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Title:

PATIENTS UNDERGOING PRE-IMPLANTATION GENETIC DIAGNOSIS (PGD) FOR A SINGLE GENE DISORDER (SGD) MAY BENEFIT FROM INCLUDING PRE-IMPLANTATION GENETIC SCREENING (PGS) FOR ANEUPLODY

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Background:

Single nucleotide substitutions account for >65% of disease-causing mutations. The majority of these loci represent highly penetrant, rare coding variants that alter amino acid composition of proteins and result in deleterious phenotypic consequences. Aneuploidy, on the contrary, refers to an abnormal copy number of one or more parts of chromosome(s), which often occurs as a result of errors in meiotic or mitotic division.

Objective:

This study sought to identify the incidence of aneuploidy in embryos undergoing PGD for SGD.

Materials and Methods:

This study was a retrospective analysis at an academic institution. All patients undergoing IVF with PGD for a SGD as well as PGS for aneuploidy screening from January 2010 to December 2015 were included. Genetic results were interpreted as Affected, Unaffected or Carrier for SGD, and euploid or aneuploid for copy number screening. Percentages of all parameters were calculated.

Result(s):

A total of 182 couples underwent 341 cycles of PGD for SGD detection. Average female age was 32.8±4.4 years (range 23.1 – 43.0). A total of 1129 embryos were analyzed for 45 different mutations: n=21 dominant (age 33.0±4.1), n=19 recessive (age 33.7±4.0), and n=5 X-linked (age 29.7±4.5) [Table 1]. For recessive diseases, an embryo was reported as carrier in 49.9% (284/569), affected in 28.1% (160/569), and unaffected in 22.0% (125/569) of the cases. For

dominant diseases, an embryo was identified affected in 51.1% (179/350), unaffected in 39.4% (138/350) of cases, no result reported in 7.7% (27/350), and the result not disclosed in 1.7% (6/350). For X-linked diseases, an embryo was reported as unaffected in 39.5% (83/210), affected in 31.9% (67/210), no result reported in 15.7% (33/210), and carrier in 12.9% (27/210) of the cases.
Overall, 657/1129 (58%) of embryos from couples known to be at risk of passing on a genetic mutation were acceptable for transfer based on single gene testing. Among the 402 embryos also screened for aneuploidy, a normal chromosomal complement was reported in 67.9% (n=273; age 32.4±3.9). A copy number variant was found in the chromosome containing the mutation in 6.2% (n=8) of embryos.

Conclusion(s):
The global prevalence of SGD is approximately 10/1000 of all births. Thirty two percent of embryos that were screened for a mutated gene and would have been considered acceptable for transfer were found by PGS to be aneuploid. Despite the fact that our study was performed on a relatively young patient population, a high incidence of embryonic aneuploidy was observed. Concurrent PGD and PGS testing should be strongly considered to optimize embryo selection.

Table 1:

LIST OF MUTATIONS ANALYZED
Adrenoleukodystrophy
BRCA1
BRCA2
Charcot-Marie-Tooth Disease Type 1A
Congenital Adrenal Hyperplasia
Congenital Disorder of Glycosylation
Cystic Fibrosis
Duchenne Muscular Dystrophy
Facioscapulohumeral Muscular Dystrophy
Familial Dysautonomia
Familial Mediterranean Fever
Fanconi anemia, complementation group C
Fragile X Syndrome
Gaucher Disease
Glycogen Storage Disease 1a
Growth Retardation Syndrome
Hemophilia
Hereditary Multiple Exostoses

Hereditary Nonpolyposis Colorectal Cancer
HLA Compatibility
Huntington Disease
Hydrocephalus
Hypertrophic Cardiomyopathy
Mitochondrial DNA depletion Syndrome 7
Mucolipidosis Type IV
Multiple Endocrine Neoplasia Type 2
Multiple Endocrine Neoplasia Type 2A (MEN2A; C634 mutation in RET gene)
Myotonia Congenita
Myotonic Dystrophy
Myotubular Myopathy 1
Neurofibromatosis Type 1
Neurofibromatosis Type 2
Neurofibromatosis Type 3
Nonsyndromic Hearing Loss
Osteogenesis Imperfecta Type 1
Pfeiffer Syndrome
Polycystic Kidney Disease (recessive)
Polycystic Kidney Disease (dominant)
Rh Sensitization
Senior-Loken Syndrome
Sickle Cell Anemia
Smith Lemli Optiz Syndrome
Spinal Muscular Atrophy
Ulnar Deficiency
Usher Syndrome Type III
Waardenburg Syndrome