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Ataxia with isolated vitamin E deficiency: neurological phenotype, clinical follow-up and novel mutations in *TTPA* gene in Italian families

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Abstract Ataxia with vitamin E deficiency (AVED) is a rare autosomal recessive neurodegenerative disorder due to mutations in the alpha-tocopherol transfer protein (*TTPA*) gene on chromosome 8q13. AVED patients have progressive spinocerebellar symptoms and markedly reduced plasma levels of vitamin E. We studied neurological phenotype at diagnosis, and long-term effect of vitamin E supplementation in 16 patients from 12 Italian families. The most common mutations were the 744delA and 513insTT. Two novel *TTPA* mutations were identified: a severe truncating mutation (219insAT) in a homozygous patient, and a Gly246Arg missense mutation (G246R) in a compound heterozygous patient. The missense mutation was associated with a mild and slowly progressive form of the disease. Vitamin E supplementation therapy allowed a stabilization of the neurological conditions in most of the patients. However, development of spasticity and retinitis pigmentosa was noted in a few patients during therapy. Prompt genetic characterization of AVED patients may allow an effective early treatment and an adequate genetic counseling.

Key words α-Tocopherol transfer protein gene • *TTPA* • Recessive ataxia • Vitamin E • Vitamin E therapy

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Introduction

Ataxia with isolated vitamin E deficiency (AVED; MIM 277460) is a rare autosomal recessive neurodegenerative disease characterized by progressive gait and limb ataxia, dysarthria, lower-limb areflexia, loss of proprioceptive and vibration sense, and extensor plantar response [1, 2]. The majority of the patients present the first neurological symptoms between 4 and 18 years of age. The phenotype closely resembles that of patients with Friedreich's ataxia (FA). However, AVED patients rarely present cardiac involvement and, more frequently than FA patients, have head titubation and retinopathy [3, 4]. The biochemical hallmark of the disease is very low levels of vitamin E in plasma, in the absence of intestinal fat malabsorption and abetalipoproteinemia. In fact, AVED patients have normal intestinal absorption of α-tocopherol (vitamin E) and normal incorporation into chylomicrons, but they have an

impairment of α-tocopherol incorporation into very low density lipoproteins (VLDL) [5]. In 1995, Ouahchi et al. [6] demonstrated that AVED is caused by mutations in the gene coding for the α-tocopherol transfer protein (*TTPA*). This cytosolic liver protein is able to select among the eight different dietary vitamin E isomers (α, β, γ, δ tocopherols and α, β, γ, δ tocotrienols) and preferentially binds RRR-α-tocopherol to VLDL proteins, which are then released into the circulation. Thus, TTPA protein is responsible for the maintenance of normal vitamin E plasma concentrations. AVED is more frequent in North-Africans populations, in whom a common genetic mutation, the 744delA mutation is found [3, 6].

We describe the neurological phenotype at diagnosis and the long-term effects of vitamin E supplementation in 16 patients from 12 Italian families. Ten of these patients belong to eight newly identified families. Two novel pathogenic mutations in *TTPA* are described.

Patients and methods

Patients

From 1992 to the present, we identified 16 patients with AVED, from 12 Italian families. The probands presented very low plasma concentrations of vitamin E, neurological features resembling those of FA, and no evidence of clinical conditions associated with fat malabsorption. Most of the patients had been referred to our center C. Besta National Neurological Institute for biochemical or genetic evaluation several years after the onset of the neurological symptoms. Clinical symptoms at diagnosis and genetic mutations (Table 1) of six patients, from four families, have been previously described [3, 7].

After supplementation therapy with vitamin E had been initiated, all the patients were evaluated for clinical follow-up approximately once a year. At each visit, the patients underwent standard neurological and physical examinations, and serum vitamin E analysis. In 11 patients, magnetic resonance imaging (MRI) or computed tomography (CT) examinations of the brain were performed. For follow-up study, walking capacities were scored as follows: stage 1, autonomous walking; stage 2, walking possible only with unilateral support; stage 3, walking possible only with bilateral support or with accompanying person; and stage 4, patient confined to wheelchair.

Sequence analysis of *TTPA* gene

Genomic DNA was extracted from blood sampled using standard procedures. The DNA regions corresponding to the five exons and to the intron-exon boundaries of the *TTPA* gene were amplified by polymerase chain reaction (PCR), as previously described [8]. Direct sequence analysis of the PCR products was performed on an automated sequencing system (Applied Biosystems 373A Foster City, California, USA). Sequences were determined on both strands.

Results

A total of 16 patients receiving long-term vitamin E supplementation for ataxia with vitamin E deficiency (AVED) were studied neurologically and genetically (Table 1). At diagnosis, plasma concentrations of vitamin E ranged from 0.08 to 0.33 mg/dl (normal values, 0.8–1.6 mg/dl). Age at initiation of vitamin E therapy ranged from 13 to 51 years. At diagnosis, most patients had gait and limb ataxia, decreased proprioceptive sense and absent deep tendon reflexes in the lower limbs. Fourteen patients (87%) had dysarthria, 7 (44%) presented head tremor, and 2 (12.5%) had retinitis pigmentosa. Mild cerebellar atrophy was present in 5 (45%) of 11 patients who underwent MRI or CT investigation.

In family M11, the 3 affected subjects showed a mild phenotype and a very slow disease progression. In this family, the patients noticed walking problems only in their third decade. At ages 48, 52, and 53 years, these patients were able to walk with support, two of them did not present dysarthria, and two had retained reflexes in upper limbs.

Neurological follow-up during vitamin E therapy

Currently, the 16 patients with AVED have been receiving vitamin E supplementation for 2–13 years (Table 2). During this follow-up period, normalization of serum vitamin E was obtained in 7 patients with a daily intake of 1000–1500 mg vitamin E, while in 5 patients higher doses were required, ranging from 1800 to 2400 mg/day. Walking capacities remained unchanged in 13 of 16 patients. In particular, three of the 8 patients who walked with support at the time of diagnosis presented a worsening of their walking capacity (P0072, P1368 and P1060). Worsening in speech capability was noted in two patients (P0597 and P0663), while one patient (P0322) developed lower limb spasticity and showed worsening of the head tremor. At the latest follow-up visit, patient H0804, aged 39 years, complained of decreased visual acuity; ophthalmologic examination revealed a pigmentary retinopathy that was not present at the time of diagnosis and during the first years of supplementation therapy.

In patient P0875, clinical improvement was observed during the first year of therapy when a significant reduction of the dystonic symptoms occurred, while no significant change in neurological conditions was noticed during the following 4 years of therapy.

Two women, neither of whom had a known clinical history of cardiomyopathy, presented acute cardiac disease. In fact, patient P0597 had an acute myocardial infarction at the age of 46 years, and patient P0570 died at the age of 38 years for sudden cardiac arrest (no autopsy data are available).

Table 1 Clinical and biochemical findings of 16 patients with ataxia with vitamin E deficiency (AVED), at diagnosis

Patient	Family[a]	Serum vitamine mg/dl	Age, years						Tendon reflexes								
			Onset	Diagnosis	Gait[c]	Dysarthria	Head tremor	Babinski sign	Upper limbs	Lower limbs	Cardiomyopathy	Retinopathy	Scoliosis	Pes cavus	Consanguinity	Cerebellar atrophy	Geographical origin
P0072	M01 (#5)	0.15	12	39	2	+	+	+	-	-	+	-	+	+	+	+	SI
P0071	M01 (#5)	NA	13	45	3	+	+	+	-	-	-	-	+	+	+	NA	SI
H0399	M02 (#10)	0.08	13	22	3	+	-	+	-	-	-	-	+	+	+	+	SI
P0597	M03	0.11	8	40	4	+	-	+	-	-	-	+	+	+	-	-	NI
P0048	M04	0.14	6	34	4	+	-	+	-	-	-	-	-	+	-	-	NI
H0793	M05	0.10	5	13	1	+	+	+	-	-	-	+	+	+	-	-	NI
P1368	M06	NA	5	22	2	+	-	+	-	-	-	-	+	+	-	NA	NI
H0804	M07	0.10	11	34	4	+	-	+	-	-	-	-	+	+	-	+	CI
P0875	M08[b]	0.14	8	14	1	+	+	+	+	-	-	-	-	-	-	-	NA
P0322	M09 (#21)	0.33	15	26	1	+	+	+	+	-	-	-	-	+	-	+	NI
P0301	M09 (#21)	0.12	27	29	1	+	+	+	+	-	-	-	-	+	-	-	NI
P1060	M10	0.16	8	35	2	+	+	+	-	-	-	-	+	+	+	-	SI
P0663	M11	0.12	27	46	2	-	-	-	-	-	-	-	+	+	-	NA	CI
P1135	M11	NA	25	51	3	-	-	NA	+	-	NA	-	-	+	-	NA	CI
P1134	M11	NA	25	50	2	+	-	-	+	-	-	-	+	+	-	NA	CI
P0570	M12	0.22	4	36	4	+	-	NA	-	-	-	-	+	+	NA	+	NA

[a] Number in parentheses corresponds to family number indicated by Cavalier et al. [3]; [b] Patient, previously described by Angelini et al. [7]; [c] Gait: *1*, autonomous walking; *2*, walking with unilateral support; *3*, walking with bilateral support or accompanying person; *4*, wheelchair; *NI*, Northern Italy; *CI*, Central Italy; *SI*, Southern Italy; NA, not available

Table 2 Principal clinical features of 16 AVED patients during vitamin E supplementation therapy

Patient	Vitamin E supplementation, mg/day	Duration of vitamin E therapy, years	Age at last examination, years	Serum vitamin E during therapy, mg/dl[a]	Gait at last examination[b]	Clinical observations during vitamin E supplementation
P0072	1200	11	50	1.40	3	Increased walking difficulty
P0071	1200	11	56	1.80	3	Stable neurological conditions
H0399	2000	10	32	1.08	3	Stable neurological conditions
P0597	1800–2400	6	47	0.91	4	Acute myocardial infarction at 46 years; increased dysarthria
P0048	1500	4	38	1.29	4	Stable neurological conditions
H0793	2100	13	26	1.10	1	Stable neurological conditions
P1368	100; 300; 900	10	32	0.80	3	Increased walking difficulty; irregular therapy intake
H0804	1000	5	39	NA	4	Diagnosis of RP at age 39 years
P0875	2400	5	19	0.92	1	Reduction of ataxia and dystonia
P0322	1200	6	32	1.12	1	Lower limb spasticity; increased head tremor
P0301	1200	6	35	0.84	1	Stable neurological conditions
P1060	2100	3	38	1.06	3	Increased walking difficulty
P0663	1200	2	48	1.99	2	Mild dysarthria
P1135	300	2	53	NA	3	Stable neurological conditions; irregular therapy intake
P1134	NA	2	52	NA	2	Stable neurological conditions; irregular therapy intake
P0570	1200	2	38	NA	4	Stable neurological conditions; sudden cardiac arrest at age 38 years

RP, retinitis pigmentosa; *NA*, not available
[a] Values are mean; [b] Gait: *1*, autonomous walking; *2*, walking with unilateral support; *3*, walking with bilateral support or accompanying person; *4*, wheelchair

Table 3 *TTPA* gene mutations identified in 16 patients with AVED

Patient	Family	Mutations in *TTPA* gene	
		Allele 1	Allele 2
P0072	M01 (#5)	744delA	744delA
P0071	M01 (#5)	744delA	744delA
H0399	M02 (#10)	744delA	744delA
P0597	M03	744delA	744delA
P0048	M04	513insTT	513insTT
H0793	M05	513insTT	513insTT
P1368	M06	513insTT	513insTT
H0804	M07	744delA	513insTT
P0875	M08	744delA	513insTT
P0322	M09 (#21)	513insTT	306A→G
P0301	M09 (#21)	513insTT	306A→G
P1060	M10	219insAT	219insAT
P0663	M11	513insTT	Gly246Arg
P1135	M11	513insTT	Gly246Arg
P1134	M11	513insTT	Gly246Arg
P0570	M12	486delT	NI

NI, not identified

Mutations in *TTPA* gene

We identified different pathogenic mutations in 23 *TTPA* alleles of the probands (Table 3). The 744delA mutation exon 5 and the 513insTT mutation, exon 3, were the most frequent mutations, accounting for 18 (78%) of the 23 mutated alleles (Table 3).

Genetic mutations of families M01, M02, M08 and M09 have been previously reported [3,7]. In family M11 (Fig. 2) one, proband was found to carry the 513insTT mutation on one allele and a new mutation on the other allele. This mutation was a G to C transversion at nucleotide position 736. This nucleotide change caused the substitution of a glycine with an arginine at residue 246 (Gly246Arg) of the α-tocopherol trans-

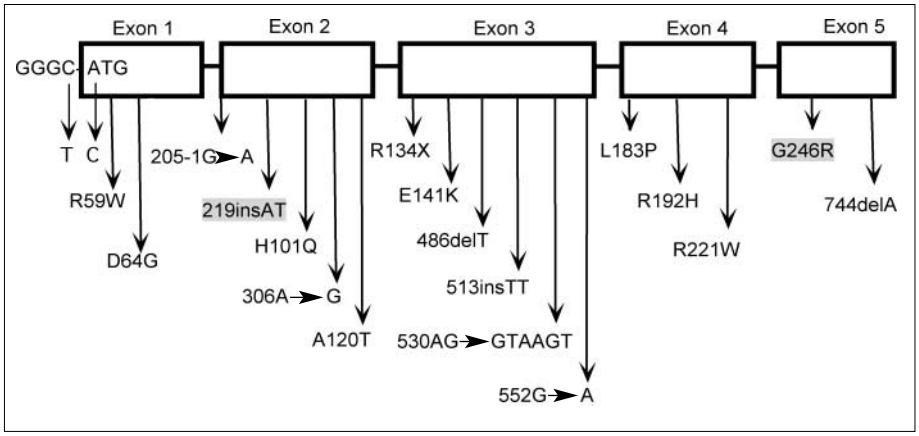

Fig. 1 Distribution of the identified *TTPA* gene mutations. The novel mutations described in this study are highlighted by gray shadow

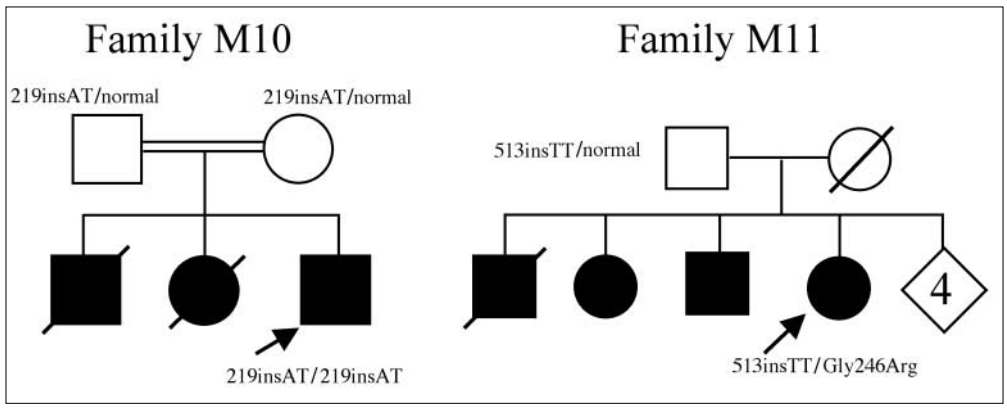

Fig. 2 Family trees of the patients carrying the two novel *TTPA* gene mutations. Black-filled symbols indicate the affected individuals; *arrows* indicate the probands

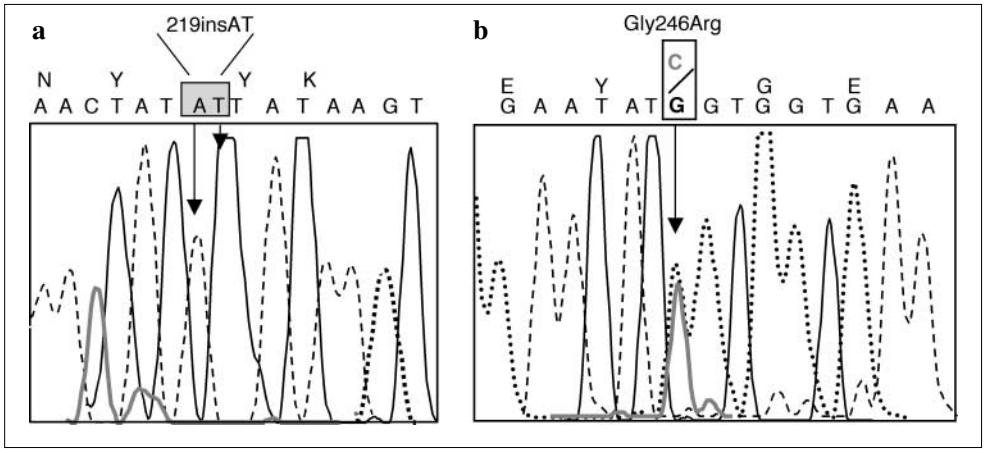

Fig. 3a, b *Newly identified mutations in* TTPA *gene in two families with AVED*. **a** Partial DNA sequence of exon 2 (nucleotides 214–226) in patient of family M10. Sequence analysis shows a homozygous two-base insertion at nucleotide position 219; this 219insAT mutation causes a frame shift in the translation process that results in a truncated protein. **b** Partial DNA sequence of exon 5 (nucleotides 730–744) in a patient from family M11. The mutation consists of a G to C transversion at nucleotide 736, resulting in the substitution of a glycine with arginine at residue 246 of the α-tocopherol transfer protein

fer protein (Fig. 3). The G to C change at nucleotide 736 was not present in 50 control chromosomes (data not shown).

In family M10 (Fig. 3a), the proband was homozygous for the presence of a two-base insertion (AT) at nucleotide 219 in exon 2. This mutation caused a frameshift in translation that resulted in the replacement of amino acids 74 to 83 and in the creation of an aberrant stop codon at position 84. The mutation was found in heterozygous form in both parents (Fig. 2).

Finally, in patient P0570 (family M12), we detected a previously known pathogenic mutation, the 486delT, in heterozygous form, but did not find other sequence abnormalities in the coding regions and in intron-exon boundaties of *TTPA* gene.

Discussion

AVED (MIM 277460) is a rare genetic neurodegenerative disorder, mostly detected in the Mediterranean populations. Clinical features closely resemble those of FA patients. However, the concomitant presence of specific neurological symptoms and very low levels of plasma vitamin E, in the absence of other clinical conditions commonly associated with fat malabsorption, can guide the differential diagnosis [1]. Since 1995, when the genetic basis of the disease had been elucidated, more than 50 AVED families and about 18 different mutations in the *TTPA* gene have been described [3, 6, 8–13]. In North-African populations, the most frequent mutation responsible for the disease is the 744delA mutation, while in AVED families of North European origin the 513insTT mutation has been identified often.

In Italian patients, these two mutations account for approximately 80% of the *TTPA* mutated alleles. In two of the eight new families described in this study, we found novel *TTPA* gene mutations: a severe truncating mutation in exon 2, and a missense mutation in exon 5. The first mutation (219insAT) was found in homozygous form in a patient presenting with an early onset FA-like phenotype, indistinguishable from that of other patients harboring the more common *TTPA* truncating mutations [3]. On the contrary, the patient harboring the new missense Gly246Arg mutation had a late-onset of the symptoms and a mild clinical presentation similar to that observed for the missense mutations R192H and A120T [3]. Neither of these new mutations was associated with the presence of retinopathy. The patient harboring the Gly246Arg mutation was compound heterozygous for the presence of the 513insTT mutation on the other allele. Thus, since the 513insTT mutation causes a truncating protein and has been associated, in homozygous patients, with a severe phenotype, it is conceivable that the milder clinical features observed in this patient may be due to the new missense mutation on the second allele. The Gly246Arg mutation causes the substitution of a non-polar to a charged polar amino acid in a position that appears highly conserved in rat and mouse TTPA proteins, and also in other correlated lipid-binding proteins, such as the cellular retinaldehyde binding protein (CRALBP), the yeast phosphatidylinositol/phosphatidylcholine transfer protein (SEC14) and the supernatant protein factor (SPF) [3, 6, 14]. These proteins, including TTPA, are members of a protein family characterized by the presence of two CRAL-TRIO lipid-binding domains, and are all involved in the intracellular distribution of specific lipids. Interestingly, mutations in another protein containing a CRAL-TRIO domain, called caytaxin, have been recently shown to cause a rare form of autosomal recessive ataxia, Cayman ataxia [15].

Biochemical characterization of *TTPA* missense mutations has been reported for six missense mutations [16, 17]. These studies indicated that *TTPA* mutations (R59W, E141K, and R221W) associated with a severe early onset AVED exhibit a clear impairment in both binding and transfer activity of TTPA, while the variants associated with the milder late-onset form of the disease (H101Q, A120T, R192H) show biochemical properties similar to the wild-type protein [17]. For other mutations, the possible implication for AVED has been hypothesized on the basis of the crystal structure of the human TTPA protein [16].

The effect of the new Gly246Arg mutation on TTPA protein function should be established by biochemical investigations. The pathogenic role of this mutation in our patient is strongly supported by the following evidence: (i) the mutation changes a highly conserved amino acid residue in the TTPA protein, (ii) it is associated with a typical clinical and biochemical AVED phenotype, and (iii) the nucleotide substitution was not present in control chromosomes.

We also found a patient heterozygous for the 486delT mutation. In homozygous form, this mutation has been associated with a severe AVED phenotype in a family from North America [10] and in two families from Morocco [3, 18]. In our patient, we had no evidence of a second mutation. However, as we did not sequence the non-coding regions of the gene, the possibility of mutations in the promoter or intronic regions cannot be excluded. Our study confirmed that the clinical presentation of AVED is variable in respect to age at onset, clinical signs and disease progression. Genotype-phenotype correlations were consistent with previous observations indicating that truncating *TTPA* gene mutations are associated with a severe form of the disease, while some of the missense mutations are associated with milder clinical presentations.

We also evaluated the effect of long-term vitamin E supplementation. Follow-up studies in AVED patients are limited [19, 20]. A recent study, monitoring 24 patients during a 1-year period of supplementation therapy, showed that vitamin E stabilized the neurological signs and led to mild improvement when early therapy was started [20]. In the majority of our AVED patients, we observed slower pro-

gression of the disease during several years of therapy. In 6 (37%) of 16 cases, however, we noticed the occurrence of new symptoms or the worsening of previous neurological deficits. Three patients had increased walking difficulties, two patients had a worsening of the speech capability, and one patient showed retinal degeneration 5 years after the initiation of supplementation therapy. A relevant clinical improvement in the first months of therapy was observed in a young patient who started vitamin E therapy early in the course of the disease. These observations strongly emphasize the importance of prompt diagnosis and treatment in AVED patients.

Sommario *L'atassia da difetto di vitamina E (AVED) è una malattia neurodegenerativa a trasmissione autosomica recessiva dovuta a mutazioni nel gene codificante per la proteina trasportatrice dell'alfa-tocoferolo (*TTPA*). I pazienti affetti da AVED hanno una ridotta capacità di incorporare l'alfa-tocoferolo nelle lipoproteine secrete dal fegato e presentano, quindi, bassi livelli plasmatici di vitamina E. A questo difetto biochimico si associa una sintomatologia clinica caratterizzata da atassia progressiva, disartria, areflessia osteotendinea e neuropatia. In questo studio abbiamo valutato 16 pazienti provenienti da 12 famiglie italiane confrontando il fenotipo neurologico alla diagnosi e durante la terapia a lungo termine con vitamina E. Nelle famiglie studiate le mutazioni 744delA e 513insTT sono risultate le più comuni. Inoltre, in due famiglie sono state identificate nuove mutazioni nel gene* TTPA. *In un caso è stata trovata un'inserzione dinucleotidica nell'esone 2 in forma omozigote, mentre in un'altra famiglia è stata identificata una sostituzione nucleotidica nell'esone 5, che causa un cambio aminoacidico a livello proteico (Gly246Arg). Questa mutazione è risultata associata ad un quadro clinico più lieve. La terapia con vitamina E ha portato ad una stabilizzazione delle condizioni neurologiche nella maggior parte dei casi. In alcuni pazienti, tuttavia, sono comparse durante il trattamento spasticità agli arti inferiori e retinite pigmentosa. La caratterizzazione clinica e genetica dei pazienti con AVED è fondamentale per instaurare un trattamento efficace nelle fasi iniziali della malattia e una corretta consulenza genetica.*

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