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Effectiveness of genetic cascade screening for familial hypercholesterolaemia using a centrally co-ordinated clinical service: An Australian experience

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ABSTRACT

Background: Familial hypercholesterolaemia (FH) is a co-dominantly inherited disorder of low-density lipoprotein (LDL) catabolism, causing elevated LDL-cholesterol and premature coronary artery disease (CAD). Several guidelines recommend genetic cascade screening relatives of probands (index cases) with genetically proven FH, but experience in a clinical service setting is limited.
Methods: Relatives from 100 index cases with genetically confirmed FH underwent genetic and lipid testing via a centralised screening program in Western Australia. The program's effectiveness was evaluated as the number of newly diagnosed relatives with FH per index case and the proportional reduction in LDL-cholesterol after treatment.
Results: Of 366 relatives tested for FH, 188 (51.4%) were found to have a pathogenic mutation. On average, 2 cases were detected per index case. Affected relatives were younger and less likely to have physical stigmata of FH and premature CAD than index cases ($p < 0.001$). Of the new cases, 12.8% had hypertension, 2.7% had diabetes and 16.0% were smokers; 48.4% were already on statin therapy and these were older ($p < 0.001$) and had more vascular risk factors and CAD ($p < 0.01$) than those not on therapy. Significant reductions in LDL-cholesterol (−24.3%, $p < 0.001$) were achieved overall, with previously untreated new cases of FH attaining a maximal average reduction of 42.5% in LDL-cholesterol after drug therapy. Over 90% of subjects were satisfied with screening and care.
Conclusion: Genetic cascade screening co-ordinated by a centralised service is an effective and acceptable strategy for detecting FH in an Australian setting. A significant proportion of new cases exhibit other CAD risk factors and are already on statins, but have not received a prior diagnosis of FH.

1. Introduction

Familial hypercholesterolaemia (FH) is a co-dominantly inherited disorder of lipoprotein metabolism characterised by elevated low-density lipoprotein (LDL)-cholesterol, tendon xanthomata and premature atherosclerotic coronary artery disease (CAD). FH fulfils the World Health Organization criteria for disease screening [1]. However, most countries do not have systematic screening

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programs, and currently the majority of people with FH are undiagnosed and often undertreated [2–4]. Individuals with untreated FH have a ~13 fold higher CAD risk than non-FH individuals [4]. On average, males with untreated FH have a 50% risk of CAD by age 50 years and females a 30% risk by age 60 years [5]. Individuals with FH generally have markedly higher LDL-cholesterol concentrations than people without FH, although there is overlap in the distribution of values [6]. However, individuals with FH have elevated LDL-cholesterol concentrations from birth and consequently a higher cumulative exposure of coronary arteries to cholesterol [4].

The Dutch Lipid Clinic Network Criteria (DLCNC) [7] constitute the preferred phenotypic diagnostic tool for FH in Australia [2]. There are other criteria for FH, but at present there is no international consensus on the best method of diagnosis, other than the detection of a pathogenic gene variant [7–10]. There are currently over 1200 LDL receptor gene (*LDLR*) mutations which account for >90% of FH mutations [11,12]. Mutations of the apolipoprotein B gene (*APOB*) are responsible for a further 5–10% and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) are found in approximately 1% of individuals [4,12]. The spectrum of mutations causing FH in Western Australia has been described previously [13].

Screening close family members of individuals with FH (cascade screening) is potentially clinically and economically effective, and is recommended in adult and paediatric FH management guidelines [2,4,14–18]. The effectiveness of cascade screening was originally based on early reports of national and regional cascade screening programs from the late 1990's and early 2000's [19,20]. However, since the late 1990's the availability and use of HMG-CoA reductase inhibitor (statin) therapy has increased markedly. Statin therapy leads to a significant reduction in LDL-cholesterol and reduces CAD mortality in individuals with and without FH [21,22]. However, only 47% of individuals with probable FH were reported to be taking statin therapy in a recent survey of a large community population [23].

We investigated the integrated effectiveness of cascade screening family members of the first 100 index cases with genetically confirmed FH in a centralised service in Western Australia. We hypothesised that in such a setting, cascade screening would provide an effective method for detecting and managing FH.

2. Methods

2.1. Assessment of subjects and cascade screening process

The first 100 index cases (probands) from kindreds with genetically confirmed FH, where at least one family member had been genetically screened, were selected for this study. The index cases were reviewed at the Lipid Disorders Clinic at Royal Perth Hospital between March 2007 and August 2013. The index cases were diagnosed using the Dutch Lipid Clinic Network Criteria, then

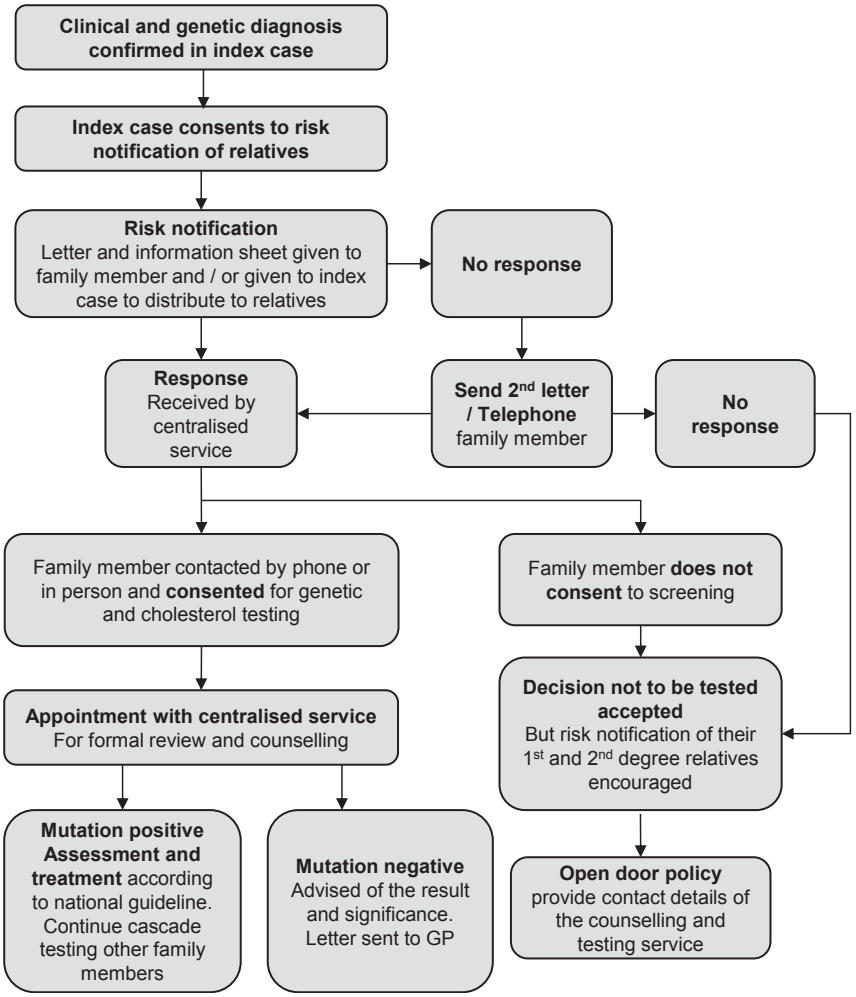

Fig. 1. Protocol describing the genetic cascade screening process employed by Lipid Disorders Clinic at Royal Perth Hospital, Perth Western Australia. Derived from the Australasian FH model of care by Watts et al. [2].