

# Septo-Optic Dysplasia Complex: A Heterogeneous Malformation Syndrome

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Septo-optic dysplasia is defined by a variable combination of dysgenesis of midline brain structures including optic nerve hypoplasia and hypothalamic-pituitary dysfunction often associated with a wide variety of brain malformations of cortical development. Multiple congenital anomalies have been reported only sporadically. Despite recent demonstration of the possible pathogenic role of *HESX1/Hesx1* gene (a homeobox gene important for development of prosencephalon), the etiology of most cases of septo-optic dysplasia still remains unclear. This report describes eight children (4 males, 4 females; age 2 to 17 years) with septo-optic dysplasia who manifested dysmorphic features (involving not only the midline facial structures) and a spectrum of additional clinical and imaging features including autism, facial hemangioma, and holoprosencephaly. Full mutational screening for the *HESX1* gene in seven of eight children was negative. Based on the extreme variability of the clinical and imaging phenotypes hereby observed, on literature review, and on septo-optic dysplasia animal models, this study confirmed that the phenotypic heterogeneity in septo-optic dysplasia is high. We suggest that: (1) dysmorphic features are more frequent than previously thought—they may represent a relevant part of the phenotype;

(2) septo-optic dysplasia should be recategorized as an heterogeneous malformation syndrome (septo-optic dysplasia complex) (encompassing multiple brain, endocrine, and systemic anomalies) rather than a single precisely defined entity. © 2006 by Elsevier Inc. All rights reserved.

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## Introduction

The syndrome of septo-optic dysplasia consists of a variable combination of defects of midline brain structures, including: (1) hypoplasia or absence of septum pellucidum (but also of corpus callosum); (2) optic nerves hypoplasia/dysplasia; and (3) pituitary-hypothalamic dysfunction (ranging from isolated deficit of pituitary hormones to pan-hypopituitarism) [1,2]. Such a constellation of lesions can also include associated cerebral abnormalities (e.g., schizencephaly and cortical dysplasia) [3]. Only rarely, all symptoms are present in a single patient. This apparent heterogeneity has resulted in some disagreement as to whether septo-optic dysplasia should be regarded as a single precisely defined entity or, rather, a group of heterogeneous disorders [1,2]. This nosologic confusion has not yet been resolved despite some promising results on the possible role of the *HESX1/Hesx1* gene (a human homeobox gene whose mouse homologue has an important role in forebrain, midline, and pituitary development) in the disease pathogenesis: homozygosis for an inactivating mutation in *HESX1/Hesx1* has been demonstrated, so far, only in one family with two siblings [4,5], in some individuals with mild pituitary hypoplasia associated with gland dysfunction or overt septo-optic dysplasia [5,6] and reproduced in a murine animal model of septo-optic dysplasia [4,5]. The etiology of most cases of septo-optic dysplasia, however, still remains unclear, and alternative pathogenic causes have been variously considered [1,2,5,7]. In all probability, the “syndrome” of septo-optic dysplasia is the end result of several different genetic abnormalities (primarily abnormal expression of genes in the basal prosencephalon causing an anomaly that proba-

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bly overlaps with lobar holoprosencephaly) or in utero injuries (e.g., vascular disruption, possibly involving the proximal trunk of the anterior cerebral artery or maternal exposure to valproic acid) [1,2,5].

From an imaging viewpoint, septo-optic dysplasia patients had been originally divided by Barkovich et al. [8] into two distinct anatomically different subgroups according to the embryo genesis and the neuropathology findings: one subset included patients with schizencephaly, normal-sized ventricles, a remnant of the septum pellucidum, and normal-appearing optic radiations; the second group of patients manifested no schizencephaly, but did exhibit complete absence of the septum pellucidum and diffuse white matter hypoplasia that resulted in ventriculomegaly. As knowledge evolved, it gradually became clear that septo-optic dysplasia was, in fact, a constellation of lesions identified, according to Barkovich [1], by at least two distinct magnetic resonance appearances. One group exhibits a high incidence of malformations of cortical development (especially schizencephaly and gray matter heterotopia and partial absence of the septum pellucidum). The small optic nerves in this group may be the result of transsynaptic degeneration of the optic nerves secondary to prenatal destruction/hypogenesis of the optic radiations. A second group, believed to overlap with lobar holoprosencephaly [1,8], has findings of complete absence of the septum pellucidum and hypoplasia of the white matter, often resulting in ventriculomegaly but normal cerebral cortex. Some patients in this second group have hypoplasia of the anterior falx cerebri or the genu of the corpus callosum. Some other patients with septo-optic dysplasia (perhaps a third group) [1] may have posterior pituitary ectopia, and a fourth subset likely includes those in the family reported by Dattani et al. [4,5] having hypogenesis of the corpus callosum. This spectrum of disease has been also classified (and further expanded) by Miller et al. [3] who divided septo-optic dysplasia into two groups [2]: (1) *isolated septo-optic dysplasia*: with absence of the septum pellucidum, hypoplasia of the optic nerves, and diffuse white matter hypoplasia; (2) *septo-optic dysplasia plus*: having a remnant of the septum pellucidum and a wide spectrum of associated brain malformations. So far, patients with isolated septo-optic dysplasia seem to have a less severe developmental prognosis, whereas those in the other groups have more guarded prognosis [1-3].

Clinically, affected individuals experience [1,2,5] visual deficits including nystagmus (wandering nystagmus when blind), diminished visual acuity, or color blindness. Associated eye abnormalities are microphthalmia and colobomas of the iris, choroids, and retina. Endocrine disturbances include growth hormone deficiency, low adrenocorticotrophic hormone and thyroid stimulating hormone secretion, diabetes insipidus, or high levels of prolactin and adrenocorticotrophic hormone. Precocious puberty may also occur. Neurologic impairment depends on the type and grade of associated brain abnormalities.

Mental retardation is not unusual. Associated multiple congenital anomalies have been only sporadically described [9].

This report describes eight children with septo-optic dysplasia and dysmorphic features. In seven of these eight cases, a full screening for the *HESX1* mutations yielded normal results. The purpose of this study was to better delineate the spectrum of imaging findings and the clinical heterogeneity of the septo-optic dysplasia phenotype.

## Patients and Methods

### Patient Selection

This retrospective (1992-1998) and prospective (1998-2004) study from two Italian University pediatric neurology units focuses on children selected from a total group of 50,000 patients and 14,000 magnetic resonance imaging examinations.

The pediatric neurology units in Catania and Rome cater to neurologically ill children from the eastern provinces of Sicily (re: Catania) and Lazio (re: Roma) (approximate populations 2.9 and 3 million inhabitants, respectively) (2600 to 2700 outpatient referrals per year during the period 1992-2004 for each center). The center in Catania is the sole referral center for the town of Catania.

### Inclusion Criteria

Cases were independently monitored in Catania and Rome. In each center, we reviewed the clinical or imaging files of patients referred for: (1) midline facial defects (not yet diagnosed as having known malformation syndromes); (2) partial or generalized optic disk abnormalities associated with visual disturbances/normal vision; (3) endocrine abnormalities of the hypothalamic-pituitary dysfunction type; (4) developmental delay/neurologic dysfunction associated with midline brain structure defects as demonstrated by neuroimaging; (5) olfactory dysfunction; and (6) any association of the above causes of referral.

### Methods

Clinical notes, laboratory results, treatment protocols, and neuroimaging (computed tomographic and magnetic resonance imaging scans) were reviewed and allowed us to detect 52 patients with a variable combination of midline facial or brain structures (principally absence/hypogenesis of septum pellucidum), hypoplasia of optic nerves/optic pathways, hypothalamic/pituitary defects, and associated brain abnormalities.

These patients, aged 2 to 19 years, were clinically reevaluated. They had initially imaged at different ages, and scans were reobtained in all after a period between 1 and 10 years (Table 1). Indications for imaging had been developmental delay/neurologic dysfunction, visual disturbances, and endocrine deficits of the hypothalamic/pituitary types. Retaken imaging consisted of computerized tomography in two cases and magnetic resonance imaging in all eight cases. All magnetic resonance imaging studies included sagittal T<sub>1</sub>-weighted images, axial T<sub>1</sub>-weighted images, axial T<sub>2</sub>-weighted images, and coronal T<sub>1</sub>-weighted or T<sub>2</sub>-weighted images. Coronal and sagittal images were used to confirm or exclude hypoplasia of the optic chiasm. Two patients were imaged at 0.5 T and all others at 1.5 T. All computed tomographic scans included both axial and coronal images. The ethics committee at the Department of Paediatrics of the University of Catania obtained approval.

After reevaluation, 44 cases were excluded: 10 children manifested overt holoprosencephaly without specific midline brain defects suggestive of septum pellucidum or optic pathways abnormalities; 9 children had mild to moderate mild midline facial defects associated with other systemic abnormalities which prompted a syndromic diagnosis other than

**Table 1. Clinical and imaging findings in eight children with septo-optic dysplasia**

| Main Features                           | 1                | 2                | 3                | 4                | 5                   | 6                | 7                | 8                | Total (%)                               |
|---|------------------|------------------|------------------|------------------|---------------------|------------------|------------------|------------------|---|
| Sex                                     | F                | F                | M                | M                | M                   | F                | F                | M                | ratio = 1                               |
| Age (years)                             | 8                | 3                | 7                | 2                | 3                   | 14               | 17               | 8                | range = 2–17                            |
| Parents' consanguinity                  | +                | –                | –                | –                | –                   | +                | –                | –                | 2/8 (25%)                               |
| Birth weight, length, OFC (percentiles) | 50 <sup>th</sup> | 25 <sup>th</sup> | 50 <sup>th</sup> | 50 <sup>th</sup> | 25–50 <sup>th</sup> | 50 <sup>th</sup> | 50 <sup>th</sup> | 50 <sup>th</sup> | 50 <sup>th</sup> = 6/8                  |
| <b>Eye abnormalities</b>                |                  |                  |                  |                  |                     |                  |                  |                  |   |
| Pale optic disk                         | +                | +                | +                | +                | +                   | +                | +                | +                | 8/8 (100%)                              |
| Retinal pigmentary anomalies            | +                | –                | +                | –                | +                   | –                | –                | –                | 3/8 (37%)                               |
| Coloboma                                | –                | –                | –                | –                | retinal             | –                | –                | –                | 1/8 (12%)                               |
| Microphthalmia                          | –                | –                | –                | –                | +                   | –                | –                | –                | 1/8 (12%)                               |
| Impaired visual acuity                  | +                | +                | ±                | +                | +                   | ±                | +                | ±                | 8/8 (100%)                              |
| Color blindness                         | –                | +                | –                | –                | +                   | –                | +                | –                | 3/8 (37%)                               |
| Nystagmus                               | +                | +                | –                | –                | +                   | –                | –                | –                | 3/8 (37%)                               |
| <b>Endocrine defects</b>                |                  |                  |                  |                  |                     |                  |                  |                  |   |
| GH deficiency                           | +                | +                | –                | +                | –                   | –                | +                | +                | 5/8 (62%)                               |
| ACTH deficiency                         | –                | +                | –                | –                | –                   | –                | –                | –                | 1/8 (12%)                               |
| TSH deficiency                          | –                | +                | –                | +                | –                   | –                | +                | –                | 3/8 (37%)                               |
| FSH-LH deficiency                       | –                | –                | –                | +                | –                   | –                | –                | +                | 2/8 (25%)                               |
| PRL elevated                            | +                | –                | –                | +                | –                   | –                | –                | –                | 2/8 (25%)                               |
| Diabetes insipidus                      | +                | –                | –                | –                | –                   | –                | –                | –                | 1/8 (12%)                               |
| Isolated defects                        |                  |                  |                  |                  |                     |                  |                  |                  | 0/8 (NA)                                |
| No defects                              |                  |                  |                  |                  |                     |                  |                  |                  | 3/8 (37%)                               |
| Multiple defects                        |                  |                  |                  |                  |                     |                  |                  |                  | 5/8 (62%)                               |
| <b>Dysmorphic features</b>              |                  |                  |                  |                  |                     |                  |                  |                  |   |
| Macrocephaly                            | –                | –                | +                | –                | –                   | +                | +                | –                | 3/8 (37%)                               |
| Microcephaly                            | –                | +                | –                | –                | –                   | –                | –                | –                | 1/8 (12%)                               |
| Frontal bossing                         | –                | –                | +                | +                | +                   | +                | +                | +                | 6/8 (75%)                               |
| Brushy eyebrows/synophris               | –                | +                | –                | –                | –                   | +                | –                | –                | 2/8 (25%)                               |
| Hypertelorism                           | –                | –                | –                | +                | –                   | +                | +                | +                | 4/8 (50%)                               |
| Small nose/depressed nasal bridge       | +                | +                | –                | +                | +                   | –                | +                | +                | 6/8 (75%)                               |
| Long philtrum                           | –                | +                | –                | –                | +                   | +                | +                | +                | 5/8 (62%)                               |
| Thin lips                               | –                | +                | –                | –                | +                   | –                | –                | –                | 2/8 (25%)                               |
| Small ears/pits                         | –                | +                | –                | –                | +                   | +                | –                | –                | 3/8 (37%)                               |
| <b>Other features</b>                   |                  |                  |                  |                  |                     |                  |                  |                  |   |
| Joint contractures                      | +                | –                | –                | –                | –                   | +                | –                | –                | 2/8 (25%)                               |
| Short neck                              | –                | +                | –                | –                | +                   | –                | –                | –                | 2/8 (25%)                               |
| Delayed bone age                        | –                | +                | –                | +                | –                   | –                | +                | –                | 3/8 (37%)                               |
| Abnormal genitalia                      | –                | –                | –                | +                | –                   | –                | –                | –                | 1/8 (12%)                               |
| <b>Neurologic deficits</b>              |                  |                  |                  |                  |                     |                  |                  |                  |   |
|   | PMD              | PMD Seiz         | PMD Seiz         | –                | PMD                 | PMD Seiz         | –                | –                | PMD = 5/8 (62%)<br>Seizures = 3/8 (37%) |
| <b>Neuroimaging findings</b>            |                  |                  |                  |                  |                     |                  |                  |                  |   |
| Age(s) at neuroimaging (years)          | 2, 6             | 2                | 1.5, 7           | 2                | 1, 3                | 3, 12            | 2, 11            | 7                |   |
| <b>Optic nerve hypoplasia</b>           |                  |                  |                  |                  |                     |                  |                  |                  |   |
| intraorbital                            | +                | +                | +                | +                | +                   | +                | +                | +                | 8/8 (100%)                              |
| extraorbital                            | ±                | +                | ±                | ±                | +                   | +                | +                | +                | 5/8 (62%)                               |
| Optic chiasm hypoplasia                 | +                | +                | +                | +                | +                   | +                | +                | +                | 8/8 (100%)                              |
| Optic radiation hypoplasia              | +                | +                | +                | –                | –                   | +                | –                | +                | 5/8 (62%)                               |
| Absent septum pellucidum                | +                | partial          | +                | +                | +                   | +                | +                | partial          | 8/8 (100%)                              |
| Corpus callosum agenesis                | –                | –                | –                | –                | –                   | +                | +                | –                | 2/8 (25%)                               |
| Enlarged ventricles                     | +                | –                | +                | –                | +                   | +                | +                | –                | 5/8 (62%)                               |
| <b>White matter abnormalities</b>       |                  |                  |                  |                  |                     |                  |                  |                  |   |
| Maturation delay                        | +                | –                | +                | –                | +                   | +                | –                | –                | 4/8 (50%)                               |
| Hypoplasia                              | –                | –                | –                | +                | –                   | –                | –                | +                | 2/8 (25%)                               |
| Fenestration anterior falx              | +                | +                | –                | +                | +                   | –                | –                | +                | 5/8 (62%)                               |
| Abnormal fornix columns                 | +                | +                | –                | –                | –                   | –                | –                | –                | 2/8 (25%)                               |

**Table 1. Continued**

| Main Features                 | 1                              | 2          | 3    | 4    | 5      | 6    | 7      | 8      | Total (%)  |
|-------------------------------|--------------------------------|------------|------|------|--------|------|--------|--------|--|
| Abnormal mammillary bodies    | –                              | +          | –    | –    | –      | –    | –      | –      | 1/8 (12%)  |
| Small hypophysis              | –                              | +          | –    | +    | –      | –    | –      | +      | 3/8 (37%)  |
| Ectopic neurohypophysis       | –                              | +          | –    | +    | –      | –    | –      | –      | 2/8 (25%)  |
| Cerebral lipoma               | –                              | –          | –    | –    | –      | –    | –      | –      | 0/8 (NA)   |
| Posterior fossa abnormalities | –                              | –          | MCM  | –    | –      | MCM  | –      | –      | 2/8 (25%)  |
| Schizencephaly                | –                              | –          | +    | –    | –      | –    | –      | –      | 1/8 (12%)  |
| Heterotopia                   | –                              | –          | +    | –    | –      | +    | –      | –      | 2/8 (25%)  |
| Holoprosencephaly             | –                              | –          | –    | –    | –      | +    | –      | –      | 1/8 (12%)  |
| Distinctive features          | Small hands<br>feet;<br>Autism | Hemangioma | –    | –    | –      | –    | –      | –      | small hands/feet 1/8<br>autism = 1/8<br>hemangioma = 1/8<br>0/7 (NA) |
| <i>Hex1</i> mutations         | –                              | –          | –    | –    | –      | NP   | –      | –      |  |
| Outcome                       | Stable                         | Impr       | Impr | Good | Stable | Good | Stable | Stable |  |

Abbreviations:

- ACTH = Adreocorticotrophic hormone
- F = Female
- FSH = Follicle stimulating hormone;
- GH = Growth hormone;
- Impr = Improved;
- LH = Luteinizing hormone
- M = Male
- MCM = Mega cisterna magna
- NA = Not applicable
- NP = Not performed
- OFC = Occipito-frontal circumference
- PMD = Psychomotor delay
- ± = MRI evaluation
- PRL = Prolactin
- Seiz = Seizures
- TSH = Thyroid stimulating hormone.

septo-optic dysplasia; 21 children manifested optic disk abnormalities consistent with a diagnosis of specific retinal pathology; in 2 children the optic disk abnormalities were consistent with the diagnosis of Aicardi syndrome; 1 mentally impaired child had growth hormone and thyroid stimulating hormone deficiency with mild midline facial dysmorphic features (hypertelorism, large nose with large lips) but no midline brain defects or optic pathways abnormalities; 1 further child had mild long-lasting growth hormone deficiency thought to be associated with septum pellucidum abnormalities which, after magnetic resonance imaging reevaluation, was excluded.

**Results**

After clinical and imaging reevaluation, eight children fulfilled the inclusion criteria for septo-optic dysplasia. Table 1 summarizes the main clinical, laboratory, and imaging findings of the eight cases with septo-optic dysplasia syndrome. Figure 1 shows MRI anomalies in case 2. Selected clinical findings in three of eight of these patients have been briefly reported previously [10].

**Molecular Analysis**

Molecular analysis for the *HESX1/Hex1* gene mutations were performed according to published protocols [4,5] by Dr. Dattani (see acknowledgments) in seven of eight cases.

**Discussion**

The eight children reported here fulfil the diagnostic criteria for septo-optic dysplasia (Table 1). Consistent with the heterogeneous clinical manifestations of septo-optic dysplasia, only in 62% were multiple endocrine deficits secondary to documented pituitary hormone deficiency recorded vs 37% who had no clinical hormone abnormalities (Table 1). Conversely, 100% had visual impairment secondary to optic nerve/optic chiasm hypoplasia (Table 1). In smaller percentages (12% to 37%), other associated eye abnormalities were observed (Table 1).

Of note, all children had *dysmorphic features* involving not only the midline facial structures (e.g., frontal bossing, hypertelorism, synophris, depressed nasal bridge, long philtrum) but also other segments of the body including the skull (macrocephaly and microcephaly), the musculo-skeletal system (small hands/feet, joint contractures), and the genitalia (abnormal genitalia). In none of them, however, was a distinctive syndromic pattern recognized. There are a handful of cases in the literature where individuals with well-recognized malformation syndromes manifested associated features reminiscent of septo-optic dysplasia [11-15]. Septo-optic dysplasia has also occasion-

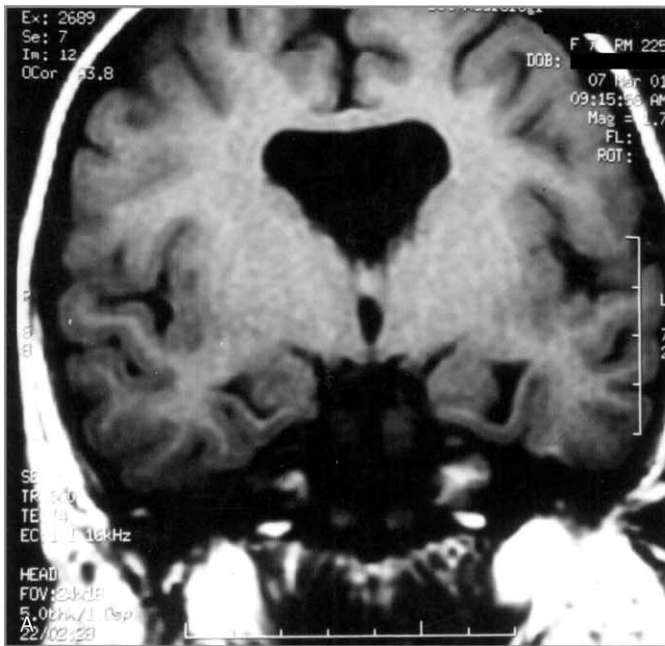


Figure 1. (A) Coronal  $T_1$ -weighted magnetic resonance image (TR, 500; TE, 14 ms) of the brain reveals complete absence of the septum pellucidum with a single ventricle and fusion of the columns of the anterior fornix which project into the former cavity of the third ventricle. (B) Sagittal  $T_1$ -weighted magnetic resonance image (TR, 400; TE, 15 ms) of the brain reveals a small pituitary gland with hypoplastic optic nerves (pointed arrow) and optic chiasm (arrow).

ally been reported in combination with digital anomalies [16-18], median cleft face [19], and cleft lip and palate [20]. Spectrums of skeletal dysplasias have been also observed in isolated septo-optic dysplasia cases [9]. By careful literature review, we recorded mild to severe isolated dysmorphic signs more frequently than previously thought [1,2,9]. Notably, in the present cases, we observed dysmorphic features strongly reminiscent of those described in the septo-optic dysplasia transgenic mouse lacking *Hesx1* that exhibited a reduced prosencephalon with skull abnormalities, abnormalities in the corpus callosum and septum pellucidum, anophthalmia or microphthalmia, and pituitary dysplasia [4,5]. Thus, based on our experience, on literature review, and on septo-optic dysplasia animal models, we suggest that dysmorphic features (involving not only the midline facial structures) may represent a relevant part of the clinical spectrum of septo-optic dysplasia syndrome.

Most infants with congenital defects of the pituitary gland or the hypothalamus share a common phenotype affecting the facial bones, the voice, the extremities, and the genitals [1,2,9]. All these findings are usually attributed to growth hormone deficiency. In particular, skeletal maturation is markedly delayed in these children and long bones tend to be slender and osteopenic. Thus, one could argue that some of the bone anomalies observed in cases 2, 4, and 7 could be the effect of growth hormone deficiency.

From a diagnostic viewpoint, the combination of functional (e.g., decreased visual acuity/nystagmus) and anatomic eye abnormalities (optic disk color/appearances) and (multiple) endocrine defects associated with dysmorphic features (especially midline facial defects but also

skeletal and systemic abnormalities) should prompt the suspicion of an underlying brain midline defect. In this latter regard, the combination of optic nerve/chiasm/tract and septal abnormalities should be considered diagnostic for septo-optic dysplasia. According to Barkovich [1] high-quality, thin-section magnetic resonance images with sagittal and coronal (rather than axial) studies may better allow the diagnosis of hypoplasia of the optic nerves and optic canals in septo-optic dysplasia. In our experience, only by re-reviewing magnetic resonance imaging films obtained in these planes were the associated (sometimes mild) optic pathways defects identified.

Careful reevaluation of magnetic resonance studies can extend the spectrum of associated brain abnormalities that help in better delineating the brain phenotype of septo-optic dysplasia. In our experience, 75% of cases had associated brain anomalies.

In conclusion, the phenotype of septo-optic dysplasia could be redefined from that originally described by de Morsier [1,2] and later expanded by other authors [reviewed in refs. 8 and 9]. Most likely septo-optic dysplasia represents a variable and wide spectrum of disorders ranging from the isolated forms of defects of the midline structures to the subtypes associated with multiple cerebral abnormalities. Dysmorphic features may be part of these phenotypes. In line with Miller et al. [3], we propose that the septo-optic dysplasia syndrome should be recategorized as a heterogeneous malformation syndrome (septo-optic dysplasia *complex*) encompassing multiple brain, endocrine, and systemic anomalies.

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