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Advance of Newborn Screenings in the Era of Biomedical Technology

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Abstract

Along with the rapid develop of detection technology, newborn screening technique is growing fast. This mini review will explore the recent developments in newborn screenings related to the use of tandem mass spectrometry, second tier screening like, urine analysis and genetic testing.

Keywords: Newborn Screening; Second Tier Screening; Tandem Mass Spectrometry; Genetic Testing

Abbreviations: NBS: Newborn Screenings; LC-MS/MS: Liquid Chromatography Coupled with Tandem Mass Spectrometry; MS: Mass Spectrometry; GC-MS: Gas Chromatography-Mass Spectrometry; PCR: Polymerase Chain Reaction; MPS: Massively Parallel DNA Sequencing; PMG: Personal Genome Machine

Introduction

Newborn screenings (NBS) provide an opportunity to identify several inherited metabolic disorders in pre-symptomatic infants, and corresponding treatment may prevent or mitigate adverse outcomes associated with these conditions. Screening is accomplished by the analysis of biomarkers in a single sample of blood collected from newborns using a variety of analytic methodologies. Since Dr. Robert Guthrie developed a bacterial inhibition assay to screen for metabolic diseases in the early 1960s, use of the newborn screening program has spread to many countries [1]. Millington et al. first demonstrated that tandem mass spectrometry (MS/MS) could be used to screen inherited metabolic disorders [2]. Chace and coworkers, and subsequently other groups, refined this method and applied it to NBS [3-4]. The use of MS/MS has extended NBS to disorders of amino acid and organic acid metabolism as well as to those of fatty acid metabolism, and recently screening has also been expanded to rare disorders include Duchenne muscular dystrophy [5], lysosomal storage diseases [6] and severe combined immunodeficiency [7] etc. However, there have been some drawbacks for tandem mass spectrometry. Genetic testing technology is believed to be another major breakthrough to improve the current newborn screening technique. Thus, the purpose of this mini review is to explore the recent developments in the field of newborn screening related to the use of tandem mass spectrometry, second tier screening like, urine analysis and genetic testing.

Tandem Mass Spectrometry and Universal Screening

High performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) is a high throughput analytical instrument widely used in newborn screening. This instrument can semi-quantify amino acids and acylcarnitines simultaneously within two minutes, which corresponding to more than fifty metabolic disorders. Generally, amino acids and acylcarnitines in a newborn's dried filter paper blood spot are extracted with methanol and derivatized with butanolic-HCl, and then analyzed by using LC-MS/MS with neutral loss scans and precursor ion scans mode, respectively. With the advances in MS detection sensitivity increasing, it is possible to quantify both amino acids and acylcarnitines as their native free acids without derivation. However, it's also reported that the use of underivatized technique may also result in the inability to differentiate isobaric acylcarnitines and increase false positive rates compared to derivation technique [8]. The analysis of amino acids and acylcarnitines in dried blood spot by LC-MS/MS had been adopted as standard primary newborn screening worldwide for about 30 years because of its efficient and economic. However, in recent years, it has been found that this

method lacks specificity and contribute to a high false positive rate [9]. As a result, second tier screening have been developed and now are available to improve screening performance for many disorders.

Second Tier Screening

As mentioned above, newborns with positive screening result are recommended for confirmatory diagnostic testing on new physiological samples, like plasma or urine. Usually, second tier screening confirmatory testing could be biochemical analysis (urine analysis, enzyme analysis) or molecular technologies (genetic testing). Urine analysis by mass spectrometry (MS) is one of the best ways to confirm organic acidemias in newborn screening, which could monitor more than 134 organic acids with one injection. Abundant molecular species may be detected by a full ion scan from m/z 50 to 550 and selected ion monitoring should be used to increase the sensitivity of detecting less abundant but clinically important molecular species (e.g., 3-hydroxyglutaric and 4-hydroxybutryic acids) [10]. Gas chromatography-mass spectrometry (GC-MS) has been proven to be a potentially useful metabolic profiling platform in urine analysis for its high sensitivity, peak resolution and reproducibility. However, the complicated composition of urine and semi-quantitative method used in GC-MS rendering data analysis challenging.

Thus, a chemometrics coupled to GC-MS or LC-MS method has developed. By chemometric methods, raw data acquired from GC-MS/LC-MS are transformed automatically into a proper mathematical model, then data was analyzed by statistical methods based on computer. In this way, statistical differences or/and similarity among different samples are showed in an easy understanding format [11]. This unique chemical fingerprint developed for every inherited metabolic disorder is promising for confirmatory diagnostic testing in the future.

Inborn errors of metabolism are genetic disorders due to genetic mutation. As the gene sequencing technology developed, the cost of gene sequencing reduced, which made genetic analysis available for accurately confirming of metabolomics disorder in NBS, or for pinpoint the type or severity of a condition. First generation sequencing: Sanger sequencing is implemented in newborn screening for targeted mutation analysis. But this sequencing technology is hampered by the genetic heterogeneity of inherited metabolic disorders, which results in delayed diagnosis [12].

And second genome sequencing called real-time polymerase chain reaction (PCR): Suspicious chunks of DNA are pulled out and artificially replicated thousands of times until there's enough material for lab equipment to analyze. With PCR, tests that once could take days can be done in minutes. In recent years, Massively Parallel DNA Sequencing (MPS) of target genes offers a useful method of identifying gene mutations and, thereby, improving the diagnostic rate. There is also a new generation of revolutionary sequencing technology: Ion Torrent Personal Genome Machine (PMG), a bench-top sequencer based on semiconductor technology, is fast and convenient with a high sequencing capacity and broad coverage, making it a good future candidate for large-scale use in newborn screening [13]. Multigene panel for inherited metabolic diseases is developed to evaluate the genetic epidemiologic characteristics of inherited metabolic diseases. With developments in genetic testing, labs are increasingly doing genetic testing as part of newborn screening. Some even predict that once genetic testing technologies are sufficiently robust and affordable, it may be applied in primary newborn screening [14].

Conclusion

Over the past decades, tandem mass spectrometry (MS/MS) has been a major technological breakthrough for the newborn screening by providing a way to detect multiple metabolites simultaneously. Although the use of MS/MS has cost-effective, rapid screening identification, there have been some bottlenecks such as high false-positive and imprecision. As second tier screening, urine analysis is applied as confirmatory diagnostic testing, have improved screening performance for many disorders. With appropriate statistical analyses, raw complicated screening data are transformed automatically into metabolic models which could be used in the understanding of relevant metabolic disorders and provide potential for confirmatory diagnostic testing in the future. With the rapid development of genome sequencing technologies, genetic testing could be another major breakthrough to improve the current newborn screening and may be used as primary newborn screening when the cost reduced to an affordable level.

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