VCGS Leaders in Genetic Health

the partumpost

The latest in cystic fibrosis genetic testing

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Cystic fibrosis

Cystic Fibrosis (CF), an autosomal recessive genetic condition, is the most common inherited life shortening condition affecting Australian children. 1 in every 25 people are carriers of CF and approximately 1 in every 2,500 babies are diagnosed with the condition in Australia, usually via newborn screening programs.

CF primarily affects the respiratory and gastrointestinal systems with a current average life expectancy around 40 years [1]. CF is caused by genetic variations in the *CFTR* (cystic fibrosis transmembrane conductance regulator) gene that codes for the CFTR protein.

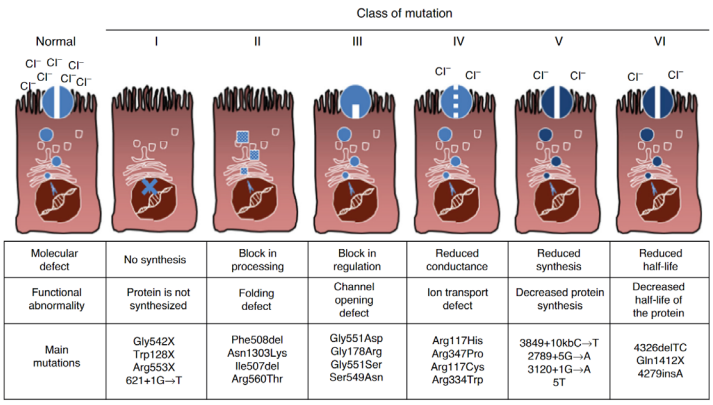
This protein controls the flow of chloride ions in and out of cells and *CFTR* gene variants can lead to reduced production and/or function of this protein. A dysfunctional chloride channel inhibits the transfer of chloride ions, therefore impairing the movement of water. This results in a thick sticky mucus in mucus-membrane lined organs leading to the symptoms of CF [2].

Although there are over 2000 variants in the *CFTR* gene, most are rare, benign variants and not CF causing mutations [3]. The most common CF causing variant is the c.1521_1523delCTT (Phe508del) which accounts for more than 70% of CF causing mutations. *CFTR* variants disrupt protein function in a variety of ways (Figure 1.) [4], leading to clinical symptoms of CF. Presentation of CF varies in part due to the type of variants the individual has, as well as environmental factors.

While there is no cure, advances in treatment and early diagnosis have improved long-term health outcomes for people with CF [5]. As our understanding of the molecular mechanisms of CF increases, treatments that interact directly with the CFTR protein and the underlying defects, will allow for better targeting and further improve outcomes for individuals with CF [6].

VCGS expand CF testing panels

Developing a CF test panel requires careful consideration to ensure only clearly disease-causing variants are included which minimises the chance of uncertain or ambiguous results.



Molecular defect	No synthesis	Block in processing	Block in regulation	Reduced conductance	Reduced synthesis	Reduced half-life
Functional abnormality	Protein is not synthesized	Folding defect	Channel opening defect	Ion transport defect	Decreased protein synthesis	Decreased half-life of the protein
Main mutations	Gly542X Trp128X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

Figure 1. Types of mutations in cystic fibrosis. From Quintana-Gallego et al. (2014)

The current VCGS test panel for *prepair* — a genetic carrier screen offered to individuals and couples who are considering, or are in early pregnancy — includes the 38 most common and severe CF causing mutations, which account for approximately 90% of carriers in the Australian Caucasian population.

In July, VCGS will increase the number of gene variants screened using *prepair* from 38 to 176 variants, and the number assessed in diagnostic testing will increase from 39 to 179. The variants selected are all listed as CF causing on the internationally recognised CFTR2 variant database.

Importantly, the diagnostic panel now includes the TG and poly-T tract variations in addition to the c.350G>A (p.R117H) variant, providing greater clarity about possible clinical effects in those with this variant.

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This increase in the number of variants will improve our ability to determine the genetic cause of CF in affected individuals as well as identifying carriers of rare *CFTR* variants.

Limitations associated with DNA quality obtained from newborn screening (Guthrie) cards means the number of variants screened in Victoria's newborn screening panel remains at the 12 most frequently seen in our population. This panel identifies the vast majority of babies with CF.

Improving access to CF testing

As of 1 July 2018, new Medicare item numbers became available for individuals who have a family history or clinical suspicion of cystic fibrosis, including prenatal diagnosis. Specifically, testing will be covered for individuals with a relationship closer than first cousins once removed and where there is clinical suspicion of CF. For more information about the new item numbers read the Medicare Benefits Schedule Book, Category 6, 1 July 2018 (pages 142-143).

When and how to offer CF carrier testing

Although the new Medicare item numbers will greatly improve access to testing in those with a close family history of CF or where CF is suspected, it is important to remember that the vast majority of individuals with CF and carriers have no family history of CF [7]. RANZCOG guidelines recommend that CF carrier screening (along with carrier screening for other common inherited conditions such as Fragile X Syndrome and Spinal Muscular Atrophy) may be offered to any woman planning a pregnancy or in early pregnancy [8]. VCGS offer this testing through the *prepair* genetic carrier screen.

If an individual has been identified as a carrier of CF (about 1 in 35 individuals tested using *prepair* [9]), their close family members (such as partner, siblings, parents and first cousins) will now have access to funded carrier testing.

For healthcare providers requesting CF testing through VCGS this can be requested either as an individual test, or through the *prepair* genetic carrier screen.

For convenience, VCGS has introduced saliva sampling for these DNA based tests. Sampling is simple and takes about 20 seconds. Saliva is robust and test quality equals that of blood samples. This option is ideal when blood collection is difficult.

The process for arranging CF testing or the *prepair* carrier screen is described in Figure 2. To organise CF testing for your patient by blood or saliva sample, complete a pathology request form requesting either the *prepair* genetic carrier screen or CF testing.

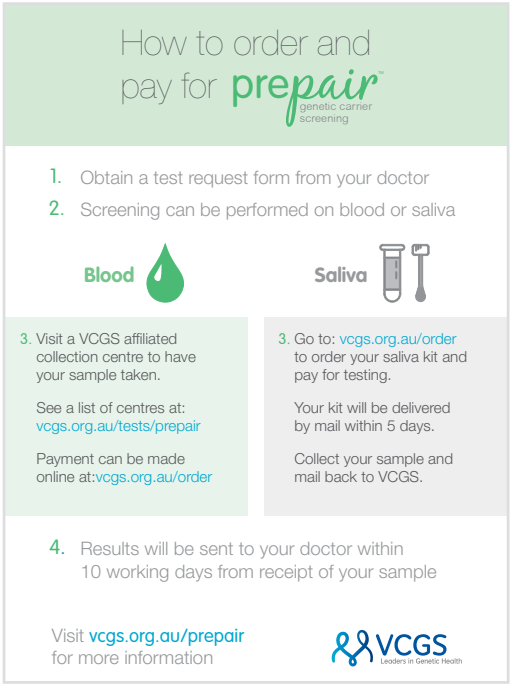

Figure 2. How to order *prepair* carrier screening

VCGS provide a fully integrated genetic testing, diagnostic and counselling service for health professionals, patients and their families. Our clinical geneticists and genetic counsellors work in close consultation with our medical scientists to provide the most accurate interpretation of complex genetic tests.

For more information about cystic fibrosis or to make an appointment with a genetic counsellor, email screeninggc@vcgs.org.au or phone the VCGS team on (03) 9936 6402.

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