REVIEW ARTICLE

Translating the genetics of cystic fibrosis to personalized medicine

HARRIET CORVOL, KRISTIN E. THOMPSON, OLIVIER TABARY, PHILIPPE LE ROUZIC, and LOÏC GUILLOT

PARIS, FRANCE

Cystic fibrosis (CF) is the most common life-threatening recessive genetic disease in the Caucasian population. This multiorgan disease is caused by mutations in the gene encoding the CF transmembrane conductance regulator (*CFTR*) protein, a chloride channel recognized as regulating several apical ion channels. The gene mutations result either in the lack of the protein at the apical surface or in an improperly functioning protein. Morbidity and mortality because of the mutation of *CFTR* are mainly attributable to lung disease resulting from chronic infection and inflammation. Since its discovery as the causative gene in 1989, much progress has been achieved not only in clinical genetics but also in basic science studies. Recently, combinations of these efforts have been successfully translated into development and availability for patients of new therapies targeting specific *CFTR* mutations to correct the CFTR at the protein level. Current technologies such as next gene sequencing and novel genomic editing tools may offer new strategies to identify new *CFTR* variants and modifier genes, and to correct *CFTR* to pursue personalized medicine, which is already developed in some patient subsets. Personalized medicine or P4 medicine ("personalized," "predictive," "preventive," and "participatory") is currently booming for CF. The various current and future challenges of personalized medicine as they apply to the issues faced in CF are discussed in this review. (Translational Research 2015;■:1–10)

Abbreviations: AAV = Adeno associated virus; ABC = ATP-binding cassette; ACMG = American College Medical Genetics; AH = Ancestral Haplotype; ASL = airway surface liquid; ATP = Adenosine triphosphate; cas = CRISPR associated; CF = Cystic fibrosis; CFTR = Cystic Fibrosis Transmembrane conductance Regulator; CFTR2 = Clinical and Functional Translation of CFTR; CRISPR = clustered regulatory interspaced short palindromic repeat; CYP3A = cytochrome P450 family 3, subfamily A; DDI = drug-drug interaction; EMA = European Medical Agency; ER = Endoplasmic reticulum; FDA = Food and Drug Administration; FEV1 = Forced Expiratory Volume in 1s; G = Golgi; gRNA = guide RNA; GWAS = Genome Wide Association Studies; HGVS = Human Genome Variation Society; HSPA1B = Heat Shock Protein A1B; iPSC = induced pluripotent stem cell; MBL2 = Mannose Binding Lectin 2; MHC = Major Histocompatibility Complex; NBD = nucleotide-binding domain; NGS = Next Gene Sequencing; P-gp = P-glycoprotein; PTC = premature termination codon; R = regulatory domain; RAGE = Receptor for Advanced Glycation Endproducts; TALEN = transcription activator-like effector nuclease; TGFB1 = Transforming Growth Factor Beta 1; TLR = Toll Like Receptor; TMD = transmembrane domain; TNF = Tumor Necrosis Factor; ZFN = zinc finger nuclease

From the INSERM, UMR_S 938, CDR Saint-Antoine, Paris, France; Sorbonne Universités, UPMC University Paris 06, UMR_S 938, CDR Saint-Antoine, Paris, France; Pneumologie pédiatrique, APHP, Hôpital Trousseau, Paris, France.

Submitted for publication November 28, 2014; revision submitted April 8, 2015; accepted for publication April 9, 2015.

Reprint requests: Loïc Guillot, INSERM, UMR_S 938, CDR Saint Antoine, Inserm, Bât. Kourilsky 2ème Étage, 34 Rue Crozatier, 75012 Paris, France; e-mail: loic.guillot@inserm.fr.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2015.04.008

INTRODUCTION

Cystic fibrosis (CF) is the most common life-threatening recessive genetic disease in the Caucasian population affecting approximately 70,000 individuals worldwide. This genetic disorder, caused by a mutation of the CF transmembrane conductance regulator (*CFTR*) gene, is mostly characterized by recurrent lower respiratory infections, exocrine pancreatic insufficiency (85% of patients), and increased electrolyte concentration in sweat. A subset of patients also presents with a variety of symptoms, which less commonly result in a CF diagnosis, such as meconium ileus, liver disease, and pancreatitis.[1] Additional CF complications may also be observed in these patients, such as CF-related diabetes. When CF was initially described in the 1930s, the patients only survived for a few months or years. Although still associated with fatality, the median predicted life expectancy in CF has dramatically increased to around the age of 40 years. However, analysis of demographic data of the European CF population highlights disease outcome disparities within Europe.[2] This improvement of CF survival within specific European populations is multifactorial, including better diagnosis, phenotype characterization, and treatment (eg, antibiotics). To extend the survival and quality of life for CF patients, specific therapies targeting *CFTR* have been developed highlighting the translational research pipeline from basic science to clinical trials.[3]

These specific therapies have directly affected the current progress in CF by the use of P4 medicine ("personalized," "predictive," "preventive," and "participatory"). Medicine is per se personalized, that is, individualized. Indeed, the best health care for each patient is chosen depending on his or her pathology and overall environment (allergic, psychological, and socioeconomic). The concept of personalized medicine was developed in the 1990s by the pharmaceutical company Roche, in regards to the fact that one specific drug can induce various reactions in different individuals, and for one individual some drugs are highly effective whereas others are ineffective. Thus, anticipating which drug will be effective in one patient vs another is the basis for personalized medicine. This concept has been extended to the "P4 medicine," which takes into account the patient as a whole[4] with as follows:

- "*P*ersonalized medicine" founded on how the individual genetic background could guide each patient's health care.
- "*P*redictive medicine" that allows the physician to assess the risk for one person to develop a disease or a disease's complication, leading to consider an individualized strategy to avoid disease appearance or progression or both.
- "*P*reventive medicine" that promotes a proactive approach, allowing to switch from a curative approach to a method based on the overall state of health and well-being.
- "*P*articipative medicine" that allows the patient to take informed decisions and to be responsible for his own health.

This concept, well known and described in cancer care, is relevant to almost all other diseases, and particularly for genetic diseases, for which large scale genomic studies have been performed, such as CF.[5]

CF transmembrane conductance regulator. *CFTR* (OMIM, 602421) was identified in 1989 as the abnormal gene for CF.[6-8] It is located on chromosome 7 (7q31.2), composed of 27 exons, and encodes for a protein, an ion channel that belongs to the adenosine triphosphate-binding cassette transporter family of proteins. Consistent with the adenosine triphosphate-binding cassette transporters, the CFTR structure has 2 transmembrane domains and 2 nucleotide-binding domains, but uniquely possesses a regulatory domain.[9] CFTR has several functions acting primarily as a chloride channel and regulating several other apical ion channels.

To date, almost 2000 mutations have been identified and collected from the international CF genetics research community (http://www.genet.sickkids.on.ca/app; http://www.cftr2.org).[10] *CFTR* mutations have been found mostly in European-derived populations and with much less frequency in African and East Asian populations.[11] Missense mutations are the most prevalent (40%), compared with frame shift (16%), splicing (12%), and nonsense mutations (8%).[11,12] The most common mutation (70% of patients) is a 3 base deletion (c.1521_1523delCTT; Refseq transcript ID, NM_000492.3) that induces a deletion of a phenylalanine at position 508 (p.phe508del [p.F508del]; Refseq protein ID NP_000483.3).

CFTR mutations are classified into 5 classes (sometimes 6) according to their resulting damaging effect on the protein (reviewed in reference[13]) (Table I). These classes are not exclusive, given that one mutation could have both a defective channel regulation ("class III") and a defective channel conduction ("class IV"), such as the c.350G > A/p.Arg117His (formerly R117H) mutation.

CFTR sequence variants are usually named using 2 systems, either *traditional* or *recommended* by the Human Genome Variation Society System (HGVS; www.hgvs.org/mutnomen/). One particular study highlighted the urgent need to move away from the traditional and historical naming toward the newer recommended HGVS nomenclature to standardize *CFTR* mutation