European Journal of Medical Genetics 52 (2009) 344–348

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Short report

C329X in *KRIT1* is a founder mutation among CCM patients in Sardinia

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ARTICLE INFO

Article history:
Received 9 January 2009
Accepted 9 May 2009
Available online 18 May 2009

Keywords:
CCM
Founder effect
KRIT1

ABSTRACT

Cerebral cavernous malformations (CCMs) are CNS vascular anomalies associated with seizures, headaches and hemorrhagic strokes and represent 10–20% of cerebral lesions. CCM is present in 0.1–0.5 of the population. This disorder most often occurs sporadically but may also be familial. Familial cases are inherited as a dominant trait with incomplete penetrance and are estimated to account for *KRIT1* 10–40% of the patients. The identification of the genes involved in such disorders allows to characterize carriers of the mutations without clear symptoms. The first gene involved in CCM1 is *KRIT1*. In addition to two other genes have been described: *MGC4607* (CCM2) and *PDCD10* (CCM3). We selected 13 patients belonging to seven Sardinian families on the basis of clinical symptoms and Magnetic Resonance results. In *MGC4607* gene an undescribed exon five deletion likely producing a truncated protein was identified in one family. In two patients with clear phenotype and in three asymptomatic relatives a 4 bp deletion in exon 9 of *KRIT1* gene, leading to a premature stop codon, was detected. A unique nonsense mutation (C329X) has been found in seven patients and two asymptomatic subjects belonging to four unrelated families. Haplotype analysis revealed a common origin of this mutation. These data suggest a "founder effect" in Sardinia for the C329X mutation, similar to other mutations described in different populations.

1. Introduction

Cerebral cavernous malformations (CCMs) are vascular anomalies, histologically characterized by abnormally enlarged capillary cavities and clinically associated with seizures, headaches and hemorrhagic strokes which have been recognized as common clinical entities after the advent of magnetic resonance imaging (MRI). They represent 10–20% of cerebral lesions and are present in 0.1–0.5 of the population. Most of the malformations are located in the CNS. This disorder most often occurs sporadically but may also be familial. Familial cases are inherited as a dominant trait with incomplete penetrance and are estimated to account for 50% of the patients in Hispanic Americans and 10–40% in other populations. Usually sporadic cases show a single lesion whereas familial cases are characterized by multiple lesions [11]. So far three genes have been identified. The first gene involved in CCM1 is *KRIT1* (Krev-1/rap1 interaction trapped 1) which accounts for 40% of the cases. *KRIT1* gene maps in chromosome 7q21-q22 and contains 16 exons that encode a 736 amino acid protein with three ankyrin domains and one FIRM domain [12]. More than 90 different mutations have been described. All *KRIT1* mutations so far identified lead to premature stop codon and are responsible for CCM1 in approximately 40% of familial cases [20]. Two other genes have been described: *MGC4607* (CCM2) in 7p13-p15 that accounts for 20% of patients and *PDCD10* (CCM3) at 3q25-q27 for 40% [14,4]. *MGC4607* gene encodes a protein called malcavernin with a phosphotyrosine binding domain, and it was found mutated in about 20% of CCM2 familial cases. No mutations were found in sporadic cases. CCM3 has been recently identified and it encodes a protein, named *PDCD10* (programmed cell death 10).

A founder effect has been reported in Hispanic Mexican population in whom a 742C>T transition in *KRIT1* gene shows a high prevalence [9,18]. Recently a high prevalence of a 14 bp deletion in exon 5 of CCM2 gene has been described also in patients belonging to apparently unrelated families from the Iberian Peninsula [13] and a high prevalence of CCM2 exons 2–10 deletion in the USA [15]. No founder effect has been reported so far in Italian and French populations [3,8,13,19].

With the present study we intended to investigate CCM gene mutations in thirteen patients belonging to seven Sardinian families and to verify in these families the presence of a possible "founder effect".

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doi:10.1016/j.ejmg.2009.05.002

2. Methods

2.1. Patients

Thirteen patients belonging to 7 unrelated Sardinian families were selected on the basis of the presence of at least one relative with multiple cavernous angiomas and/or clinical manifestations such as severe headache, seizures cerebral haemorrage. Relationship between the families since third generation was excluded by interviewing the family members. The pedigrees are shown in Fig. 1. Diagnosis was based on brain Magnetic Resonance Imaging (MRI) features. The age of onset ranged from 1 to 30 years.

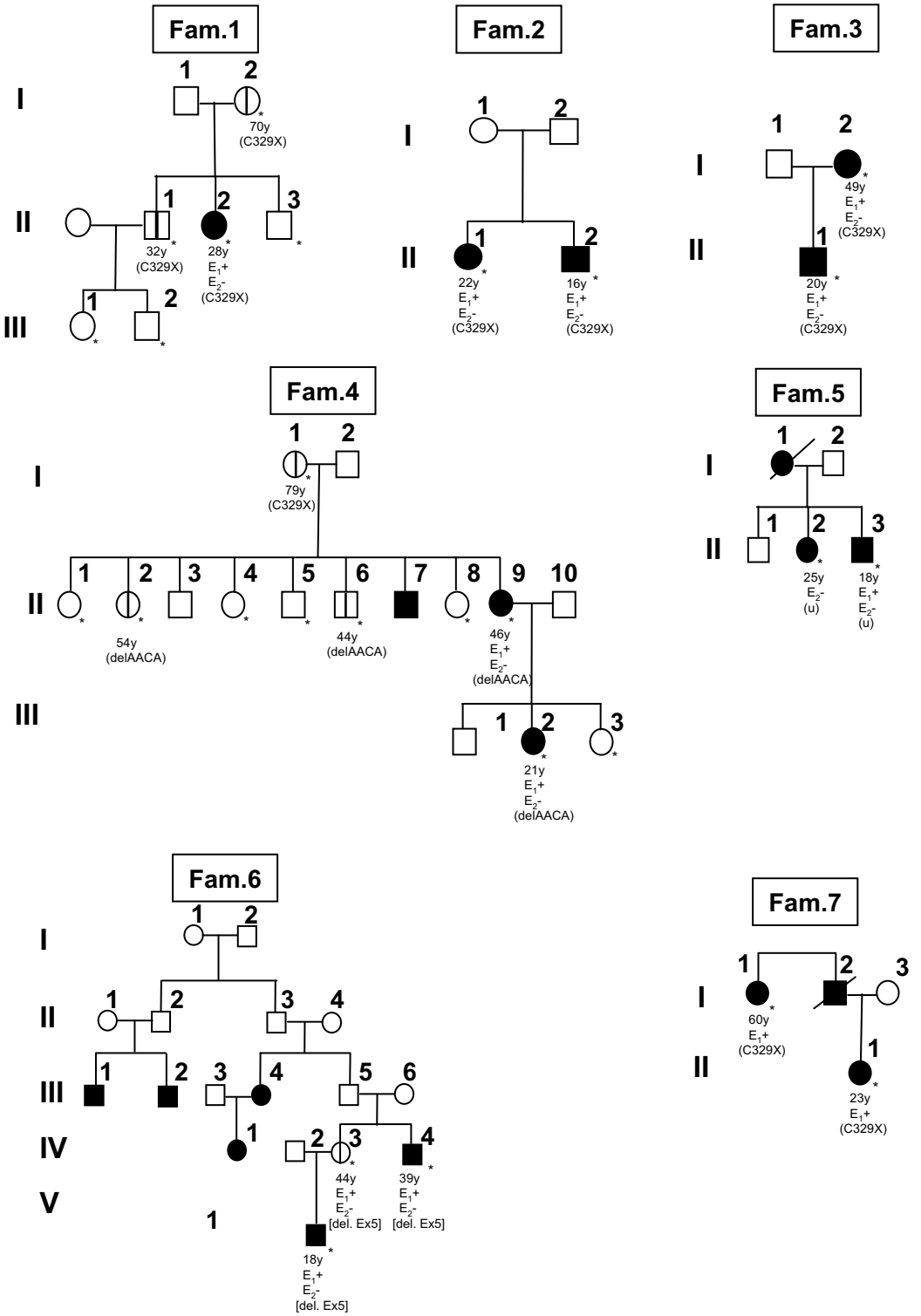

Fig. 1. Pedigrees of the CCM families: E1 = MRI exam; E2 = evaluation of hyperkeratotic cutaneous vascular malformation; * = examined personally; portioned symbols = asymptomatic carriers; y = years (age of subjects); (C329X) = C329X of *KRIT1* gene; (delAACA) = c.800_803del of *KRIT1* gene; [del. Ex5] = exon 5 deletion of *MGC4607* gene; (u) = unidentified mutation. Pedigree symbols follow the recommendations for standardized human pedigree nomenclature. Journal of Genetic Counselling 4: pp. 267–279, 1995.