



## **Genetic carrier testing for cystic fibrosis among CF family members**

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When a baby is diagnosed with cystic fibrosis, many things change. The learning curve is steep for parents who must understand the medical needs and lifestyle changes that are part of living with cystic fibrosis. For most parents, the support of family members at this time is vital. Stories of family involvement are commonly retold by parents as part of an intertwined memory of their child's diagnosis with cystic fibrosis [1].

Family are also connected to a diagnosis of cystic fibrosis in another way. Cystic fibrosis is genetic, the result of mutations in the CFTR gene, but it is necessary to have mutations in both copies of the CFTR gene (one from each parent) for the child to have cystic fibrosis. A person who has a mutation in one copy of their CFTR gene and not in their other copy does not have cystic fibrosis, but is a healthy 'carrier'. In this way, a CF mutation can be 'carried' by people in a family and passed from generation to generation. This mode of inheritance explains why most children with cystic fibrosis are born into families with no prior family history of cystic fibrosis. In Australia, with a population of 20 million, there are about one million healthy carriers of a CF mutation, but only about 3,000 affected individuals.

Once a diagnosis of cystic fibrosis is made, family members of a child diagnosed with CF are at increased risk of being a carrier of a CF mutation, and therefore are at higher risk of having a child affected by CF if their partner is also a carrier of a CF mutation. For example, the aunts and uncles of a child with cystic fibrosis each have a 50% (1/2) chance of carrying a gene change, compared to a 4% (1/25) chance for someone in the general population in Australia. It is important that family members are provided the opportunity to make an informed decision about carrier testing.

Because most children who are diagnosed with CF are born into families with no prior family history of the disease, there has been a lot of interest regarding offering cystic fibrosis carrier testing to everyone in the general population, whether or not they have any relatives with CF. This would allow people who wish to learn if they are a cystic fibrosis carrier to do so before a child is born to them or a member of their family. This information can be used for reproductive planning for couples who know they are at risk of having a child with CF because both are carriers. Although offering carrier testing this way will detect most CF carriers in the population, many challenges to population testing have been identified, especially how to access the 'general population'.

Some published studies have shown a very high uptake of carrier testing, while others have demonstrated a lack of interest from the community [2-4]. These differences reflect many issues: whether the test is free or at a cost, when the test is



offered, whether the national health system provides free care for those with CF or requires payment, whether prenatal diagnosis is available and whether termination of pregnancy for a disease such as CF is permitted, the level of knowledge about CF in the community, and whether people think that things are getting better or worse for those living with CF.

In a recent study we undertook to explore the views of community members in the State of Victoria, Australia, about population-based carrier testing, it was clear that in the absence of a family history of cystic fibrosis, there is little motivation to undertake cystic fibrosis carrier testing [5]. This view is illustrated in the quote below.

*"I must have heard of it but it is never something I think about, 'I should have testing', because it is not in my world I suppose, or my family."* (Kate\*, a pregnant woman with no family history of cystic fibrosis)

For family members, the situation is different. They will know something about CF from their own family experiences, and are at increased risk of being carriers. But for parents of a child with cystic fibrosis, talking about genetics can be a difficult conversation to initiate; there are feelings of frustration when family members do not react in a way that parents imagined.

To be able to assist parents of a child with cystic fibrosis to talk with their family members about genetics it is important to understand more about the attitudes of family members towards cystic fibrosis carrier testing.

*"Because it doesn't directly affect them, it is more of an 'Oh well, OK, we'll look at that later on'....therefore I become emotional about it...frustration, disappointing perhaps".*

(Michelle\*, mother of a child with cystic fibrosis)

*"[My husband] is a little bit frustrated that his brother is not getting tested."*

(Mary\*, mother of a child with cystic fibrosis)

We are currently undertaking a study with family members to explore some of the barriers and facilitators that arise when relatives make a decision about carrier testing. We are also investigating family members' understanding of CF, the genetics of CF, and their attitudes towards deciding about carrier testing. We will involve as many family members of children with CF as possible. Family members of the child with cystic fibrosis may be aunts or uncles, grand parents, siblings, or cousins. This will be the first study to take a multi-generational approach to understanding family members' attitudes and the factors that influence their decision-making.

To provide background to the study we wanted to find out the uptake of cystic fibrosis carrier testing amongst Victorian CF families, which has not been studied previously.

In the State of Victoria, Australia, CF carrier testing is available free of charge to people with a family history of cystic fibrosis. The vast majority of CF carrier testing for family members is performed by a single laboratory service, with all records stored in a confidential centralised database. Our study has focused on families where the diagnosis of cystic fibrosis was made through the newborn screening program (about 97% of CF diagnoses are made in this way in Victoria). Standard



clinical practice following a diagnosis of CF is to offer parents intensive education. At the Royal Children's Hospital, Melbourne, Australia, this typically involves a 5-day full time educational program, where parents and the infant stay on campus and meet with all the members of the cystic fibrosis team, including geneticists and genetic counsellors. This program allows for consistent service delivery after a diagnosis of CF through newborn screening.

One component of this program is meeting with the cystic fibrosis genetic counsellor specifically to discuss the option of prenatal screening for future pregnancies, and the availability of carrier testing for other family members. The CF genetic counsellor draws a family tree and parents are provided with a letter for distribution within the family to assist them when discussing carrier testing with their family members. The letter states that a CF mutation has been detected in the family and if carrier testing is desired, this can be arranged through the genetic counsellor.

We have audited the genetics files (a subset of medical records) of children diagnosed with cystic fibrosis who were born in the State of Victoria, Australia, in 2000-2004. The number of relatives who would be eligible for carrier testing was determined by examining the family trees drawn at the time of diagnosis. Family members were eligible if the familial mutation was known and detectable, if they were aged 18 years or older, and if they had a chance of being a carrier of 100% (1/1), 50% (1/2), 25% (1/4) or 12.5% (1/8). We excluded family members who lived overseas or interstate (as we would not be able to find out if they have had carrier testing), and first cousins and siblings of the child with cystic fibrosis if their age was not known to be 18 years or more.

We linked the data in the family trees to that available in the laboratory database to determine the number of family members who have had cystic fibrosis carrier testing following the child's diagnosis. There may be a small number of family members who have had carrier testing elsewhere, but the vast majority of CF carrier tests for family members are performed by a single laboratory and recorded in the database accessed in this study.

The preliminary results of this audit suggest that the majority of family members (about 80%) of a child who has been diagnosed with cystic fibrosis have not had carrier testing. This prompted us to want to learn more about why some people have testing and others do not, an issue we hope to address in the study we are now conducting.

Excluding the parents of the child with cystic fibrosis, the highest uptake of cystic fibrosis carrier testing is seen for aunts/uncles and grandparents (28% and 26% respectively). These findings generate some interesting points for discussion.

Firstly, aunts and uncles of the child are more likely to be of an age when they are having their own children and this may bring carrier testing into 'my world'. The role of life stage is illustrated in the quote below from Cameron\* who participated in the initial interview study.

*"Certainly before I was to have children, it would be something I would go through...It is something that only really becomes relevant I suppose when you are looking to have kids, from my perspective."*

(Cameron\*, brother of an adult with cystic fibrosis)

Secondly, grandparents who have passed their reproductive years may choose to have cystic fibrosis carrier testing to provide information to other family members. If one of the grandparents clarifies their carrier status and finds they are not a carrier,



entire branches of the family tree are no longer at increased risk of carrying the mutation.

Thirdly, these two groups of family members potentially represent the closest social relationships in the family. Thus the information about carrier testing may be most readily passed on to them rather than to relatives who are more distant, leading to greater rates of uptake of testing.

While these three points may explain why the highest uptake rates are seen in aunts/uncles and grandparents, even for these groups the majority have not had testing. Some aunts and uncles may have just finished having children and therefore deem carrier testing to be irrelevant for them. Grandparents may be concerned that the family, or indeed themselves, may apportion blame regarding passing on the mutation. The potential to feel guilty may deter grandparents from having testing, preferring instead for the generation below to undertake testing.

The complexity of relationships within families and the complexity of genetics make research in this area an exciting but challenging prospect. We hope that exploring the views of family members can inform clinical service in order to make cystic fibrosis carrier testing more accessible to family members.

\* All names of participants have been changed

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Belinda McClaren is a PhD student at the Murdoch Childrens Research Institute, the University of Melbourne and the Royal Children's Hospital, Melbourne. For more information regarding this research, contact [belinda.mcclaren@mcri.edu.au](mailto:belinda.mcclaren@mcri.edu.au).

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