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Mutation analysis in Irish families with glomuvenous malformations

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Summary

Background Glomuvenous malformations (GVMs) are rare bluish lesions that can affect the skin and mucosal surfaces. They represent defects in vasculogenesis. Lesions can occur sporadically or in an autosomal dominant mode of inheritance. Recent studies have shown that mutations in the glomulin gene (GLMN) on chromosome 1p21-22 are responsible for familial GVMs.

Objectives To search for mutations in GLMN in Irish families with GVMs.

Methods We identified four Irish families with GVMs and confirmed linkage to chromosome 1p21-22 in these cases. We sequenced the glomulin gene in all affected and unaffected members of the families.

Results Linkage analysis showed that affected individuals from the families shared a common haplotype. Mutation analysis revealed a delAAGAA mutation in exon 3 of the glomulin gene in all four families with GVMs.

Conclusions We confirm that mutations in the glomulin gene are responsible for GVMs and suggest a founder Irish mutation in the glomulin gene in four Irish families.

Glomuvenous malformations (GVMs) (OMIM #138000) are also known as ‘glomangiomata’ or ‘venous malformations with glomus cells’. Typically they are blue or violaceous lesions, which can occur at any site on the skin or rarely on the mucosa. Clinically the lesions may be macular, nodular or thickened plaque-like lesions. They may be firmer than purely venous malformations and are sometimes painful to palpation. They vary from single banal lesions to extensive large disfiguring lesions. Most cases are sporadic but familial cases are autosomal dominant. It has been estimated that penetrance rises from 70% at age 5 years to 100% by age 30 years. Isolated GVMs may have a later onset.

Histologically, GVMs are distinguished by the presence of basophilic rounded cells (glomus cells) around loose distended vein-like channels. Glomus cells probably represent incomplete or defective smooth muscle cells.

In 2000 Brouillard et al. identified the FAP48 gene within a narrowed region of 1p21-22 which linked to familial GVMs. In 2002, upon finding that 14 different disease-causing mutations in this gene caused GVM, they renamed the gene ‘glomulin’. In addition to germline mutations they found a somatic ‘second hit’ mutation in affected tissue of a patient with an inherited genomic deletion. The glomulin gene (GLMN) is composed of 19 exons extending over 55 kb (GenBank AJ302727–AJ302730). We searched for mutations in GLMN in Irish families with GVMs.

Patients and methods

Case series

We identified four Irish families with GVMs. Three of the families were from Northern Ireland and one from south-east Ireland. All pedigrees showed that the disease followed an autosomal dominant mode of inheritance (Fig. 1). Lesions in the affected individuals varied from small solitary lesions (Fig. 2) to more substantial, cosmetically noticeable lesions (Fig. 3). Within families there was different disease expression and lesions varied from solitary lesions to more extensive cosmetically obvious areas of involvement (Fig. 1). All lesions were confined to the skin with no mucosal involvement and in most cases were clinically asymptomatic except where the affected sites were at trauma-prone areas. Skin biopsies from the probands in each family showed a similar histological...
Methods

DNA extraction and polymerase chain reaction (PCR) amplification were carried out using standard techniques. DNA samples from the families underwent PCR with the fluorescently labelled microsatellite marker D1S2868 (Applied Biosystems PRISM linkage mapping set version 2) and two fluorescently labelled oligonucleotide primers (designed in-house, and synthesized by Invitrogen Life Technologies; available on request) from the region of chromosome 1p21-22. This allowed haplotyping of individuals from the families.

appearance (Fig. 4): basophilic glomus cells around loose channels lined with endothelial cells.

Fig 1. Pedigrees of four Irish families (a–d) with glomuvenous malformations demonstrating autosomal dominant mode of inheritance, clinical features and common haplotype of affected individuals. All affected individuals share the 210, 260 and 341 alleles. Δ, solitary lesion; O, three or fewer lesions; #, four or more lesions; ‡, extensive cosmetically obvious lesions.

Fig 2. Small nodular glomuvenous malformations on abdomen.

Fig 3. Cosmetically noticeable glomuvenous malformations on forearm.

Fig 4. Histological appearance of a glomuvenous malformation: loose venous channels surrounded by basophilic glomus cells (haematoxylin and eosin; original magnification × 500).
Mutation analysis of the glomulin gene was performed using primers designed by Brouillard et al. Primers used for exon 3 were redesigned after poor amplification and were:

forward primer 5’TATTGAATGCTAATTTGATACG-3’;
reverse primer 5’TGGGTAAATTAAATGAC-3’.

The sequence around the mutation on exon 3 was cloned in patients with cutaneous GVMs. However, management of large disfiguring lesions remains very difficult.

In conclusion, mutation analysis has been useful in these families to establish the diagnosis firmly and to allow counselling of the genetic risks of passing on the condition. It has also allowed the clinician to tailor investigations in these families. The 157delAAGAA mutation may be a founder mutation in the Irish population and this raises the possibility of a straightforward molecular test to confirm the clinical diagnosis in patients with cutaneous GVMs.

References