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Situs Inversus: Organ inversion causes and its clinical implications

Mónica Olivares-Rojas [1,*], Samantha S. Rodríguez-Martínez [1], Jonathan O. Roldán-Vázquez [1], Sandra F. Retana-Moreno [1], Aurora S. Galindo-Jara [1] and Brissia Lazalde [2]

[1] *Faculty of Medicine and Nutrition, Universidad Juárez del Estado de Durango, Mexico.*
[2] *Department of Genetics, Faculty of Medicine and Nutrition, Universidad Juárez del Estado de Durango. Durango, Dgo. Mexico.*

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Abstract

A finding that stands out in diagnostic imaging techniques and, certainly, in the operating room is the strange anomaly of *Situs Inversus*. Recent studies show the close relationship that exists between genetic traits and the probability of presenting this anomaly. Furthermore, the genetic traits found repeated in the population that presents it, seem to indicate a series of syndromes that imply a better understanding of this pathology. Today, *Situs Inversus* continues to be studied since it is still unknown the rotation mechanism, which not only may affect each patient's treatment, but also medicine in general.

Keywords: *Situs Inversus*; Kartagener Syndrome; Congenital Condition; Variants; Mutations; Opposite

1. Introduction

Situs inversus (SI) is a congenital anomaly, which means that the visceral organs are located on the opposite side of the thoracic and abdominal cavities. Normally, the heart is on the left side of the chest, the liver on the right side, the spleen on the left side, etc. But in this case it's the opposite [1]. There are different variants of SI where only certain organs are translocated; when present with dextrocardia (only 3-5% of cases showing congenital heart disease, primarily transposition of the great vessels), it is termed as *Situs inversus totalis* (SIT) (figure 1) [2,3]. This condition might cause difficulties during diagnostic and therapeutic procedures, and it's usually diagnosed later in life from imaging studies due to other health concerns [3]. In this article we will be focusing on SIT where all the organs are affected and its association with other detrimental conditions.

Since this is a birth defect, the genetics are what determine the existence of SI, so in this text we will present why it occurs and what exactly is involved in these patients. Uncomplicated cases are frequently undiagnosed in neonates. Most diagnoses are made later through radiographic examinations for unrelated conditions. For example, Harrington et al. described a six-week-old infant presenting with vomiting and weight loss, leading to the identification of SIT [3].

Diagnosis of SIT typically does not occur in the neonatal period; it is diagnosed in neonates only after radiographic evaluation for respiratory distress or another reason [4].

This tends to be familial and occurs in association with many different types of syndromes with cardiac anomalies in approximately 3–9 percent of cases [3].

* Corresponding author: Mónica Olivares-Rojas

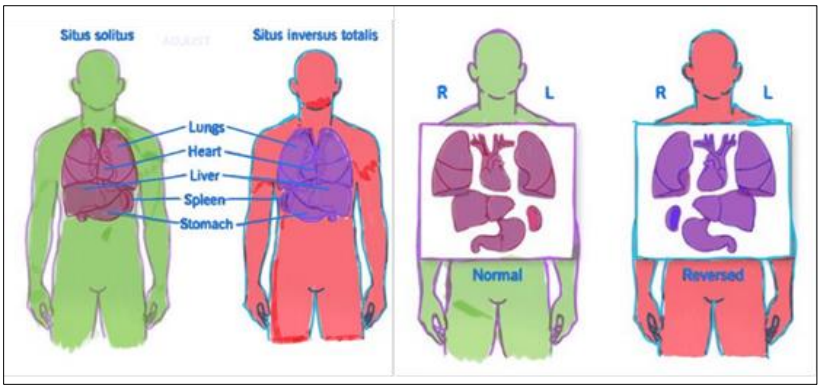


Figure 1 Comparison between the normal location of organs "*Situs solitus"*, and the opposite of it "*Situs inversus totalis*". [5]

2. Associated genes

The most likely monogenic cause for SI are Kartagener syndrome or primary ciliary dyskinesia (PCD), also there are non-PCD SI cases. The associated genes in these syndromes are in Table 1 [6-19].

Table 1 Associated genes with SI

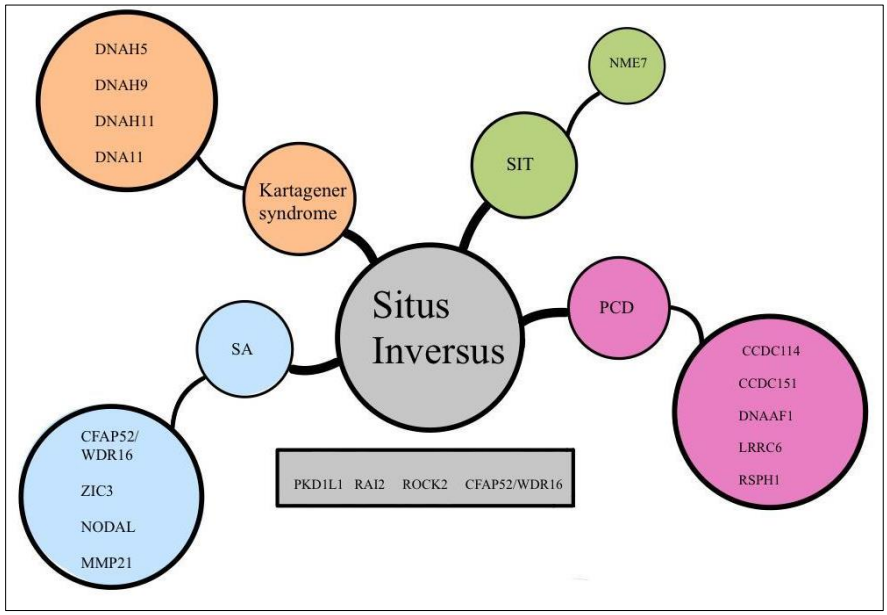
Gene	Syndrome	Mode of inheritance
CCDC114	PCD	AR
CCDC151	PCD	AR
CFAP52/WDR16	SI/SA	AR
DNAAF1	PCD	AR
DNAH5	Kartagener	AR
DNAH9	Kartagener	AR
DNAH11	Kartagener	AR
DNAI1	Kartagener	AR
LRRC6	PCD	AR
MMP21	SA	AR
NME7	SIT	Deletion
NODAL	SA	AD
PKD1L1	SI	AR
RAI2	SI	XLR
ROCK2	SI	AD
RSPH1	PCD	AR
ZIC3	SA	XLR

*PCD, Primary ciliary dyskinesia; SI, *Situs inversus*; SIT, *Situs inversus totalis*; SA, *Situs ambiguus*; AR, Autosomal recessive; AD, Autosomal dominant; XLR, X-linked recessive.

3. Exploring the complexities of *Situs Inversus*: associated syndromes

SI, typically inherited as an autosomal recessive pattern, can be linked to a diverse spectrum of syndromes [5]. Such syndromes can impact multiple organ systems, with some leading to respiratory complications, while others may affect

reproductive health, gastrointestinal function, or immune system performance [20-23]. Patients with SI may experience varying levels of symptoms depending on the specific syndrome present, with conditions like Kartagener syndrome – marked by chronic respiratory issues due to ciliary dysfunction– being among the most notable [24]. Understanding these syndromic associations is essential for tailoring effective medical care and supporting long-term health outcomes for individuals with SI.



SIT: *Situs inversus totalis*, PCD: Primary ciliary dyskinesia, SA: *Situs ambiguus*

Figure 2 Syndromes and their respective genes, related to *Situs Inversus*

3.1. Primary ciliary dyskinesia

Predominantly inherited as an autosomal recessive rare disorder leading to recurrent and chronic upper and lower respiratory tract infections [25]; caused by genetic mutations that affect the tiny hairline cilia in the lungs, nose, and ears, thus impairing the ability to remove pollutants and germs, allowing the mucus buildup and some infections [23]. Approximately 40-50% of cases have mirror-image organ arrangement and other forms of heterotaxy [25].

3.2. Kartagener syndrome

It is an autosomal recessive genetic rare disease, usually accompanied by SI and PCD [13, 26]. Implies the alteration of not only the function but also the structure of the flagellum, affecting all the ciliated epithelium of the organism [27]. Clinically, there is a classical triad: chronic sinusitis, bronchiectasis, and SIT; it is worth mentioning that SIT is a unique feature of this syndrome since it occurs in approximately 50% of patients diagnosed with PCD [27, 28].

3.3. Asplenia syndrome

Asplenia talks about the absence of the spleen; such a condition can occur in a variety of clinical settings, and it can refer to an anatomical absence of the spleen or functional asplenia secondary to a variety of disease states [29]; the absence could be acquired or congenital.

Asplenia syndrome, inherited as an autosomal dominant pattern, is characterized by right isomerism or attempted bilateral sidedness [30]. It includes congenital asplenia in association with complex congenital cyanotic heart disease and situs anomalies of other thoracoabdominal organs [31]. It is important to emphasize that immune function will be affected.

3.4. Carpenter syndrome

This is a, rare, autosomal recessive multiple congenital malformation disorder characterized by multisuture craniosynostosis and polysyndactyly of the hands and feet, in association with abnormal left-right patterning and other features, most commonly obesity, umbilical hernia, cryptorchidism, and congenital heart disease [32]. As a clarification, the parents of a child with an autosomal recessive condition usually do not have the condition.

3.5. Polysplenia syndrome

Also known as left isomerism, it is a type of heterotaxy syndrome where there are multiple spleens congenitally as part of left-sided isomerism [33].

Usually predominantly seen in female patients, diagnosed in childhood or adulthood; only those with mild anatomical abnormalities reach adulthood without a diagnosis, later than asplenia syndrome, since associated congenital heart diseases tend to be less severe than those encountered in the later [33, 34].

4. Medical approach

Once the anomaly is identified, the patient will be referred to different specialists according to their needs. These are some examples of approaches and ways to treat different organic systems [35].

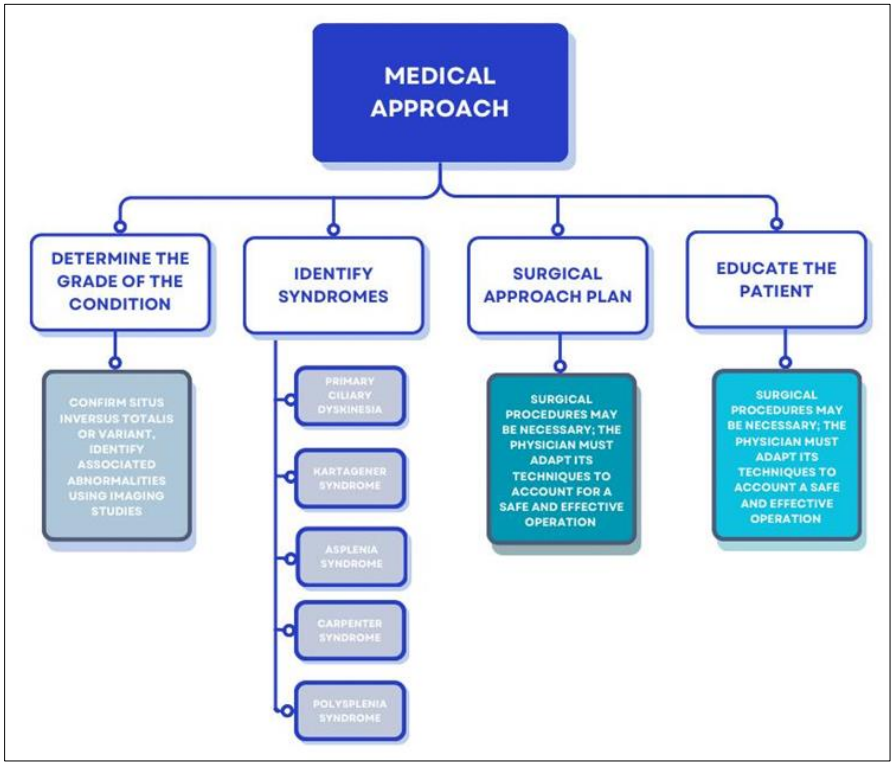


Figure 3 Brief guide for a medical approach in *Situs Inversus* [35]

5. Conclusion

Situs inversus is a surprising genetic malformation for its variations. In most cases, patients with this condition get to live a normal life, sometimes not even knowing that they present it; however, the diagnosis of common diseases can become complicated because of the ill-assorted anatomy.

That's why it is essential to keep it present in most medical fields and keep educating health personnel to reduce the chances of misdiagnosing and giving inadequate treatment. Common usage of imaging tests may help to quicken the problem-solving processes, and detecting whether or not the anomaly has an isolated or syndromic cause is crucial for an accurate prognosis and genetic counseling.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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