



Artificial Human Mutation Controls for Clinical Diagnostic Genetic and Proficiency Testing

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BACKGROUND

The rapid pace of disease gene discovery, fueled by the Human Genome Project, has caused an explosion in the number of analytes tested by molecular diagnostic laboratories, especially those involved in heritable disease testing. The lack of well-characterized control materials containing mutations of interest to serve as positive controls in the assays creates a major problem for genetic testing facilities. The lack is also an impediment for nationwide proficiency testing programs, such as that offered jointly by the college of American Pathologists (CAP) and the American College of Medical Genetics (ACMG). Procurement of suitable human mutation control materials from natural sources is hampered by the rarity of many disease mutations, the limited quantity in clinical specimens, the dependence on clinicians to recognize the need and take the trouble to deposit patient samples in existing repositories, and onerous informed consent, sample ownership and genetic privacy constraints. There is a recognized need for a comprehensive set of positive controls for clinical testing of human genetic mutations that is reliable, reproducible, widely available and readily utilized in standard testing platforms.

INNOVATION

UCLA investigators and their colleagues have developed a generalized method for constructing artificial DNA samples containing any gene mutation of interest. The artificial DNA samples perform like conventional human-derived material on most of the commonly used technical platforms in molecular genetic testing. The method is far less expensive than clinical or laboratory approaches involving patient sample collection and/or human cell culture. It is anticipated that the artificial human mutation controls may be most easily commercialized as analyte-specific reagents (ASRs) sold to clinical diagnostic testing laboratories for use in home brew assays.

APPLICATIONS

- ▶ The primary market for the artificial human mutation controls will be as positive controls in genetic tests performed by clinical diagnostic laboratories.
- ▶ The artificial DNA samples will also be useful in the nationwide proficiency testing of more than 200 genetic testing facilities that is conducted by CAP/ACMG.
- ▶ The method may be applied to non-genetic diseases as well, including cancer markers and even pathogen and host markers of infectious diseases.

ADVANTAGES

- ▶ The protocol for constructing the artificial DNA samples is relatively simple, robust and reproducible.
- ▶ Scale-up to provide enough control material to last for years is easy and inexpensive.
- ▶ The procedure may be readily applied to a wide variety of mutation samples for many genes and diseases.
- ▶ It is amenable to a wide range of testing platforms.
- ▶ Artificial human mutation controls have the practical advantage of eliminating the burdensome requirements associated with collecting samples from patients.

STATE OF DEVELOPMENT

The method of producing artificial human mutation samples was initially developed and tested using two known mutations of the cystic fibrosis gene (CFTR): G85E in exon 3 and 1078delT in exon 7. The artificial DNA samples of the CF gene were formulated for each of the following five genotypes: wild type (homozygous normal), homozygous G85E, homozygous 1078delT, heterozygous G85E, and heterozygous 1078delT. The

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OTHER INFORMATION

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- ▶ Medical
- ▶ Diagnostics

RELATED CASES

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samples were constructed to approximate the relative molar concentration of a heterozygous mutation or a homozygous mutation that would be expected in a typical patent genomic DNA specimen used in a standard CAP/ACMG proficiency sample (50 mg DNA in 20 mL buffer). Each sample behaved indistinguishably from natural samples when assayed with PCR/restriction digest assay and standard reverse line blot technology. In a blinded pilot test, the five artificial DNA samples were sent to 9 genetic testing facilities that together employ a wide range of technical platforms for CFTR mutation screening. The results indicate that the five DNA mutation control samples were remarkably reproducible in mimicking the desired human genotypes across multiple testing platforms.

RELATED MATERIALS

► [Quality in molecular genetic testing. Nature Rev. Genet. Sept 2001; 2\(9\), 717-723. \[more\]](#)

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	8,603,745	12/10/2013	2004-099

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