PREVALENCE AND FEASIBILITY OF NEWBORN SCREENING FOR CHROMOSOME 15 IMPRINTING DISORDERS: PROGRESS TO DATE FROM 20,000 INFANTS

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In 2016, we have developed a sensitive workflow to cost effectively screen newborns for 6 rare diseases simultaneously including Fragile X, Prader-Willi (PWS), Chromosome 15 duplication (Dup15q), Angelman (AS), Klinefelter (KS) and Turner (TS) syndromes, to be used on materials consented for de-identified research from over 30,000 newborns. These conditions can benefit from early intervention, and newborn screening (NBS) results may also prevent further affected births through informed reproductive options for the families identified. Moreover, these disorders have active clinical trials for specific treatments. However, an effective newborn screening workflow is required for prospective screening of these conditions to close the translational gap between promising drug discovery trials, and a need to treat very early in neurodevelopment for rare neurological diseases. Use of the innovative cost-effective first line screening test, called Methylation Specific Quantitative Melt Analysis (MS-QMA) is an attractive feature of our workflow. MS-QMA is specific for abnormal DNA methylation associated with the conditions tested, but does not detect unrelated variants of incomplete penetrance. The approach has low cost (~$1 per infant per condition), and works on only one 3 mm punch of NBS material per infant as part of a fully automated approach. A set of accurate, but more expensive 2nd and 3rd-line genomic and genetic tests are then applied to a small number of MS-QMA positive samples (rather than to the whole population) to confirm the MS-QMA results, while differentiating between disorders. This presentation will focus on preliminary data collected to-date using this workflow focusing on AS, and other chromosome 15 imprinting disorders, on NBS materials from 20,000 infants. The preliminary data suggests that the developed workflow is feasible for population wide newborn screening, with prevalence that may be significantly higher for some of the disorders (e.g. ~1 in 4,500 for AS) than previously reported.