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Original Article

Cascade testing in families of carriers identified through newborn screening in Western Brittany (France)

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Abstract

Background: Newborn screening (NBS) for cystic fibrosis (CF) can lead to the detection of healthy carriers. We report a unique assessment of family testing following the identification of carriers by NBS for over 20 years, in an area where CF is frequent.
Methods: We reviewed all of the carriers identified by NBS between 1991 and 2010 and registered the tests done in those families.
Results: NBS identified 0.1% of the newborns as carriers, which correspond only to 2.6% of the expected carriers born within the period, and 1/3 of those with an increased IRT level. Of the 195 families, 75.9% requested testing (2.5 tests per family).

We identified 183 carriers and five 1-in-4 risk couples. Reassurance about genetic status was provided to 96% of the couples.
Conclusions: Carriers detected by NBS appeared to be well managed in our area, and cascade testing that informs on genetic status seems relatively active.

Keywords: Family testing; Carrier; Cystic fibrosis; 1-in-4 risk couple; Newborn screening

1. Introduction

Despite the absence of a cure, newborn screening (NBS) for cystic fibrosis (CF) has been implemented in many areas, allowing patients to receive early care with measurable nutritional and respiratory benefits [1]. The introduction of DNA analysis has greatly improved the test performances. However it has led to the identification of some newborns carrying a single CF mutation.

Although being a carrier has no influence on the development of the newborn, the knowledge of that status is nonetheless important, as there may be reproductive implications. Indeed, in adulthood the carrier should be offered the opportunity to discuss his/her status and the possible reproductive implications with a genetic counsellor. For parents, this means that one of them is an obligate carrier and, therefore one *CFTR* gene mutation segregates in the family. The parental couple is, moreover, more likely to be a 1-in-4 risk couple (if the partner is also a carrier) with the potential risk to give birth to an affected child (a priori, this risk is approximately 1 in 100). Initially offered only to CF-affected family members, family testing (also called cascade testing) has, since NBS was implemented, been offered to families in whom a CF carrier was identified. Parents and relatives can be informed of their

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genetic status by testing and can request prenatal diagnosis for future pregnancies [2].

Only few articles focused on cascade testing in families with CF carriers children identified at birth [3–7]. Most of them reported few requests for testing in extended family members. To our knowledge, no similar measurements have been done in France.

Finistère (Brittany, Western France) was a pioneer district in the implementation of NBS for CF. It was established in May 1988, and the procotol combining immunoreactive trypsin (IRT) measure and DNA was introduced in January 1991 [8–12]. CF is particularly common in Brittany (incidence: approximately 1 in 2500; carrier rate close to 1 in 25) and the population, mostly of Celtic origin, is particularly aware of and mobilised against the disease [13].

The present study aimed to assess the achievement of cascade testing in parents and relatives of carrier children identified through NBS and born over a 20-year period (1991–2010) in a district of western France (Finistère), where CF is frequent and that was a pioneer in the implementation of NBS.

2. Material and methods

2.1. Newborn screening

The aim of NBS for CF is the early detection of patients. Our protocol, which consists of a three-step strategy, has been described previously [10,14].

Children with one or two mutations are referred to the CF centre, where a sweat test is performed. If the sweat test result is below 30 mEq/l and only one mutation is present, the child is considered as a carrier. If the sweat test result is between 30 and 60 mEq/l or slightly greater, further gene analyses are performed. The child is considered as a carrier if no additional mutation is identified and no clinical sign evidenced. If an additional CF causing mutation is identified, CF is diagnosed.

Parents are invited to meet a paediatrician, who explains the test results in terms of child health and implications for the family. They are also directed to a consultation at the Medical Genetics Unit of the University Hospital.

2.2. Cascade testing

During this consultation, genetic aspects and possible risks are discussed and cascade testing is first offered to the parents of the carrier newborn. The aim of the genetic analysis is threefold: to identify the parent sharing the mutation with the child, to identify any couple who is at 1-in-4 risk and those low risk couple. As no active cascade programme exists in France, the genetic information is then disseminated by the parents to family members. Individuals from the family branch in which the mutation segregates who want to know their status regarding CF have to contact the Medical Genetics Unit for an appointment with the geneticist. Our strategy of testing for relatives is summarised in Fig. 1.

2.3. Study population

We reviewed all carriers born in the district of Finistère (893 000 inhabitants; approximately 10 000 births per year) identified by NBS since the introduction of the IRT/DNA protocol (period 1991–2010). The census was performed using data from the Laboratory of Molecular Genetics of the University Hospital (Brest). It is the sole genetic unit of our area and one of the reference laboratories for CF in France. The validation was

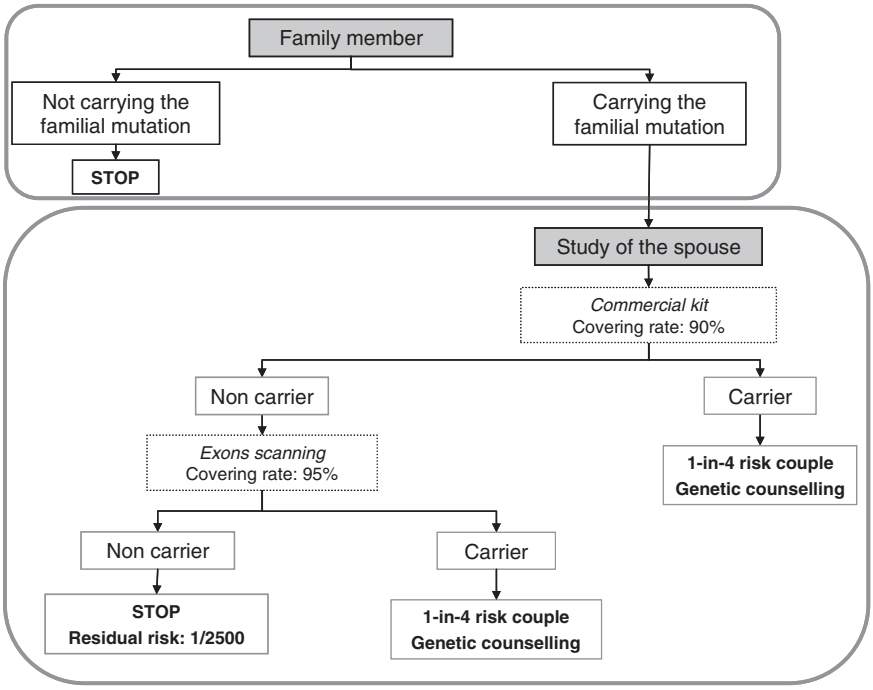

Fig. 1. Flowchart of the cascade testing strategy used in our laboratory.