

Novel Epigenetic Biomarker for Fragile X Syndrome

Introduction

Bio-Link presents a novel diagnostic for Fragile X Syndrome that offers significant advantages over existing tests. Researchers at the Murdoch Children's Research Institute (MCRI) in Melbourne, Australia have identified a new epigenetic marker for FMR1-related disorders including Fragile X Syndrome, and have developed an improved diagnostic assay based on the epigenetic profiles of novel genetic regions called Fragile X-related Epigenetic Elements (FREE). This new biomarker assay overcomes several difficulties associated with current methods used for the analysis of tri-nucleotide expansions in the FMR1 genetic locus, and aims to facilitate wide-scale screening of fragile X syndromes. Importantly, FREE also provides a potential new target for the development of therapeutics for the treatment of FMR1-related diseases.

Background

Fragile X syndrome (FXS) is the most common inherited type of mental retardation with approximate frequencies of 1/4000 males and 1/800 females. Other more common pathologies associated with the tri-nucleotide (CGG) expansions in the FMR1 gene include Fragile X-associated Tremor Ataxia Syndrome (FXTAS) and premature ovarian failure (POF). Fragile X testing is recommended for all females who have reproductive or fertility problems before the age of 40, and for all female carriers of the expanded alleles for prenatal foetal samples. Current tests for FXS involve a complex and expensive combination of techniques such as Southern blot which requires large quantities of high quality DNA. Therefore it is not yet economically feasible and practical to conduct wide-scale pre-pregnancy and prenatal screening.

Technology

MCRI researcher Dr David Godler has identified new genetic regions related to FMR1 that can be utilised for the development of novel FXS diagnostics and possibly new drugs targeting the epigenetic control of FMR1 for the treatment of FMR1-related disorders. Recently it was discovered that epigenetic island shores can be distal from the known promoter (Irizarry, 2009). Dr. Godler has discovered two such regions, designated as Fragile X-related Epigenetic Elements, FREE1 and FREE2, and has developed a novel diagnostic assay based on the pattern of methylation of CpG residues within these regions. The superior performance of the assay was proven in experiments (see Figure 1) that demonstrated:

- Rapid and highly accurate discrimination of healthy control subjects from subjects known to have full mutations
- Utility in both males or females
- Applicability to various sample tissues including blood or chorionic villi

- The ability to distinguish between patients that have a smaller expansions (e.g. premutation versus full mutation)
- Bi-directional transcription originating from the FMR1 promoter following specific de-methylation of FREE1 (see Figure 1F)
- An assay sensitivity of >99% for the detection of FXS
- A lower limit of detection at 10% methylation
- The requirement for ~100 fold less DNA quantity than Southern blot analysis
- Reduced reliance upon the quality of DNA samples
- Suitability for newborn or prenatal screening

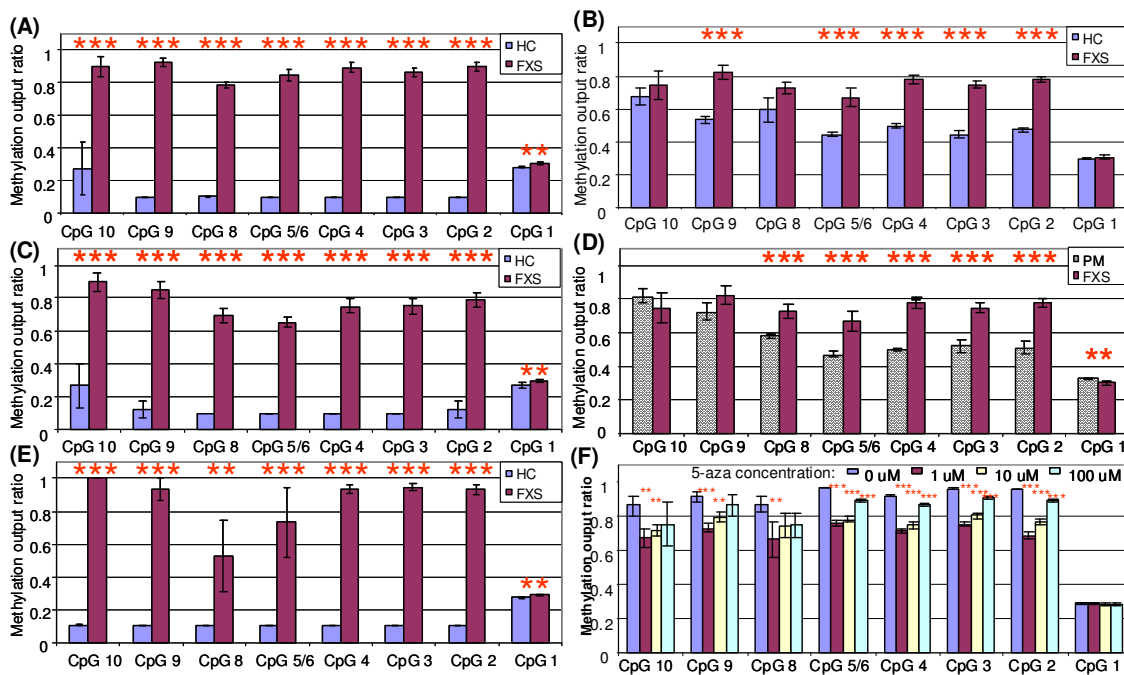


Figure 1. Methylation patterns of CpG residues within FREE1. (A) to (E) DNA isolated from Healthy controls, patients with full mutations (FXS) or premutation (PM). (F) DNA from FXS cell line with re-activated FMR1 expression after 5-aza-2'-deoxycytidine (5-aza) treatment. Males (A, C, E); Females (B); Blood (A, B); Chorionic Villi (C); Premutation vs. Full Mutation (D). Statistical significance: *** (p<0.001); ** (p<0.05); * (p<0.09)

Intellectual Property

The technology is covered under a provisional patent application filed in 2009.

Murdoch Childrens Research Institute (MCRI)

MCRI is an independent non-profit research institute based at the Royal Children's Hospital and affiliated with the University of Melbourne in Australia. The Institute has approximately 900 staff including 100 postgraduate students, and now represents the largest research institute specialising in adolescent and child health in Australia. MCRI's areas of research include cerebral palsy, cancer, genetics, muscular dystrophy, diabetes, asthma, allergies, deafness, infectious diseases, depression and behavioural problems. MCRI also leads genetic ethics research and community debate of controversial issues

such as stem cell research. The Institute receives over AUD\$65 million annually for laboratory, clinical, and public health research. Indicative of the MCRI's commitment to conduct research of the highest quality, the Institute publishes over 400 internationally peer-reviewed articles each year and holds over 60 patent applications.

Commercial Opportunity

Bio-Link is an independent biotechnology business development company that works with Australian and international biotech companies and biomedical research institutions to facilitate commercialisation of new diagnostics and therapeutics. The present technology provides a novel epigenetic biomarker for FMR1-related disorders and an enhanced diagnostic assay which enables more rapid, cost-effective, and informative analysis of epigenetic contributions to fragile X syndromes. Bio-Link is seeking to license the technology on behalf of MCRI to companies for clinical validation and development of advanced medical diagnostics, as well as for research-use-only kits.

Interested parties please contact Mr. Christopher Boyer, Executive Director, Bio-Link:

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References

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2. Irizarry et al. (2009) The human colon cancer methylome shows similar hypo- and hypermethylation at conserved tissue-specific CpG island shores. Nature Genetics 41 (2): 178-186.