019).

Human genome analysis can also be done with CNVs (copy number variant) techniques. The term CNVs refers to intermediate-scale genetic changes, which are generally defined as segments longer than 1,000 base pairs but usually less than 5 megabases, which is the level of cytogenetic resolution. CNVs include both extra copies of sequence (duplications) and loss of genetic material (deletions) (Mudassir et al., 2023). Since CNVs alter genome structure, such mutations formed along with inversions and translocations are collectively classified as forms of genome structure variation (Tyagi et al., 2024). From the results of several tests conducted, it is known that CNVs are responsible for human variability, one of which is human height. In studies conducted in the USA and Egypt, it was proven that homozygous IGF1R gene mutations have an impact by having abnormal length and birth weight and experiencing growth failure which causes postnatal short stature (Batey et al., 2014; Fadel et al., 2021).

The Role of Genetics in the Incidence of Stunting

In severe stunting or short stature (status deviation (SD) < -2.5), short st ature is classified as having idiopathic short stature (ISS) or small for gestational age (SGA), also known as being born small (Zhao et al., 2024). Many of the healthy short stature children have short parents, thus strongly indicating the influence of genetic factors on their height. Studies conducted in the USA found a similarity of mutations in the IGF1R p.R36Q gene between ISS patients and their parents who both have a height SD < -2.5 (Fadel et al., 2021).

In another study conducted in China in the case of a Chinese boy with a diagnosis of SGA, a missense mutation c.926C>T (p. S309L) in IGF1R was identified, with the patient's mother and grandfather having the same IGF1R gene mutation, and both having SD < -2.5 (Batey et al., 2014). These studies may support the hypothesis that rare allelic variants (many of which only occur in one family) have a large impact on height determination without other significant findings. In some patients the lack of major symptoms often makes their condition clinically unrecognizable and, therefore, these patients are often classified as ISS or SGA (Zhao et al., 2024). This classification can only be done with a genomic approach, so it is hoped that this knowledge will have a major impact on the follow-up and treatment of these children.

Influence of GHSR and IGF Genes on the Incidence of Stunting

GHSR has an important role in the regulation of growth hormone and can affect human body growth. If there is a genetic abnormality or genetic variation in GHSR, it can contribute to growth disorders and potential short stature or stunting (Yuan et al., 2016). It is estimated that up to 80% of the diversity in short stature among individuals is influenced by genetic composition. The anterior pituitary releases growth hormone when it is secreted together with ghrelin (Andrews et al., 2021). Acid Labile Subunit (ALS), insulin-like growth factor binding protein 3 (IGFBP3), and IGF-I-like growth factor are all synthesized in the liver in response to growth hormone (GH). Through IGF-I, GH both directly and indirectly promotes linear bone development. Apart from the hypothalamus, gherlin alone controls the pituitary's release of growth hormone. Generally speaking, IGF1R has been utilized as a stand-in marker for GH because of its extended half-life. GH-independent metabolic variables, however, also have an impact on IGF1R (Ndandala et al., 2022).

Several studies have shown an association between the GHSR and IGF1R genes in the incidence of stunting. In a study conducted in the Czech Republic, it was found that the height of Asians generally involves protein tyrosine phosphates (PTP) and family, IGF and GHSR with the discovery of SNPs in nearly 900 patients with a family history of stunting and 74 of them were shown to be related to the cause of stunting (Plachy et al., 2019). In another study, it was found that there was an association between obesity and the incidence of stunting which was influenced by the GHSR-1R snp rs292216 gene in 78 obese adolescents in Indonesia (Muhammad, 2018). Then this statement is supported by research conducted in the USA, with clinical observations in individuals carrying genetic variants in the IGF regulatory system with mouse studies as controls resulting in growth failure with loss of function of IGF1R, IGF-II, ALS, PAPPA-2 and IGF1R (Qian et al., 2022).

GHSR and IGF Gene Polymorphisms in Stunting

The role of GHSR and IGF gene SNP variations on gene activity affecting stunting incidence has been extensively studied in recent years (Ozhegov et al., 2020). In a study conducted in Egypt, 2 GHSR gene mutations were found with one new variant reported It is found in exon 2 of the GHSR gene and includes a previously known uncommon variant (c.1021G>A) as well as a unique frameshift heterozygous variant in exon 2 (c.1043dup). The constitutive signaling activity of GHSR is significantly impacted by these alterations (Ammar et al., 2024). The data is then supported by findings conducted in Japanese patients with short stature families found 4 point mutations associated with GHSR activity including ΔQ36 (c.106-108 del CAG), P108L (c.323C>T), C173R (c.517T>C), and D246A (c.737A>C). A number of processes contribute to the acquisition of these alterations, including as intracellular retention, decreased ghrelin binding activity, and compromised agonist and reverse agonist-stimulated receptor signaling (Inoue et al., 2011). In certain situations, GHSR can reduce appetite, which delays puberty and stunts growth. Studies done in Brazil provide evidence for this; of the five discovered mutant variations, two (p.Ser84Ile and p.Val182Ala) led to reduced basal activity, which was partly attributed to lower expression on the cell surface. Ghrelin potency abnormalities are also linked to the p.Ser84Ile mutation (Pugliese-Pires et al., 2011).

IGF1R gene mutations at nucleotide position c.3405C>G have been found to occur in another study carried out in Japan. These mutations lead to abnormalities in the tyrosine phosphorylation of IGF1R receptors and have a dominantly negative effect on IGF1R receptors (Xiao et al., 2020). Additional IGF1R mutations were discovered in a different investigation conducted in Japan. Two novel heterozygous nonsense mutations, p.Q1250X and p.W1249X, have been identified. The C-terminal region of IGF1R is impacted by these mutations, and this lowers IGF1R expression via the ERAD pathway. The signaling system known as IGF-I/IGFIR is crucial for both prenatal and postnatal growth. IGF1R haploinsufficiency results in decreased IGF1R signaling, albeit occasionally normal IGF-I responses can still occur. Allelic IGF1R loss resulting from chromosome 15q26 deletion or allele-specific IGF1R mutations that disrupt the mRNA can cause IGF1R haploinsufficiency (Fujimoto et al., 2015). In a different Egyptian investigation, out of 40 individuals (2.5%), a heterozygous deletion of IGF1R (exons 4 to 21) was found in patients with short stature and their families (Batey et al., 2014). This result is in line with the findings of another group that identified 2 out of 100 patients in one trial as having IGF1R gene mutations and 2 out of 128 SGA patients in another study as having IGF1R heterozygous deletions (Labarta et al., 2013).

CONCLUSION

Genetic studies on GHSR and IGF highlight the importance of genetic factors in regulating growth hormone production and the body's response to it. Genetic variations in GHSR and IGF1R can affect growth signaling pathways, with several studies showing an association between genetic variations in GHSR and IGF and the risk of growth hormone production or response leading to stunting. Understanding the genetic aspects of stunting is increasingly important, it is hoped that this review can provide more insight into how genetics can moderate the risk of stunting, especially through the regulation of growth hormones GHSR and IGF.

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