PGD FOR A COUPLE AT RISK OF TRANSMITTING BOTH AUTOSOMAL RECESSIVE POLG DISEASE AND THE MATERNAL MELAS SYNDROME.

Jos Dreesen[1,4], Aimee Paulussen[1,4], Marion Drüsedau[1], Sabine Spierts[1], Suzanne Sallevelt[1], Debby Hellebrekers[1], Merel van Maarle[2], Edith Coonen[3,4], John Dumoulin[3,4], Ron van Golde[3,4], Christine de Die[1,4], Bert Smeets[1,4]

[1]*Department of Clinical Genetics, Maastricht University Medical Centre, Netherlands*
[2]*Department of Clinical Genetics, Academic Medical Centre Amsterdam, Netherlands*
[3]*Department of Obstetrics & Gynaecology, Maastricht University Medical Centre, Netherlands*
[4]*School for Oncology & Developmental Biology (GROW), Maastricht University Medical Centre, Netherlands*

Preimplantation genetic diagnosis (PGD) is a reproductive option for couples transmitting mitochondrial disorders, which are severe metabolic disorders caused by either maternally transmitted mitochondrial DNA mutations (10-15%) or mutations in nuclear genes (85-90%). Here, we present PGD for parents of a severely affected child (died at the age of 3), who was compound heterozygote for two *POLG* mutations (c.2243GC and c.2740AC) and additionally carried the m.3243AG (MELAS) mutation with a mutation load of 12% to 17% in different tissue samples (blood, urine, fibroblasts, muscle and buccal swap). The m.3243AG mutation was not detected in tissue samples of the mother. Embryos without or heterozygous for one of the POLG mutations and a mutation load below the threshold of 15% for the m.3243AG mutation were eligible for transfer to the uterus. From each embryo two blastomeres were bioptied, one for the *POLG* mutations and the second to establish the m.3243AG mutation load. Six embryos were obtained following IVF/ICSI. For *POLG*, one embryo was compound heterozygous and all the others carried one or two wild type alleles. The m.3243AG mutation was absent in 5 out of 6 embryos, but the analysis failed in one, carrying two wild type *POLG* alleles. Therefore, 4 embryos were eligible for transfer and based on developmental criteria a morula stage embryo was transferred, resulting in a pregnancy and birth of a healthy boy. The absence of the m.3243AG mutation in all embryos suggests a *de novo* mutation in the affected child, although a relation with the POLG mutations cannot be excluded. Umbilical cord blood analyses confirmed the PGD analysis.