Decoding Pregnancy Loss: Validating a Novel Genetic Biomarker of Poor Egg Quality
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Background
Aneuploidy: the presence of an incorrect number of chromosomes in a cell, such as an egg.1

- Egg aneuploidy is the leading genetic cause of miscarriage.2.3.4
- Currently, maternal age is the only biomarker for a patient’s risk of ovulating an aneuploid egg.2.5

However, some patients (red dots in figure above) have higher or lower egg aneuploidy than predicted by maternal age alone.6
- For these patients, age is an insufficient biomarker.
- Genetic variants may account for age-disproportionate aneuploidy, but no genetic biomarker exists.7

RESEARCH OBJECTIVE
Identify causal genetic variants as predictive biomarkers of high egg aneuploidy relative to maternal age

Hypothesis
Maternal genetic variants cause age-disproportionate egg aneuploidy.

Methods: Study Design

- Identify genetic variants enriched in women with high egg aneuploidy relative to maternal age.
- Screen variants in vitro for ability to affect egg development (Result 1).
- Validate in vivo the top candidate variant in a CRISPR knock-in mouse model (Results 2 & 3).

Results
1. In vitro screening: KIF18A overexpression causes abnormal spindle formation in mouse oocytes.

2. In vivo phenotyping: KIF18A knock-in mice have abnormal egg morphology.

3. In vivo validation: KIF18A knock-in mice have increased egg aneuploidy.

Conclusions

KEY FINDING

Increased frequency of aneuploid eggs (p = 0.0005)

- Maternal KIF18A mutation
- High-aneuploidy patient variant
- KIF18A knock-in mouse model

- 6.7% WT v. 49.0% KIF18A

Summary of Study
- High egg aneuploidy patients
- KIF18A overexpression in vitro
- KIF18A knock-in mouse

- Maternal KIF18A
- Maternal egg aneuploidy
- Maternal egg aneuploidy

- 1 KIF18A
- 1 KIF18A
- 1 KIF18A

Significance
KIF18A should be further studied as a novel potential biomarker for age-disproportionate egg aneuploidy.

Our Vision of the Future: Precision Reproductive Medicine

Patient’s age
- Early genetic testing for predisposition to aneuploid eggs
- Informed reproductive decision-making

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References

5. Han H, et al. The origin of human aneuploidy, where we have been, where we are going. Hum Genet 2007; 120:308-316.
6. Krawetz SA. In the sky of human aneuploidy, why we have been, where we are going. Hum Genet 2007; 120:308-316.

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