Long-term clinical data and molecular defects in the STAR gene in five Greek patients

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Abstract

Context: Steroidogenic acute regulatory (STAR) gene mutations lead to adrenal and gonadal failure. Interestingly, though as yet unexplained, features are the formation of ovarian cysts and the potential presence of CNS findings.

Objective: To report biochemical, genetic, and long-term clinical data in five Greek patients from four different families with STAR gene defects (three 46,XX and two 46,XY).

Methods and results: All patients presented in early infancy with adrenal insufficiency. The STAR gene mutation c.834del11bp, detected in three of our patients, completely alters the carboxyl end of the STAR protein and has not thus far been described in other population groups. These three patients belong to three separate families, possibly genetically related, as they live in different villages located in a small region of a Greek island. However, their interrelationship has not been proven. A second mutation, p.W250X, detected in our fourth family, was previously described only in two Serbian patients. Ovarian cysts were detected ultrasonographically in our 46,XX patients and seemed to respond to a low dose of a contraceptive. The histology of an excised ovarian cyst was diagnosed as a corpus luteum (CL) cyst. In two out of the four patients who had undergone brain magnetic resonance imaging, asymptomatic Chiari-1 malformation was observed.

Conclusions: The occurrence of STAR gene mutation c.834del11bp in three families living in a restricted geographic region could indicate either a founder effect or simply reflect a spread of this defect in a highly related population. The ovarian histological findings suggest that ovarian cysts detected ultrasonographically in 46,XX individuals with STAR gene defects may be CL cysts. The Chiari-1 malformation in two of our patients may be part of the STAR gene mutation phenotype. Nevertheless, more data are needed to confirm or disprove the existence of specific CNS pathology in patients with STAR gene mutations.

Introduction

Steroidogenic acute regulatory (STAR) protein mediates the transfer of cholesterol from the outer to the inner mitochondrial membrane. This process provides the substrate for the initiation of steroidogenesis and constitutes a rate-limiting step in the acute response of steroidogenic cells of the adrenal cortex and the gonads to the corresponding tropic hormones. The gene encoding the STAR protein mapped on chromosomal locus 8p11.2 consists of seven exons and six introns and is expressed in the adrenal cortex and the gonads but not in the placenta (1, 2, 3, 4). Interestingly, STAR is also expressed in other tissues, including the brain (5, 6). Most mutations of the STAR gene are located in exons 5–7, affecting the STAR-related lipid transfer domain (START), resulting in a drastic reduction of STAR cholesterol transfer activity, while deletion of 28 carboxyl terminal residues suppresses all activity (7, 8, 9).

Mutations in the STAR gene lead to a defect at an early step of steroidogenesis, resulting in severe adrenal insufficiency and gonadal failure (congenital lipoid adrenal hyperplasia (CLAH)), usually manifested in infancy (3, 4, 9). There have been cases, however, characterized by late onset of adrenal failure and normal male genitalia (10, 11) or by a phenotype that could be misinterpreted as familial glucocorticoid deficiency (12, 13).

Adrenal insufficiency does not differ in 46,XY and 46,XX individuals with STAR gene mutations, while the gonadal defect shows gender dimorphism. Thus, testicular failure is manifested antenataly, leading to sex reversal in most cases, whereas ovarian function
is normal for many years, leading to normal puberty and menarche but premature menopause (14, 15, 16, 17, 18). We herein present long-term data of five Greek patients with STAR gene mutations.

Materials and methods

Patients

Six patients belonging to four families were admitted to our center in infancy with vomiting, failure to thrive, electrolyte abnormalities, low cortisol and androgen values, and high corresponding ACTH values, with initial diagnosis being primary adrenal insufficiency. Clinical and biochemical characteristics of all patients are shown in Tables 1 and 2.

Family 1 Patient 1, a female, now aged 30 years, was examined at the age of 8 months because of vomiting and failure to thrive since the age of 4 months and was diagnosed with adrenal insufficiency (Table 1). The first child of the family had presented with vomiting and dehydration and died at the age of 3 months. Two other siblings are healthy. On replacement therapy with hydrocortisone and 9α-fludrocortisone, the patient grew well, reaching a final height of 160 cm (SDS, −0.6; target height (TH) SDS, −0.2). Breast Tanner II stage was noted at 9 years and menarche at 12 years. She married at the age of 16 years. Up to the age of 24 years, she could not conceive. An ovarian cyst was detected sonographically at the age of 20 years during a workup for infertility (Fig. 1A) and was excised before the STAR gene mutation diagnosis (see histology in the Results section). At the age of 24 years, molecular genetic analysis revealed the presence of STAR gene mutation. As the same mutation was detected in her husband in the heterozygous state, she underwent IVF and preimplantation diagnosis and gave birth to a normal girl (19). Following her pregnancy, menses were irregular and ovarian cysts were again detected on ultrasonography (U/S). On half dose of a contraceptive (estrogen content 20 μg), the ovarian cysts disappeared and reappeared whenever the patient herself interrupted treatment.

Family 2 Patient 2, a female, now aged 28 years, was first examined at the age of 2 months and diagnosed with adrenal insufficiency (Table 1). On replacement therapy with hydrocortisone and 9α-fludrocortisone, she grew well and reached a final height of 162 cm (SDS, −0.2; TH SDS, −1). Breast development started at age 11 years and menarche occurred at age 13 years. Pelvic U/S at age 5 years showed normal-for-age ovarian size. Ovarian cysts were first detected at 19.5 years during a workup for menstrual irregularities. Molecular genetic analysis revealed the presence of STAR gene mutation. Patient 3, a phenotypic female, was diagnosed with adrenal insufficiency and microcephaly at the age of 3 months and replacement therapy for the adrenal failure was initiated. Nevertheless, the infant died at the age of 14 months at home. Unfortunately, no details are available; no autopsy or molecular genetic analysis was carried out, but a STAR gene mutation is strongly suspected. Four other children in this family (three males and one female) are healthy, but they declined the molecular genetic analysis.

Family 3 Patient 4, a female, now aged 19.5 years, was first examined on the 20th day of life and diagnosed with adrenal insufficiency (Table 1). On replacement therapy with hydrocortisone and 9α-fludrocortisone, she has been well and reached a final height of 154.5 cm (SDS, −1.7; TH SDS, −1.8). At the age of 6.6 years, as well as at 12.1 years, the ovaries were sonographically normal. Thelarche and pubarche Tanner stage II were noted at the age of 13 years, at which time ovarian cysts were first identified (Fig. 1B). She was then started on a contraceptive regimen (estrogen content 20 μg), and 1 month later, the ovaries were of normal size and architecture. After 1 month, the contraceptive pill was discontinued and an ovarian cyst was detected on the left ovary. Normal ovaries were seen soon after resumption of the contraceptive pill. At the age of 14.5 years, half dose of the contraceptive regimen (estrogen content 20 μg) was initiated, and during 6 years on this regimen, no cysts have developed, while she has regular vaginal bleeding. A brain magnetic resonance imaging (MRI) at age 19 years disclosed Chiari-1 malformation. No neurological deficit has been

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Biochemical, hormonal, and sonographic data of the patients with STAR gene mutations at diagnosis. Normal values are shown in parenthesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (months)</td>
<td>8</td>
</tr>
<tr>
<td>Serum Na (mmol/l) (138–150)</td>
<td>115</td>
</tr>
<tr>
<td>Serum K (mmol/l) (3.5–5.5)</td>
<td>8.0</td>
</tr>
<tr>
<td>Cortisol baseline (nmol/l) (138–552)</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Cortisol post ACTH (nmol/l) (&gt;500)</td>
<td>NA</td>
</tr>
<tr>
<td>ACTH (pmol/l) (1.1–13.2)</td>
<td>NA</td>
</tr>
<tr>
<td>170OH progesterone (nmol/l)</td>
<td>6.9 (0.7–4.7)</td>
</tr>
<tr>
<td>Adrenal sonography</td>
<td>Not visualized</td>
</tr>
</tbody>
</table>

NA, not available.

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## Table 2 Clinical, hormonal, histological, and genetic characteristics of the patients with CLAH.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents' relation</td>
<td>Third cousins</td>
<td>Second cousins</td>
<td>Second cousins</td>
<td>Second cousins</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pregnancy/delivery</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Uneventful</td>
<td>Cesarean section</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3000</td>
<td>3000</td>
<td>3000</td>
<td>4100</td>
<td>3140</td>
<td>3300</td>
</tr>
<tr>
<td>External genitalia</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Karyotype</td>
<td>46,XX</td>
<td>46,XX</td>
<td>NA</td>
<td>46,XX</td>
<td>46,XY</td>
<td>46,XY</td>
</tr>
<tr>
<td>Initial symptoms</td>
<td>Vomiting and FT</td>
<td>Vomiting and diarrhea</td>
<td>FT</td>
<td>Vomiting, anorexia, and hyperpigmentation</td>
<td>Vomiting and FT</td>
<td>Vomiting and hyperpigmentation</td>
</tr>
<tr>
<td>Age first symptomatic</td>
<td>4</td>
<td>1.7</td>
<td>3</td>
<td>0.3</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>0.7</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Molecular defect</td>
<td>C834del11bp</td>
<td>C834del11bp</td>
<td>–</td>
<td>C834del11bp</td>
<td>W250X</td>
<td>W250X</td>
</tr>
<tr>
<td>Sonography of gonads</td>
<td>20 years ovarian cysts</td>
<td>5 years: normal ovaries</td>
<td>NA</td>
<td>6, 8, 12 years: normal ovaries</td>
<td>Small tests in inguinal canal</td>
<td>Small tests in inguinal canal</td>
</tr>
<tr>
<td>Age at gonadectomy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Menarcheal age (years)</td>
<td>12</td>
<td>13</td>
<td>–</td>
<td>13.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>LH/FSH (age in years)</td>
<td>22/6.6 (23)</td>
<td>17.5/6.3 (22)</td>
<td>–</td>
<td>3.6/4.8 (11.5)</td>
<td>1.6/5.7 (8)</td>
<td>0.5/14.8 (1.75)</td>
</tr>
<tr>
<td>Gonadal histology</td>
<td>Corpus luteum cyst</td>
<td>–</td>
<td>–</td>
<td>12/8 (13), 15/77 (13.5)</td>
<td>–</td>
<td>0.3/14.2 (2.3)</td>
</tr>
<tr>
<td>Current status (age in years)</td>
<td>Well. Has one child (30)</td>
<td>Well. Married (28)</td>
<td>Died at age 14 months</td>
<td>Well (19.5)</td>
<td>Sertoli cells and rare germ cells (see text)</td>
<td>Well (15.5)</td>
</tr>
<tr>
<td>Mental development</td>
<td>Normal. Finished first grade of high school</td>
<td>Normal. Poor school progress</td>
<td>Retardation and microcephaly</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Normal</td>
<td>NA</td>
<td>–</td>
<td>Chiari-1 malformation</td>
<td>Nonspecific spotted alterations in the white matter of the R hemisphere</td>
<td>Normal</td>
</tr>
</tbody>
</table>

NA, not available; FT, failure to thrive.
detected, but her school progress has been poor. Molecular genetic analysis revealed the presence of STAR gene mutation. One older male sibling is healthy but declined molecular genetic analysis.

**Family 4** Patient 5 was admitted at the age of 25 days and diagnosed with adrenal insufficiency (Table 1). The external genitalia had normal female appearance. However, the pelvic U/S revealed gonads in the inguinal canal, which resembled testes, and no uterus was identified. The karyotype was 46,XY. Gonadectomy was carried out at the age of 8 years. The patient, now aged 14 years, has been doing well on replacement therapy with hydrocortisone and 9α-fludrocortisone. A brain MRI carried out at age 10 years revealed no pathological findings and the school progress was reported as good. Molecular genetic analysis revealed a STAR gene mutation in both patients 5 and 6.

### Methods

**DNA sequencing analysis** DNA was extracted from peripheral blood leucocytes using the QIAamp DNA Blood mini kit (Qiagen) after informed consent was obtained from the parents that genetic analysis be carried out. The seven exons and their flanking intronic sequences of the STAR gene (Ensembl Transcript ID, ENST00000276449) were PCR amplified and directly sequenced on an automated sequencer (ABI 3100 Avant, Applied Biosystems). The PCR and sequencing primers were designed using the Primer 3 (v.0.4.0) program and are available on request.

**Immunohistochemical studies** Tissue sections from the ovarian cysts and the testes, formalin fixed and paraffin embedded, were stained with hematoxylin–eosin. The Bond Polymer Detection Kit (Vision Biosystems, Norwell, MA, USA) was used on paraffin sections for the detection of inhibin α subunit (Biocare Medical, Concord, CA, USA, 1/100), calretinin (Novocastra (Newcastle, UK), 1/150), placenta-like alkaline phosphatase (PLAP; DAKO (Glostrup, Denmark), 1/50), progesterone receptor (Spring Bioscience (Pleasanton, CA, USA), SP2 1/40), and Melan-A (Novocastra, 1/50). Melan-A, a product of the MART1 (MLANA) gene, is an antigen recognized by antibody A103, and although its primary utility is in the identification of melanoma cells, it also stains steroid-producing cells. Control experiments with anti-peptides were conducted to show specificity of the antibodies.

**Hormonal studies** LH, FSH, cortisol, and ACTH were measured by electrochemiluminescent immunoassays on a Cobas e411 automatic analyzer (Roche Diagnostics GmbH (Mannheim, Germany); precision CV: LH 1.1%, FSH 1.7%, cortisol 1.2%, and ACTH 2.3%). Testosterone was measured by chemiluminescent immunoassay on an Immulite 2000 automatic analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, USA; precision CV: 9.5%). 17OHP was determined by RIA employing reagents from ICN Pharmaceuticals, Inc. (Costa Mesa, CA, USA; precision CV: 9.1%).

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**Figure 1** (A) Ovarian ultrasonography of patient 1 showing multiple cysts in both ovaries at the age of 20 years. (B) Ovarian ultrasonography of patient 4 showing a cystic allantoid structure across the entire length of the right ovary.
### Results

Hormonal data are depicted in Table 1. Patients 1, 2, and 4 (Families 1, 2, and 3) were shown to be homozygotes and their parents were heterozygotes for the deletion c.834del11bp (p.K236delfsX43) in exon 6 of the STAR gene (Table 2, Fig. 2). This 11 bp deletion results in a frameshift, which alters the carboxyl end of the protein, from amino acid 235 onward. It also creates a new stop codon at amino acid 278, making the protein shorter than the wild type by seven amino acids (Fig. 2). The three families that harbor the 11 bp deletion reside in different villages located in a small region of the island of Crete. In all three families, the parents were second- or third-degree relatives. However, the interrelationships between the three families are not known.

In both 46,XY siblings of Family 4 (patients 5 and 6), the mutation p.W250X was detected (Table 2). The parents, heterozygotes for the p.W250X mutation, originated from the island of Rhodes but mentioned no consanguinity.

The ovarian cyst excised from patient 1 (Family 1) was shown to be a corpus luteum (CL) cyst. Specifically, the immunohistochemical analysis disclosed: i) cytoplasmic focal distribution of Melan-A (a marker of steroid-producing cells); ii) cytoplasmic focal distribution of inhibin \(\alpha\) subunit indicating the presence of granulosa cells; and iii) immunostaining of progesterone receptors in a moderate number of cells of the cyst and the stroma, Envision X200. These sections represent typical findings from the wall of the cyst.

The histological studies of the testes removed from patient 5 (Fig. 4 A, B and C) revealed prepubertal testes at a static stage of development, consisting of testicular tubules with Sertoli cells and rare germ cells some of which were large. The Sertoli cells had a focal vesicular appearance. A significant number of Leydig cells were observed in the interstitial tissue with microvesicular appearance. The immunohistochemical study showed positive staining for inhibin \(\alpha\) subunit as well as Melan-A and calretinin expression (Melan-A and Calretinin are markers expressed in Leydig cells; calretinin data not shown). PLAP was not identified in the isolated spermatogonia. There was no evidence of intratubular germ cell neoplasia. The only difference observed between patient 6 and his sibling (patient 5; Family 4) was the lower number of Leydig cells in the interstitial stroma containing microvesicular vacuoles. The MRI results are depicted in Table 2 and in patients’ descriptions.

### Discussion

The majority of reported STAR gene mutations are located in exons 5–7. Various studies have shown that the C-terminal region of the STAR protein is important for cholesterol transfer and, hence, for steroid
might not be present before puberty but appear with the rise of gonadotropins, i.e. at a stage of higher functional demands when initiation of follicle recruitment occurs.

The mechanism of ovarian cyst formation in girls with STAR gene mutations remains an enigma (25), and especially the proneness to recurrence, as was illustrated in patient 4. The mechanism of an increased LH/FSH ratio (25, 26), also detected in our 46,XX patients, and its relation to cyst formation is not clear. In a failing ovary, a high FSH/LH ratio is found, whereas an increased LH/FSH ratio is detected in women with polycystic ovary syndrome (27). The analogy between the latter entity and the 46,XX women with STAR gene mutations regarding the LH/FSH ratio is not apparent. It must be mentioned, however, that targeted overexpression of LH in transgenic mice leads to infertility, ovarian cyst formation, and enlarged ovaries (28).

The histological data of the ovarian cyst, surgically excised from patient 1 at the age of 20 years, indicate CL cyst. The CL is a ‘temporary endocrine organ’ producing steroids for which the STAR gene is required (29, 30). In an infertile cycle, the CL undergoes a process of regression known as luteolysis. We may thus assume that in 46,XX women with STAR gene mutations, ovulation takes place but the function of the CL is impaired, this possibly leading to cyst formation, as well as to low progesterone synthesis, and infertility. Only one previous report described histological findings from the ovary of a 22-year-old woman, which, however, had undergone torsion. In that particular case, the expected decrease in steroidogenesis was demonstrated by histochemical studies. No CL was detected, while corpus albicans, a regressed form of CL, was present. In STAR knockout mice, no CL was found (31).

The role of ovarian cysts in causing ‘mechanical damage’ to the ovary is not known, but such an effect is theoretically expected. We must emphasize that ovarian torsion has been reported in 46,XX subjects with STAR gene mutations (26, 32). Hence, early recognition and management of ovarian cysts is imperative. Most likely, by prompt suppressive therapy of gonadotropin secretion, depletion of normal follicles and the presumed mechanical damage from ovarian cysts could be prevented and thus normal ovarian architecture and potential for fertility may be preserved for longer periods. It is quite possible that half dose of the low estrogen pill might prove effective, as demonstrated by the course of events in our patients 1 and 4. A limited number of successful pregnancies of patients with STAR gene mutations have been reported (19, 33).

The synthesis of data related to testicular histology in STAR patients, both from the literature (34, 35, 36, 37, 38, 39) and those of our patients, indicate that at an early development stage (fetal and early postnatal life), the testes have normal architecture and a normal number of germ cells, whereas Leydig cells are either scattered or absent. It appears that germ cells are normal prenatally and in early postnatal life but
decrease in number and become large later on. This observation indicates that although germ cells follow a different lineage than steroidogenic cells of the testis, endogenous testosterone production is required for normal germ cell evolution and maintenance. It must be mentioned that testicular biopsy in a 36-year-old male with mild STAR gene mutation, investigated for infertility, showed partial atrophy with interstitial fibrosis, many Reincke crystalloids (confirming the presence of Leydig cells), and reduced spermatogenesis (12). In a 15-year-old patient (23), a carcinoma in situ was detected in the excised testis. Moreover, in a 1-year-old patient, the excised testes showed positive PLAP and octamer binding transcription factor staining, indicative of neoplastic potential (39). This information is of considerable interest and should be considered when deciding the timing of gonadectomy.

The CNS findings in two of our patients are intriguing. STAR protein, a key factor in steroidogenesis, is widely expressed in the brain and specifically in neurons, glial cells, and proliferating precursors (5, 6, 8) and therefore STAR gene defects could lead to CNS malfunction. Nevertheless, thus far, convincing evidence for the existence of impaired brain function or structure in CLAH patients is lacking (20, 39). A possible interpretation could be the following: i) brain steroidogenesis is not essential for brain formation and/or function in humans; and ii) a search for pertinent brain pathology has not been systematically carried out to uncover possible defects. Specifically, brain MRI scans or cognitive and other related studies have not been performed systematically in an adequately large number of CLAH patients to offer reliable data.

To our knowledge, of the few children with STAR gene mutations in whom an MRI was performed, Chiari-1 malformation was detected in one. In two of our four patients in whom a brain MRI was carried out, Chiari-1 malformation was detected. Other CNS abnormalities have also been detected in such patients, like frontal and temporal lobe atrophy, supratentorial white matter lesions, mental retardation, and hemiatrophy of the temporal lobe. In all of these patients, like our two patients with Chiari-1 malformation, the exact prevalence of Chiari-1 malformation in the general population remains unknown. In a study carried out in a general population sample of individuals younger than 20 years (n = 5248), the prevalence of Chiari-1 malformation was 0.7/10,000, whereas in subjects who had an MRI for CNS symptoms, it was 1% (40). Of note is the report that 37% of the subjects with Chiari-1 younger than 20 years were asymptomatic at the time of diagnosis, as were our two patients with Chiari-1 malformation. Thus, the existence of CNS pathology (functional or morphologic) in this nosologic entity remains uncertain. Obviously, data from a systematic study with brain MRI scans even in asymptomatic patients and pertinent functional studies in a significant number of patients with STAR gene mutations might offer a satisfactory answer to the questions raised above.

In conclusion, the mutation c.834del11bp has thus far been identified only in our three patients who belong to different families living in a restricted geographic region. The p.W250X mutation detected in two 46,XY siblings from the island of Rhodes has previously been reported only in two Serbian patients. The Chiari-1 malformation in two of our patients may be part of the STAR gene mutation phenotype. Nevertheless, further studies are needed to confirm or disprove CNS pathology in patients with STAR gene mutations. The histological findings of an excised ovarian cyst, indicating a CL cyst, represent a novel observation with implications for the elucidation of the pathophysiology involved in ovarian cyst formation in this entity. An estrogen–progesterone regimen at half the usual dose, initiated at puberty, may preserve normal ovarian architecture and fertility for longer periods.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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