stimulation cycle, harvested eggs were fertilized using intracytoplasmic sperm injection (ICSI), and resultant normally fertilized embryos cultured to day 5 and day 6 blastocyst stage. Suitable blastocysts were biopsied with assistance of a near-infra-red laser. The 1-6 cells obtained had their DNA extracted and either PCR amplified using the established multiplexed PGD-PCR test (PGD-PCR cycle) or WGA amplified (combined cycle). From 2007-2014, 109 couples presented for PGD-PCR for 16 different familial single gene disorders, predominantly beta-thalassemia (61/109) or alpha-thalassemia (25/109). In 2012 we introduced PGS-CGH for 24 chromosome screening of infertility couples, and soon after offered PGD-PCR patients the option of a combined PGS-CGH and PGD-PCR cycle; to date 19 patients had requested the combined cycle. For PGD-PCR only, 97 patients had 154 cycles with 85 embryo transfers (114 embryos). 57/85 (67%) were clinically pregnant with an implantation rate of 50%. For requested combined cycles, 5/19 patients (all alpha-thalassemia) failed the WGA check and reverted to PGD-PCR test/cycle only. 11/14 had 14 cycles with 8/14 cycles freeze-all (with no transfers to date) and 4 embryo transfers (5 embryos). 4/4 (100%) were clinically pregnant with an implantation rate of 80%. Early results, while low numbers, indicate offering patients presenting with a hereditary single gene disorder the option of having all 24 chromosomes screened prior to implantation may significantly increase their chance of a healthy pregnancy.

Keywords: Preimplantation genetic diagnosis (PGD); preimplantation genetic screening (PGS); array comparative genome hybridization (aCGH)

Cite this abstract as: Marshall J, Tiewsiri K, Thaijaroen P, Benjaponwattana P, Pingsuthiwong S, Jantapanon TK, Jiaranai P. Efficacy of combined preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS) cycles—early results. Ann Transl Med 2015;3(S2):AB094. doi: 10.3978/j.issn.2305-5839.2015.AB094

AB095. Comparison pregnancy of day 6 fresh blastocyst and day 5 frozen-thawed blastocyst transfer following array comparative genome hybridization (aCGH)

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Abstract: Advances in assisted reproductive technologies (ART) have benefitted many infertile couples. However while many modern technologies were applied in ART, pregnancy rates remained lower than expected. Some studies have suggested that successful embryo implantation depends on many factors including genetic anomalies such as aneuploidy. While pre-implantation genetic screening (PGS) using fluorescent in situ hybridization (FISH) was introduced around 20 years ago to screen for aneuploidy in selected subsets of chromosomes, it failed to improve pregnancy rates and reduce miscarriage rates. FISH had technical limitations, some inaccuracies, and could only screen up to 8-11 chromosomes. Recent more modern technology, array comparative genome hybridization (aCGH), has been shown to significantly improve pregnancy rates and decrease miscarriage rates by allowing the detection of aneuploidy in all 23 pairs of chromosomes, and allowing the transfer of euploid embryos. Couples have an ovarian stimulation, eggs are collected and fertilized using intracytoplasmic sperm injection (ICSI), and any normally fertilized embryos are cultured to the blastocyst stage. Suitable blastocysts are biopsied on either day 5 or day 6 of embryo culture with the assistance of a near-infra-red laser, and the removed cells amplified in a whole genome amplification (WGA), fluorescently labelled, hybridized and scanned using the BlueGnome (Illumina) 24Sure CGH microarray system. Advances in aCGH means the total process from biopsy to result can be done overnight, allowing for a suitable embryo from a day 5 biopsy to have potential fresh embryo transfer on day 6 of culture. Alternatively, following biopsy, embryos can be frozen immediately and euploid embryos transferred in a subsequent frozen-thaw cycle. We retrospectively compared pregnancy outcomes of good quality blastocysts biopsied and analysed using aCGH following by fresh embryo transfer on day 6 (n=50) versus frozen embryo transfer of

embryos biopsied and frozen on day 5 (n=61). The average age of patients having a fresh embryo transfer on day 6 is 32±3.2 and having frozen embryo transfer is 30±3.7 years old. The results showed that pregnancy rates were not significantly different between frozen embryo transfer and fresh embryo transfer (59% *vs.* 52% respectively, P value >0.05). Nevertheless, as well as indicating that not only is frozen embryo transfer as good as or better than fresh embryo transfer, frozen embryo transfer can also have advantages in in-vitro fertilization in allowing optimal embryo transfer planning for couples.

Keywords: Array comparative genome hybridization (aCGH); *in vitro* fertilization, fresh blastocyst transfer; frozen-thawed blastocyst transfer

Cite this abstract as: Thaijaroen P, Benjaponwattana P, Jiaranai P, Marshall J, Tiewsiri K. Comparison pregnancy of day 6 fresh blastocyst and day 5 frozen-thawed blastocyst transfer following array comparative genome hybridization (aCGH). Ann Transl Med 2015;3(S2):AB095. doi: 10.3978/j.issn.2305-5839.2015.AB095

AB096. Pharmaco-genetic guided personalized medicine: discovery of a maturity onset diabetes of the young (MODY2) novel mutation [S441W in glucose kinase (GCK) gene] by next generation sequencing (NGS)

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Background and objective: Monogenic diabetes or maturity onset diabetes of the young (MODY) is characterized by young-onset (<45 years old), non-insulin dependence and a strong family history (autosomal dominant mode of inheritance). The major candidate genes include HNF4α (MODY1), glucose kinase (GCK) (MODY2) and HNF1α (MODY3). MODY is an attractive model for pharmaco-genetics because an accurate diagnosis may inform specific choice of anti-hyperglycemic therapy for better clinical outcome. We report a slim lady (BMI 22.4 kg/m^2) with Type 1 diabetes diagnosed based on abnormal fasting glucose and oral glucose tolerance test at age 21. She was started on multiple daily insulin injections (total daily dose 18-22 units/day) with good glycemic control (HBA1c 6.2%). Glutamic acid decarboxylase (GAD) autoantibody was negative. On occasions when she ran out of insulin supply, there was no incidences of diabetic ketoacidosis. We aim to identify proband with monogenic diabetes phenotype to perform high through-put exonic mutation screening using next-generation sequencing (NGS) on an extended panel of candidate genes (i.e., beyond GCK, HNF1A and HNF4A) for these individuals. We will also recruit other members within the pedigree for segregation analysis to strengthen causality of discovered variant (this is necessary primarily because more variants-of-unknown-significance are expected to be observed in an extended gene panel).

Methods: DNA from peripheral blood cells was subjected to high-throughput targeted nucleotide sequencing for all 16 known MODY candidate genes including exons, un-translated (UTRs) and promoter regions using the Ampliseq kit (Life Technologies).

Results: We discovered a novel non-synonymous mutation (c.1322C>G, p.Ser441Trp) in the GCK gene, which was confirmed by bi-directional Sanger's sequencing. The mutation is predicted to be functionally deleterious using multiple bioinformatics tools (e.g., SIFT and PolyPhen-2). In accordance with clinical practice guideline, insulin replacement was successfully discontinued with no deterioration of glycemic control.

Conclusions: The successful treatment-conversion based on genotype exemplifies how pharmaco-genetics can improve disease-stratify to inform diagnosis and treatment. This can translate into improved clinical outcome and quality of life.

Keywords: Diabetes; maturity onset diabetes of the young (MODY); mutation; sequencing

Cite this abstract as: Clara TS, Fen AS, Jessie FC, Ester YC, Subramaniam T, Fang SC, Chi LS. Pharmaco-genetic guided personalized medicine: discovery of a maturity onset diabetes of the young (MODY2) novel mutation [S441W in glucose kinase (GCK) gene] by next generation sequencing (NGS). Ann Transl Med 2015;3(S2):AB096. doi: 10.3978/j.issn.2305-5839.2015.AB096