Genetics of rare bleeding disorders in the Scottish population

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Introduction

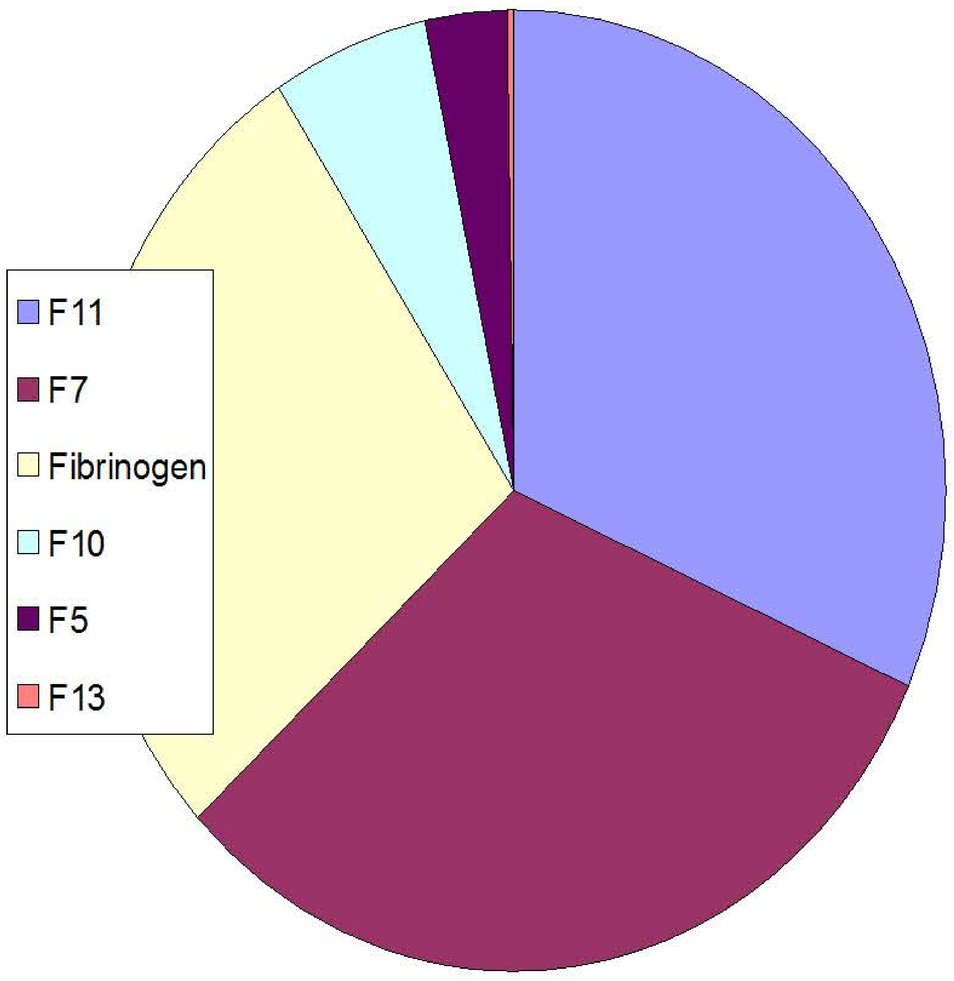
Rare haemostatic disorders affecting coagulation factors other than factor VIII or factor IX represent challenges in terms of diagnosis and management. The application of molecular diagnostics in the investigation of such disorders has added to our understanding of these conditions, with identification of defects in genes encoding coagulation factors as well as those responsible for the production of chaperone proteins essential for intracellular transport. The Molecular Haematology Department at the Royal Infirmary of Edinburgh provides a national service for the genetic investigation of disorders of haemostasis for all patients in Scotland. Since 2009 this has included rare bleeding disorders affecting coagulation factors V, VII, X, XI, XIII, and fibrinogen.

Service Provision in Scotland

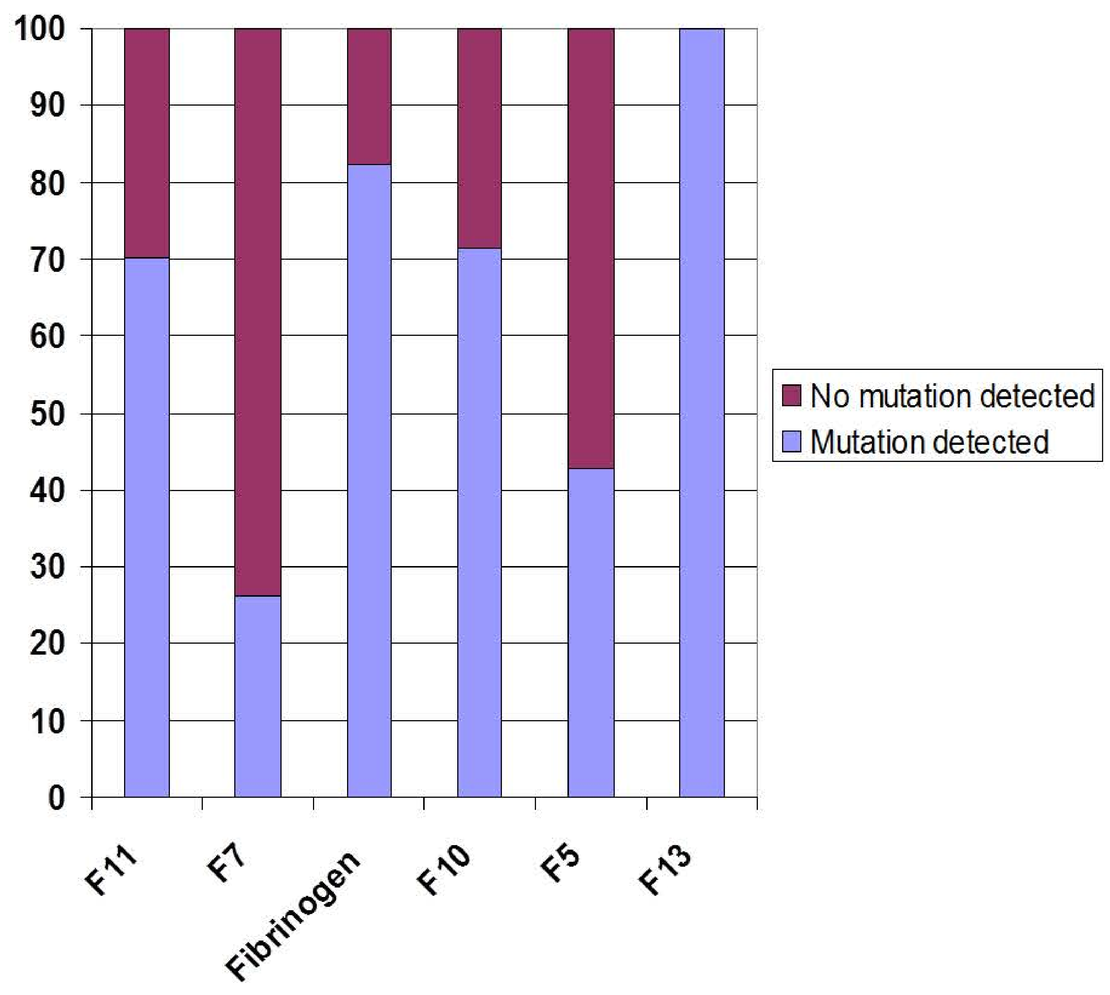
National Services Scotland commissions specialist laboratory services for Scotland. Specialist Molecular Genetics Services are provided in four centres, Aberdeen, Dundee, Edinburgh and Glasgow, each of which has its areas of specialism. The Genetics of bleeding disorders is carried out in the Edinburgh Centre. While the majority of requests are associated with Haemophilia A, Haemophilia B and von Willebrand's disease, there has been a growing referral workload for rarer bleeding disorders.

Results

Spectum or referral for rare bleeding disorders 2009- 2014



Percentage of referrals were mutation was detected



There is considerable variation in the rate of identification of candidate mutations in these patent groups. While the rate is lowest in the F7 gene referrals, this patient group have a high frequency common polymorphisms known to influence FVII levels. Of the 54 patients with mutations identified in the F11 gene, two were homozygous, and two showed compound heterozygosity. Similarly, of the 68 samples investigated for Mutation in the Fibrinogen genes, 4 had mutations in more than one gene, and 4 were compound heterozygotes within the same gene.

Conclusion

The in-depth study of candidate genes in this well characterized cohort of patients adds valuable data to assist in our understanding of the incidence, genetic basis and transmission of these rare autosomal disorders in the Scottish population. The frequency of compound heterozygosity and multiple gene mutations adds further support to the need to perform complete gene analysis rather than targeted sequencing in these patients.

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