APPLICATION NOTE

LabChip GX Touch platform applications in epigenetic studies.

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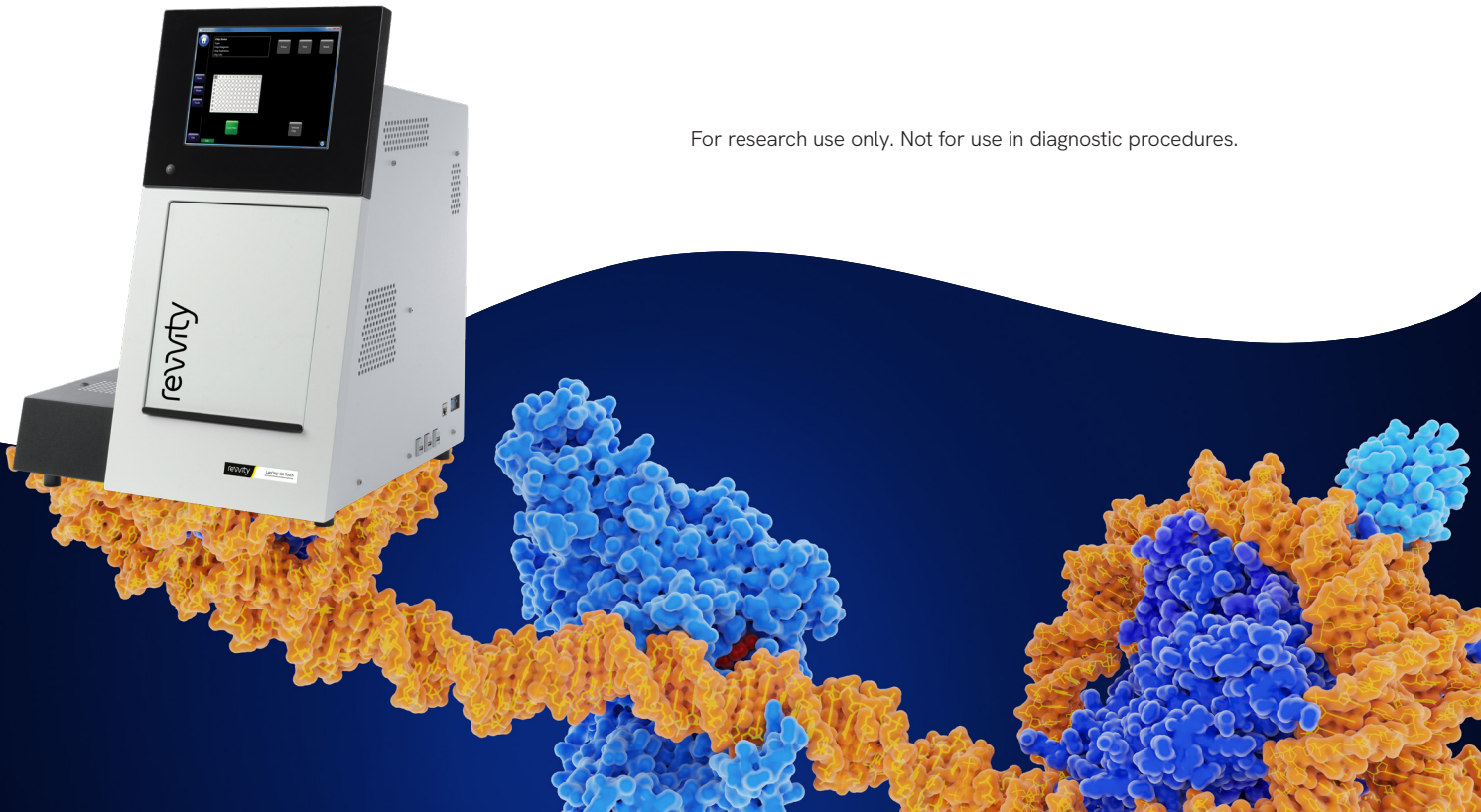
Revvity

Introduction

Understanding the multiple contributors to a particular disease is an important focus for clinical and non-clinical researchers alike. Changes in the nucleotide sequence of DNA – such as deletions, inversions, SNP, and other mutations – have long been implicated in the initiation and progression of many diseases. Now, in addition to sequencing mutations, an increasing level of effort is being made to understand the contribution of epigenetic events to disease. Epigenetics is the study of changes in gene expression that do not involve changes to the nucleotide sequence. Gene expression in cells is implicated by these epigenetic changes driven by physiological and environmental signals. An abnormal change in gene expression can contribute to disease development.

LabChip GX Touch Nucleic Acid Analyzer



For research use only. Not for use in diagnostic procedures.

One such epigenetic mechanism in the cell is higher-order, three-dimensional arrangement, wherein two gene loci that are distant from each other along DNA's linear structure can come into spatial proximity forming a loop structure. These long-range interactions, called chromatin conformation signatures (CCS) or "gene loops," affect gene expression and regulation (Figure 1). Chromatin conformation capture (3C) technology is used to isolate and analyze such signatures, and researchers are using 3C protocols to investigate the use of specific CCS as biomarkers of disease.

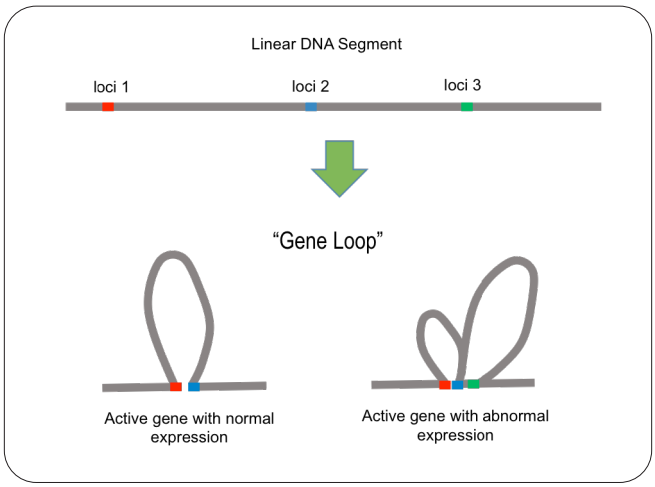


Figure 1. DNA's high-order, three-dimensional structure includes chromatin conformation structures, or "gene loops," that bring loci that are distant from each other linearly into spatial proximity.

Epigenetics R&D

Oxford BioDynamics Plc, a global leader in epigenetics research, developed the EpiSwitch™ biomarker discovery platform to evaluate potential CCS biomarkers of specific diseases. One area of research at Oxford BioDynamics is identifying CCS that are indicators of early-stage melanoma. The only current means of accurately diagnosing melanoma is to excise and biopsy the suspicious skin lesion. This protocol, in addition to being very invasive for the patient, is useful only for detecting advanced melanoma when the skin lesion becomes visible. Oxford BioDynamics's research is focused on potential epigenetic markers of early-stage melanoma that can be found in the DNA present in the bloodstream1.

Oxford BioDynamics researchers use the EpiSwitch™ platform to identify CCS and develop biomarkers known to be associated with melanoma. Oxford BioDynamics does so with blood samples from volunteers who have been diagnosed with melanoma, other skin cancers, benign skin conditions, and no skin conditions. Figure 2 shows the workflow used to prepare and detect the CCS library.

The final library is quantitated and fragment sized, traditionally through the use of slab gel electrophoresis. That manual protocol, however, requires long processing times that ultimately slow and limit sample throughput. The Oxford BioDynamics researchers have overcome these limitations by integrating the LabChip® GX Touch™ platform into their workflow.

The LabChip GX Touch platform automates and replaces the multiple, manual steps of slab gel electrophoresis, and does so with high levels of accuracy, sensitivity, and throughput. It quantifies DNA libraries at concentrations as low as 2 pg/µL with accurate fragment size determination and can analyze up to 384 samples per run.

Results are provided within 68 seconds per sample, which is a great improvement over the hours or days required by traditional slab gel electrophoresis methods. These capabilities allow Oxford BioDynamics researchers to process the large number of samples needed to provide a dataset from which valid conclusions can be drawn.

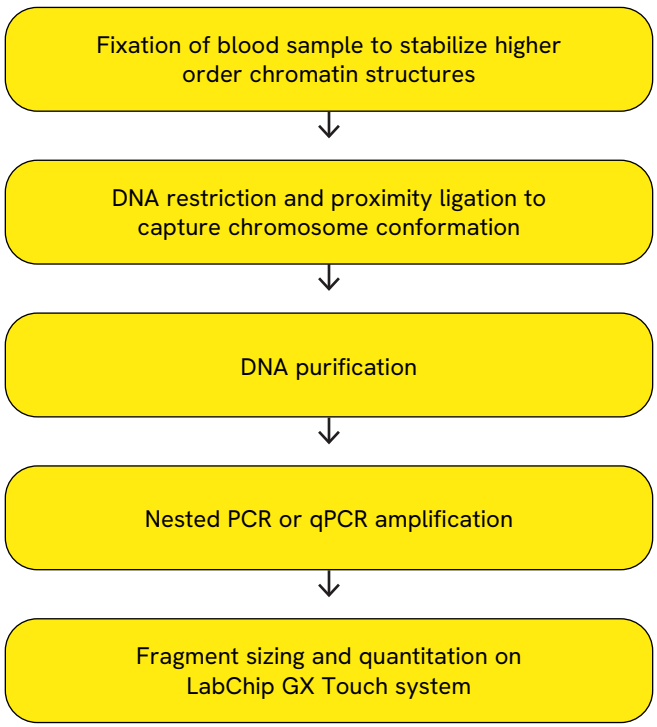


Figure 2. The Oxford BioDynamics 3C biomarker workflow. Once the target library is prepared, the LabChip GX Touch platform provides rapid, accurate, high-throughput sizing and quantitation of the fragments.

The LabChip GX Reviewer software provides the data in electropherogram format and virtual gel view, as well as in tabular format for easy evaluation or export. The virtual gel image presented in Figure 3 shows the fragment size results for three melanoma samples. These results demonstrate that the LabChip GX Touch platform offers a high level of resolution that allows for different fragment sizes to be differentiated, even when the differences are slight. Figure 4 presents an electropherogram depicting fragment size and quantitation results for one of the samples, demonstrating the LabChip GX Touch platform's high resolution and sensitivity even at low concentrations.

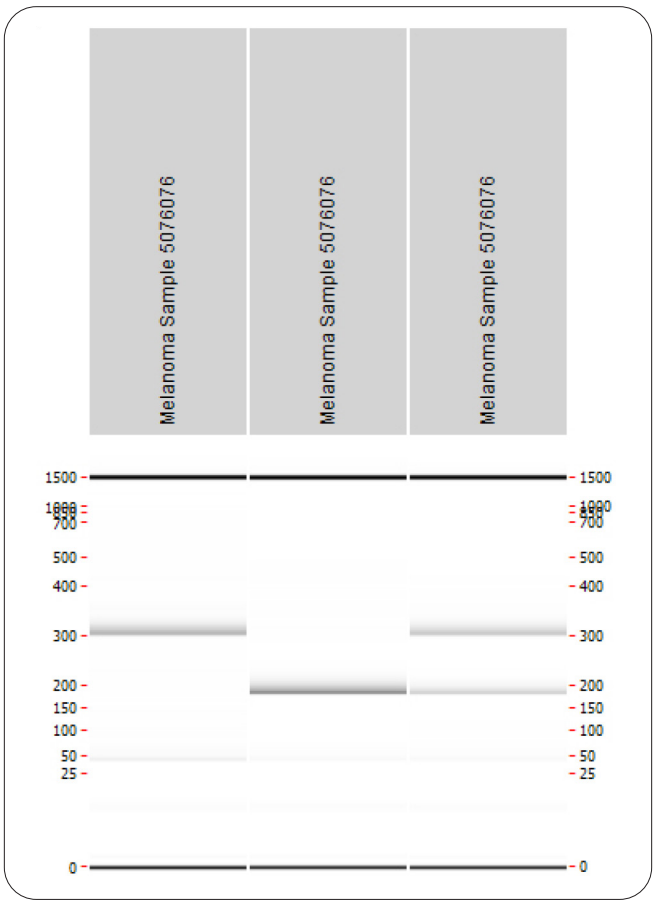


Figure 3. Virtual gel image produced by the LabChip GX Reviewer software for three samples. The LabChip GX Touch platform provides high resolution for differentiating fragments of different size.

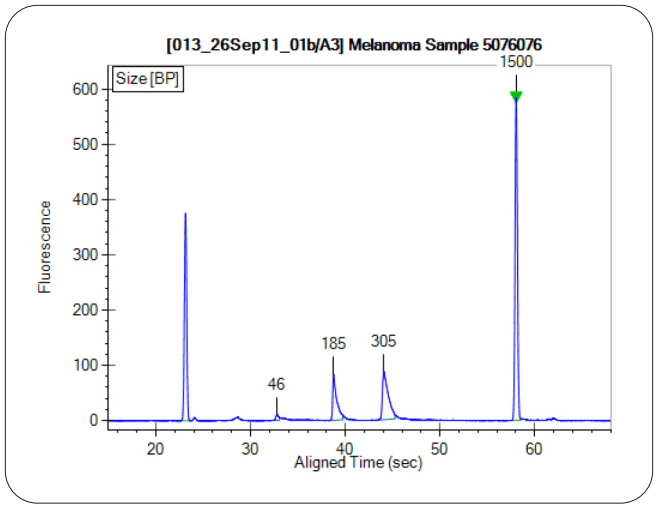


Figure 4. Electropherogram produced by the LabChip GX Reviewer software showing the quantitation and fragment size results for one sample. The sensitivity and high resolution provided by the LabChip GX Touch platform is demonstrated by the differentiation of slightly different fragment sizes even when present at low concentrations.

Conclusion

The LabChip GX Touch platform is an important component of Oxford BioDynamics research in epigenetic biomarkers of disease and their viability for disease detection, prognostic testing, and drug screening for the development of personalized treatment plans. The LabChip GX Touch platform provides rapid, high-throughput capabilities so that researchers can generate the robust datasets they need to confidently evaluate the accuracy and reliability of CCS biomarkers for the detection of melanoma.

Reference

1. Jakub, James W.; Grotz, Travis E.; Jordan, Philip; Hunter, Ewan; Pittelkow, Mark; Ramadass, Aroul; Akoulitchev, Alexandre; Markovic, Svetomir. (2015). A pilot study of chromosomal aberrations and epigenetic changes in peripheral blood samples to identify patients with melanoma. Melanoma Research: Volume 25 - Issue 5 - p 406–411.

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