Azienda Ospedaliera
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FONDAZIONE PER LE NEUROSCIENZE MASSIMO COLLICE ONLUS

Extensive genetics of Cerebral Cavernous Malformation in Italy

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Background. Cerebral Cavernous Malformations (CCM; OMIM 116860) (also known as cavernous angioma or cavernoma) are major vascular malformations having a raspberry-like appearance and consisting of closely clustered, abnormally dilated and leaky capillary channels (caverns) lined by a thin endothelium layer devoid of normal vessel structural components, such as pericytes. Cavernous malformations can occur anywhere in the body, but usually produce serious signs and symptoms only when they occur in the central nervous system, where they account for 5%-15% of all vascular malformations. Within the brain, CCMs occur as single or multiple lesions ranging in size from a few millimeters to a few centimeters and, depending on the size and location, can be clinically silent or give rise to serious clinical symptoms such as headaches, neurological deficits, seizures, stroke, and intracerebral hemorrhage that can result in death (1).

Symptomatic disease typically begins in the third through fifth decades of life, although lesions have been described in all age groups, including young children, with no sex predominance. Diagnosis is most commonly made by routine magnetic resonance imaging (MRI) screening (Fig. 1), although detection is far more likely via specific imaging techniques known as gradient-echo (GRE) or susceptibility-weighted imaging (SWI), which can unmask small lesions that may otherwise remain undetected (2; 3). Hundreds of lesions may be identified in the same patient, depending on the sensitivity of brain imaging used. Because of large series of MRI and autopsy studies, this disease has been recognized as a common clinical entity: CCM lesions are estimated to occur in approximately one out of every 500-600 people (worldwide prevalence ranges from 0.1 to 0.5%; www.angiomaalliance.org). These lesions are most frequently found in the Central Nervous System (CNS); however, they may also be found localize at other sites, including liver, skin (Fig2), vertebral bodies, and retina

Figure 1. MRI presentation of CCM

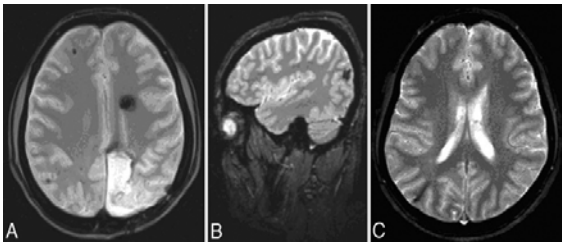


Figure 2. cutaneous cavernomas

Indeed, the CCM disease affects millions of people worldwide with a major impact on quality of life and significant socio-economical consequences. Nevertheless, knowledge and risk awareness of this disease is generally poor within the society and very low even among medical doctors.
Cavernous Malformations occur both sporadically (with single malformation) and as an autosomal dominant inherited disorder (with multiple cavernous malformations-FCCM) (4). Three forms of autosomal dominant CCM have been mapped (5). The disease gene products are known for all three loci and the nature of their mutations in patients with CCMs strongly suggests a loss of function (6). CCM1 is caused by truncating mutations in KRIT1 encoding a protein containing ankyrin repeat motifs and a FERM domain. CCM2 results from mutations in MGC4607, encoding the phosphotyrosine binding (PTB) domain protein malcavernin, the murine ortholog of which was characterized as a mitogen-activated protein kinase (MAPK) scaffold named osmosensing scaffold for MEKK3 (OSM). CCM3 has been shown to result from mutations in PDCD10 (programmed cell death 10), a gene up regulated in the human myeloid cell line TF-1 upon induction of apoptosis.

Methods. The study population consists of 87 Italian FCCM. All the patients were offered genetic counselling and all signed the informed consent approved by the Ethics Committee of our Hospital.
Cycle Sequencing Kit Version 1.1 (Applied Biosystems) was used for analysis of the three genes *KRIT1*/CCM1, *MGC4607*/CCM2 and *PDCD10*/CCM3. All probands negative at the genetic screening were subjected to MLPA analysis.

Figure 3. Pedigree of one italian FCCM;
most of the tested famlies are as large as this one

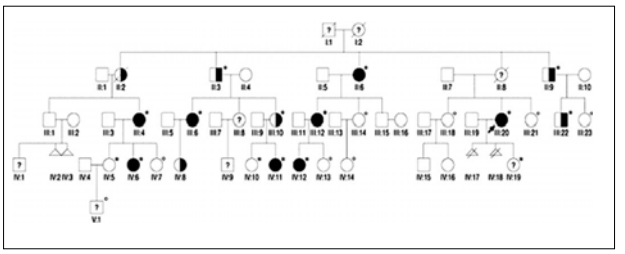
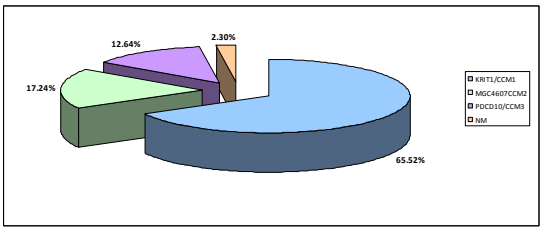


Figure 3. Graphic distribution of the genetic results



Results.
We identified KRIT1/CCM1 mutations in 65.52%, MGC4607/CCM2 mutations in 17.24%, PDCD10/CCM3 in 12.64% and no mutations in 2.3% of the analysed cases.
According to our results, more than 90% of the familial form of the disease present a genetic mutation.

Conclusions. The results here presented derive from a network of clinicians and researchers with complementary expertise and interests related to different aspects of this genetic disease. The network should provide useful insights into the underlying pathogenetic mechanisms and risk factors as well as a framework for the definition of accurate and appropriate diagnostic and clinical management procedures and the development of novel, more safe therapeutic strategies, specially required for inoperable or multiple lesions.
To date there are not direct therapeutic approaches for the CCM disease, besides the surgical removal of accessible lesions.
FCCM has been extensively studied in our Centre since 2002 (see produced publications), our Centre is the principal in Italy together with S.Giovanni Rotondo in south of Italy.

Acknowledgments. The authors thank the "Fondazione per le Neuroscienze Massimo Collice" for supporting MSC and part of this study

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