Hirschsprung Disease in Jordan: A Review and Status Update

Shadi Shahatit and Asem M Alkhateeb

Abstract

Hirschsprung disease (HSCR) is a congenital disorder characterized by the absence of neuronal ganglions in the intestine, leading to impaired bowel movement and serious constipation. It affects 1 in 5,000 live births. HSCR can be syndromic or non-syndromic and the genetics behind it is complex as many genes are implicated with its etiology and prognosis, most importantly, the RET gene. HSCR is diagnosed from colon biopsies, but novel molecular testing of many gene panels is promising. Furthermore, HSCR prevalence across English, Hispanic, African American, Asian, or Arabian populations have been investigated, and the alleles frequencies of RET ClinVar entries provided. In this review, we aim to discuss the status of the disorder in Jordan. Seven publications were summarized and subgrouped into: (1) case reports, (2) mortality rates, and (3) genetic testing. Also, information was gathered from Jordanian families with HSCR children about health and social aspects in Jordan. The research in Jordan is modest and demands further investigation on the molecular basis of the diseases within the Jordanian population so that optimal management can be expected and awareness raised for this rare disease in the society.

Keywords: Hirschsprung, Jordan, intestine, RET gene

INTRODUCTION

Hirschsprung disease (HSCR) is a neurodevelopment disease classified as a rare condition of neurocristopathies. It involves the absence of parts of the enteric nervous system that surround the intestine of the digestive system, resulting in the malformation of the GI tract, peristalsis, and defecation. This leads to colon enlargement due to the accumulated feces (aka, congenital megacolon) (Figure 1).

Figure 1: Normal colon vs. megacolon in HSCR (adapted from [1])

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The pathology of the disorder lies in the inability to develop fully migrated, proliferated, and differentiated neural ganglions in the distal part of the colon. These arise from neural crest cells in the developing embryo but leave these parts without their commander in chief: the enteric nervous system (ENS). Hence, HSCR is also called colonic aganglionosis [2]. The signs and symptoms of HSCR vary depending on the severity of the individual case, but, generally, they appear very early with the inability to defecate within 48 hours after birth. Other symptoms may manifest as a swollen belly, vomiting, constipation or gas, diarrhea, and delayed passage of meconium. However, sometimes symptoms may appear later in life in older children, including abdominal distension, chronic constipation, failure to thrive, and fatigue [3].

In this review, the genetic architecture, allele frequency, prevalence, and the available molecular genetic testing of HSCR will be discussed as well as the status of the disease in Jordan, including published research locally and internationally and the social/health experience of Jordanian families with HSCR. This will give us a better understanding which will lead to better management for HSCR in our region.

**Enteric Nervous System Physiology**

During embryogenesis, the zygote develops into a gastrula that consists of three germ layers: the ectoderm, mesoderm, and endoderm. The ectoderm is responsible for creating the whole nervous system, alongside other structures. After neurulation, cells in the ectoderm form two structures:

1. Neural tube, which develops into the central nervous system (brain and spinal cord);
2. Neural crest cells (NCCs), which develop into the peripheral nervous system (sympathetic, parasympathetic, and enteric nervous system).

Enteric neural crest cells (ENCCs) are the stem cells that migrate into the region of the GI tract, proliferate, and further differentiate into mature ganglions (a group of neuronal cell bodies) and nerves (a group of neuronal axons). These early crest cells are the precursors for the ENS, so any malformation in their development is called neurocristopathies. ENS, also known as the second brain, is a complex structure generally organized similarly to the brain and mostly operating autonomously. Its major role is to organize the digestion process, regulate the absorption of water and nutrients, and excite/inhibit smooth muscles to cause relaxation/contraction to move the GI content in one direction into the rectum.

The ENS is organized into two distinct but interconnected plexuses (Figure 2):

1. Submucosal plexus, which lies in the submucosa layer of the intestine;
2. Myenteric plexus, which lies in between the two muscular layers in the muscularis externa.

![Figure 2: The GI tract tissue layers](image)

**Hirschsprung Disease Genetics**

Hirschsprung disease has a complex genetic architecture. It can be non-syndromic or part of a syndrome with certain chromosomal anomalies that are a definitive feature of the associated syndrome, such as Down syndrome, Waardenburg syndrome, Bardet-Biedl syndrome, multiple endocrine neoplasia 2A, Mowat-Wilson syndrome and many others [3, 5, 6]. About 12% of HSCR patients are reported to have chromosomal abnormalities and 10% can have Down syndrome as well, which increases the disease risk by 50- to 100-fold; Down syndrome is the most common anomaly associated with HSCR [3, 7–9].
Moreover, HSCR can be sporadic or familial. In the cases of familial/syndromic HSCR, these appear to follow a dominant mode of inheritance, where one abnormal copy is sufficient to cause the phenotype. However, it still has incomplete penetrance and variable expressivity, shedding more light on modifier gene effects and gene-environment interactions [10].

Continuous research is required to understand the molecular biology behind HSCR, especially the sporadic forms. Until now, the genes involved in its development fall into four major categories:

1. RET/GDNF pathway
2. EDNRB/EDN3 pathway
3. Transcription factors (e.g., SOX10, PAX3, PHOX2B, ZFHX1B, TITF-1)
4. Others, including morphogens (e.g., Hedgehog/Notch, Netrins, Semaphorins) or cytoskeleton-related genes (e.g., KIAA1279).

Most prominently, the RET gene has been implicated as a major risk factor with ~200 mutations and ~20% of cases are caused by such mutations, and so 30% of the HSCR heritability can be explained by RET gene. Approximately 50% of familial and 20% of sporadic HSCR cases are associated with variants of this gene [10]. The RET gene, located on chromosome 10 q11.2, is a proto-oncogene which encodes a tyrosine kinase transmembrane receptor.

The produced protein has a large extracellular domain, a transmembrane domain, and an intracellular kinase domain, with four ligands: GDNF, NRTN, ARTN, and PSPN. The binding of such ligands, especially GDNF, activates downstream signaling pathways that promote cell growth, migration, proliferation, and differentiation, as well as the survival of neurons in the ENS [11].

In addition, recent research from NGS, iPSC, and gene editing technologies links the amyloid precursor protein (APP) with the pathology of HSCR. APP is heavily involved in Alzheimer’s, once cleaved into the Amyloid-β (A-β) that accumulates and causes neural death [12]. A rare variant was detected in BACE2, which is a homolog of BACE1 that expresses a protein that cleaves APP and prevents the accumulation of A-β. This variant reduces the protein’s activity, leading to higher levels of enteric neuron apoptosis [9, 13].

Overall, the development of the ENS in the distal colon is a tightly regulated spatiotemporal process that requires the coordination of several proteins, morphogens, transcription factors, signaling pathways, and even miRNAs and epigenomes. Thus, it is not surprising to annotate so many risk factors and genes with the same aganglionic phenotype of HSCR. In conclusion, insights into the biology of HSCR can be provided by scenarios of major changes in singlets with modestly sensitive genetic predisposition, or accumulative polygenic factors with a highly sensitive genetic predisposition and the spectrum in-between.

**Molecular Genetic Testing**

Diagnostic evaluation tests for HSCR include [3]:

- Contrast enema radiographs: a safe contrast agent is pumped into the rectum and intestine of the patients, and then a special type of x-ray image is taken;
- Anorectal manometry: the pressure of the rectum muscles, and the mural fluxes necessary for the bowel movement, can be tested after the introduction of a special type of measuring balloon in the rectum;
- Biopsy from the rectum/colon tissue: this is the gold standard method of HSCR diagnosis, whereby the pathologist can view the biopsy by searching for signs of aganglionicism.

Herein, the most critical factor is the pathologist’s experience and familiarity with the disease’s biopsy, and the advantages/disadvantages of the approach being used in the laboratory.

Regarding molecular testing, MedlinePlus mentions a number of clinical tests in the Genetic Testing Registry (GTR/NIH) for HSCR susceptibility, organized into categories, for example, targeted variant analysis, sequence analysis of the entire coding region, deletion/duplication analysis, or RNA analysis [14]. Nevertheless, such tests are not a specialized diagnosis for HSCR as they include many other conditions under investigation simultaneously. Additionally, genetic panels including multiple factors can be helpful in personalized cases. Blueprint Genetics, a genetic testing company, offers a 15-gene panel test with an assessment of the non-coding variants as well. The genes are RET, EDNRB, EDN3, BDNF, PHOX2B, CELSR3, KIF1BP, L1CAM, MITF, NRG1, NRTN, PAX3, ZEB2, RMRP, and SOX10 [15].

The complexity of HSCR genetics can be mirrored by several genetic changes in more than 20 genes acting as susceptibility risk factors. Therefore, an analysis of mutations/variants may have moderate to limited diagnostic power as HSCR has incomplete penetrance. In the future, it is hoped that further research will improve understanding of the etiology and genetics of HSCR so that gene panels with many risk factors can be harvested to calculate...
the susceptibility with higher diagnostic power, and eventually molecular technologies can be well-established in the standardized clinical settings.

**Allele Frequency and Prevalence in Different Populations**

The worldwide incidence of Hirschsprung disease is approximately 1 in 5,000 live births [11]. Yearly, ~140,000,000 babies are born around the globe; hence, ~28,000 cases of HSCR are born per year. The epidemiology of the disease varies across ethnic groups, with Asians having a higher prevalence than others. More specifically, Hispanics have 1/10,000, Caucasian-Americans 1.5/10,000, African Americans 2.1/10,000, and Asians 2.8/10,000 cases per live birth. Also, there is a sex bias, with a preponderance of affected males and a sex ratio of 4:1 [5]. In Europe, the UK and Ireland have 1.8/10,000 cases per live births, and a male/female ratio of 3.3:1 [16]. In the Arabian Gulf, Parkash Mandhan published an article in 2011 discussing the current status of HSCR diagnosis and operated surgeries at the time of publication from several surgeons’ points of view. In Muscat, Oman, 85 patients with HSCR had surgical intervention in an eight-year period (2001–2009) with a mortality rate of 0% at the Royal Hospital and, in Dubai in the United Arab Emirates, 68 patients with HSCR were diagnosed in a ~6-year period starting from 2004 at Al-Wasal Hospital. In Doha, Qatar, 39 patients were diagnosed with HSCR during a ten-year period at the Hamad Medical Corporation [17].

As explained earlier, the genetic landscape of this disorder is variable and involves many risk factors with many scenarios, but the RET gene is the most frequently mutated in this realm. It has more than 200 hundred mutations associated with the disorder, and so to simplify the allele frequency of this particular gene, Table 1 presents all allele entries with their corresponding frequency on various genome databases as linked to HSCR on the ClinVar database. This is a well-established public database that aggregates information about genomic variations and their relationship to human health, initiated by the National Institute of Health (NIH/NCBI).

### Table 1: Allele frequency of RET gene mutation reported in ClinVar with a link to HSCR.

<table>
<thead>
<tr>
<th>Allele</th>
<th>Global minor allele frequency (GMAF)</th>
<th>The Genome Aggregation Database (gnomAD)</th>
<th>1000 Genomes Project</th>
<th>Trans-Omics for Precision Medicine (TOPMed)</th>
<th>The Genome Aggregation Database (gnomAD), exomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NM_020630.5(RET)c.-200A&gt;G</td>
<td>0.26318</td>
<td>0.77447</td>
<td>0.73682</td>
<td>0.77508</td>
<td>-</td>
</tr>
<tr>
<td>NM_020630.5(RET)c.-196C&gt;A</td>
<td>0.40955</td>
<td>0.40699</td>
<td>0.40955</td>
<td>0.42386</td>
<td>-</td>
</tr>
<tr>
<td>NM_020975.6(RET)c.-187C&gt;A</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NM_020975.6(RET)c.-173A&gt;G</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>NM_020975.6(RET)c.-160G&gt;T</td>
<td>0.00140</td>
<td>-</td>
<td>0.00140</td>
<td>0.00033</td>
<td>-</td>
</tr>
<tr>
<td>NM_020975.6(RET)c.-158G&gt;A</td>
<td>-</td>
<td>0.00001</td>
<td>-</td>
<td>0.00003</td>
<td>-</td>
</tr>
<tr>
<td>NM_020975.6(RET)c.-132G&gt;T</td>
<td>-</td>
<td>0.00103</td>
<td>-</td>
<td>0.00097</td>
<td>-</td>
</tr>
<tr>
<td>NM_020975.6(RET)c.-51C&gt;T</td>
<td>-</td>
<td>0.00012</td>
<td>-</td>
<td>0.00029</td>
<td>0.00026</td>
</tr>
<tr>
<td>NM_020975.6(RET)c.18C&gt;T (p.Met6=)</td>
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<td>0.00001</td>
<td>-</td>
<td>0.00001</td>
<td>0.00001</td>
</tr>
<tr>
<td>NM_020975.6(RET)c.73+9277T&gt;C***</td>
<td>0.24261</td>
<td>0.77443</td>
<td>0.75739</td>
<td>0.79885</td>
<td>-</td>
</tr>
</tbody>
</table>

***Note that regarding the last entry (NM_020975.6(RET)c.73+9277T>C), Karim et al. reported it (rs2435357) as a common variant with large effects, with frequency information for the Qatari population as follows: T=0.282 (61/216, Qatari).***

**Status in Jordan**

In Jordan, a limited amount of primary research has been published on the status of HSCR. Seven publications are discussed here, grouped as: (1) case reports, (2) mortality rates, and (3) genetic testing. We note that the primary focus of the studies was not HSCR, although the latter was involved in the studies.

**Case Reports**

**Case report #1:** In 2014, a study by Saleem et al. at Jordan University Hospital published an extremely rare case report of a female infant diagnosed with three abnormalities: (1) Hirschsprung disease; (2) Cat eye syndrome, a rare chromosomal disorder characterized by...
malformations in the eye, heart, skin, and many others, caused by an extra portion of chromosome 22 and leading to partial tetrasomy or trisomy; and, (3) anorectal malformation—an imperforate anus or ano-rectal malformations are birth defects in which the rectum is malformed, leading to problems with defecation. Only three patients in the English literature have been reported with this clinical history, and so the authors argue that this case is the fourth to be reported. We provide a table with a brief clinical comparison between the three cases and this recent fourth addition.

Unfortunately, the patient had a severe prognosis and she passed away after medical complications in the intensive care unit. Finally, an essential remark that can be a guide for future research is the association of potential genes in the duplicated segment of chromosome 22, specifically 22q11.2 which caused cat eye syndrome in the development of the ENS, especially when ano-rectal malformations are also manifested in this trinity of suffering [18].

Case report #2: In 2021, a study by Suoub et al. at Mut’ah University in Karak, Gardens Hospital, and Jordan Hospital in Amman discussed from a clinical perspective the rare case of a 21-year-old male patient in Jordan. The patient was diagnosed with HSCR at an early age and surgery was performed when he was two years old; as a consequence of the treatment, he had a urethral injury that was treated accordingly. In the future, he experienced recurrent symptoms related to urethral narrowing and haematuria and, after an attempt at treatment in the emergency room, he had a pseudoaneurysm (i.e., leaking of blood into the surrounding tissue after blood vessels ruptured). He was immediately transferred to the operating room and his bleeding was controlled.

The authors do not discuss in-depth the effect of past HSCR history on the current health problems of the disease, but instead present a clinical perspective with a literature review and treatment/diagnosis options that are not directly related to the scope of this research on HSCR [19].

Mortality Rates
In 2021, Aloweidi et al. investigated the mortality rates in Jordan University Hospital, a teaching and referral hospital. They studied the period from 1990 to 2007 with 200,901 patients and 241,300 performed procedures; as 1,290 patients died, the surgical death rate was 0.64%. Death causes were divided into four classes: (1) surgical adverse events, (2) anesthetic adverse events, (3) patient’s condition, and (4) indeterminate causes.

What is noteworthy about this study is that 13 patients of the 1,290 deceased were diagnosed with HSCR, representing 1% of the sample. Unfortunately, the paper does not discuss any more specific analysis regarding HSCR [20].

In 2009, Sarayrah also studied mortality rates, albeit those related specifically to Neonatal Intestinal Obstruction (NIO) at King Hussein Medical Center, between 2008 and 2009. HSCR was included as a cause of NIO, alongside many other disorders. The mortality rate was 28.6% with 36 deaths among a total of 126 neonates. The major factors affecting death rates in NIO at the center were sepsis, repeat surgery, postoperative bleeding, and associated congenital anomalies [21].

In 2020, Almajali et al. conducted research on neonatal records of NIO at Jordan University Hospital (JUH), spanning six years from 2012 to 2018; this comprised 59 neonates with a male to female ratio of 1:1.07 [22]. The mortality rate was 5%, and 5% reported chronic constipation as a long-term complication. In JUH, HSCR was the second leading cause of NIO with 16 cases (27% of the total cases), after anorectal malformation. The average age of diagnosis for HSCR was 9.9 days, whereas most surgical procedures were generally performed by one year, with a range of seven to 18 months. One patient suffered from both HSCR and imperforate anus. Also, the paper presented some general statistics of HSCR in agreement with the literature and showed an appreciation of the complexity of the disorder. The management of the disease in their institute covers, initially, stoma creation and biopsy collection for the histology laboratory. Then, pull-through surgeries with the Duhamel procedure are performed that cut out the aganglionic portions and channel back the ganglionic portion of the colon to the anus. The results are similar to other research in medical centers in developing countries such as Nigeria, India, and Ethiopia. Finally, the authors advised regular follow-ups in the pediatric surgery clinic to better address long-term complications [22].

In 2005, Al-Momani et al. [23] conducted more sophisticated research on children with intestinal obstruction at JUH spanning 30 years from 1973 to 2003, which comprised 306 children with data on age, sex, clinical presentation, diagnostic investigations, treatment mode, and results. The mortality rate was 3.9%, and the recurrence rate was 7.8%, but 13.4% was the postoperative complication rate, with wound infection being the most common complication. In JUH, congenital abnormalities were the second leading cause of intestinal obstruction, with 90 cases (29.4% of the total cases)
and an average age of 1.8 years. Of the congenital abnormalities, HSCR was the second most common cause with 21 cases and an average age of 1.2 years, again after anorectal malformation. In this way, HSCR was the third leading cause after intussusception and anorectal malformation, respectively. Treatment-wise, 79.7% of patients underwent surgical intervention. The etiology of intestinal obstruction varies widely across the globe and from time to time; however, the seriousness of the condition compels the best management possible for the children. Finally, the authors aimed to better understand the presentation, etiology, management, and outcome of intestinal obstruction in Jordan [23].

Genetic Testing
In 2020, Altamimi and collaborators from Jordan University of Science and Technology and the University of Jordan, as well as a number of research institutes in the USA, published an article studying the effect of genetic testing on diagnosing gastrointestinal pediatric patients with previously undiagnosed diseases [24]. They showed the importance of whole exome sequencing (WES) and its diagnostic potential in the pediatric clinic, especially in cases of undetermined diagnosis. The study focused on four consanguineous Jordanian families with five unresolved cases within one family (family 2, the pedigree is shown in Figure 3) which had an initial diagnosis of HSCR. Their symptoms started at birth and included a distended abdomen, fecaloma, food intolerance, enterocolitis, vomiting, and failure to thrive. With the presentation of a form of intestinal obstruction, the patient underwent appendectomy and colostomy creation to create a stoma in the abdomen in the colon region for feces secretion. Unfortunately, some symptoms reoccurred and further intestinal pathology analysis with multiple biopsies showed that ganglions were present in the rectum, which thus excluded HSCR. An ileostomy was performed to create a stoma in the small intestine region, but feeding intolerance and severe distention of the abdomen were still present. This has suggested the diagnosis of a different condition called chronic intestinal pseudo-obstruction (CIPO). Whole exome sequencing was performed to reach a more accurate diagnosis at the molecular level. After WES, the patient (II-1) was found to be heterozygote for a missense mutation in exon 7 of ACTG2 gene in chromosome 2 (rs587777387): c.769C>T, p.Arg257Cys. As seen in the chromatogram in Figure 3, the patient has de novo heterozygous mutation (C/T) while the parents are homozygous wild type (C). This variant is in agreement with a previous finding in the literature, a de novo heterozygous ACTG2 variant in association with CIPO [25]. The malfunctioning of ACTG2 is associated with visceral myopathy, with involvements in the bladder and intestine. Sadly, the patient’s condition worsened and the child passed away aged 1.5 years. The overall results of this research are a 100% diagnostic rate for the four families and finding causative variants for each case, creating the potential to implement WES in the diagnosis of pediatric diseases to achieve optimal management of the disorder as early as possible [24].

Figure 3: The pedigree and chromatogram of Family 2 in Altamimi et al. [25]. The proband II-2 was misdiagnosed with HSCR, and then correctly diagnosed with CIPO. The chromatogram of the parents (I-1 and I-2) has the wild type allele only (C), whereas the patient’s (II-2) has heterozygote alleles (C/T)
Social and Health Experiences

Aside from a scientific literature review in Jordan, an investigation was conducted with regards to the social and health aspects of HSCR from the experience of Jordanian families having children with the disease and receiving management in Jordan. Contact was made via social media, a Facebook group founded by the mothers of affected children to offer support to each other when needed. To organize the focus of their perspectives, four fields of questions were implemented:

1. Personal Experience
A feature of HSCR is its clinical variability, as each individual has a unique experience. Generally, the diagnosis is hard to reach, and a number reported several misdiagnoses with misleading doctors’ advice before reaching the correct diagnosis. As a negative experience, some proposed that more collaboration between different clinics (surgeons, gastroenterologists, and pediatricians) is needed to achieve better outcomes, and others complained about poor practices in dealing with children post-operation, as well as the overall ignorance observed regarding such rare diseases, even among healthcare providers (nurses, ER workers), except for the operating doctors.

2. Treatment Process and Healthcare Services
Surgical interventions and healthcare services were excellent, including the operating surgeons and pediatricians who provided extensive help to patients. Also, almost all cases were successfully treated after surgery, despite a few complications including long-term severe intertrigo, skin rashes, gas, and constipation. Some had a short delay in the surgery appointment due to the lack of a device.

3. Financial Cost
HSCR surgical costs are relatively high, ranging from 3000–5000 JOD. Generally, health insurance companies do not provide support for congenital disorders unless specified. Also, the cost of the post-operative treatments and tools are relatively high (e.g., intestinal bags, drugs for constipation, and intertrigo).

4. Psychological Health and Social Support
Unfortunately, the psychological support for the family after receiving the diagnosis and throughout the treatment plan was generally absent, although it plays an essential role since such diseases can cause severe psychological issues. In Jordanian society, social support varies depending on the families themselves; some were able to spread awareness to their social groups, whereas others were less supported due to the rareness of this disease.

We note that the data provided were merely according to the inspirational mothers who generously shared their experiences, but some limitations may exist as no standard questionnaires were completed or statistical analysis with a representative sample conducted, which may affect how the results can be generalized. However, investigating individual Jordanian experiences is vital and useful.

As a general trend, Jordanian health management for HSCR is extremely good in regard to surgical interventions. However, it lacks health education, genetic counseling services, and mental health support; most of those affected educated themselves on HSCR and special care requirements, without a structured presentation from the healthcare providers, and they still lacked a clear understanding of the heredity of HSCR. Hopefully, awareness of this rare disease can be increased among the Jordanian population and healthcare providers, including of its psychiatric effects and complex genetics, as more research is produced in the future.

In conclusion, Hirschsprung disease is an important disease that has been seen frequently in Jordan. This review gives an updated comprehensive reference for those interested in following up the clinical, genetic, and social aspects of Hirschsprung disease in the region.
REFERENCES


16. Bradnock TJ, Knight M, Kenny S, Nair M, Walker GM; British Association of Paediatric Surgeons
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مرض هيرشسبرنج: مراجعة وتحديث الحالة في الأردن

شوتي شحاتيت، عاصم الخطيب

الملخص

مرض هيرشسبرنج هو اضطراب خلقي يتميز بغياب العقدة العصبية في الأمعاء مما يؤدي إلى ضعف حركة الأمعاء وإمساك خطير. يصيب 1 من كل 5000 مولود حي، يمكن أن يكون متلازمًا أو غير متلازم، والجينات التي تقف وراءه معقدة مع وجود العديد من الجينات المترابطة في مسببات التشخيص، وأهمها جين RET. يتم تشخيص HSCR من خلال خزعات القولون، ولكن الاختبار الجيني الجديد للعديد من المجموعات الجينية يمكن أن يكون واعداً في المستقبل. علاوة على ذلك، يختلف انتشار HSCR عبر المجموعات السكانية المختلفة كذي الأصول الأوروبية، أو الأصول الإسبانية، أو الأمريكية الأفراقة، أو الآسيويين، أو العرب، ويختلف ترددات نماذج الجين RET في هذه المراجعة. نهدف إلى مناقشة سمات مرض الاضطراب في الأردن. تم تلخيص سبع منشورات وتجميعها في (1) تقارير الحالات، (2) معدلات الوفيات، و (3) الاختبارات الجينية. كما تم جمع معلومات من العائلات الأردنية التي لديها أطفال HSCR حول الجوانب الصحية والاجتماعية في الأردن. البحث في الأردن متواضع ويطلب المزيد من التحقيق. المراجع المذكورة هنا تشير إلى الأدوار الأساسية للأردن في الأمراض حتى يمكن توفير الإدارة المثلى بالإضافة إلى زيادة الوعي بهذا المرض النادر في المجتمع.

الكلمات الدالة: هيرشسبرنج، الأردن، أمعاء، جين RET.