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Whole-Exome Sequencing in Idiopathic Female Infertility Identifies Novel Candidate Targets for Non-Hormonal Contraceptive Discovery

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Abstract

This study aims to identify safe, reversible, non-hormonal contraceptive targets using whole exome sequencing of women with idiopathic infertility. Genes with rare, deleterious loss-of-function variants that temporarily impair fertility without causing other effects were prioritized. We have developed a Biomarker Discovery Portal to integrate genetic, clinical, and public data for multi-study exploration and accelerated target discovery.

Subject recruitment

- Consenting female subjects aged between 21-35 years
- Clinical diagnosis of unexplained infertility
- Trying to conceive for at least 1 year
- Normal uterine cavity
- At least one patent fallopian tube
- Antral follicle count (AFC) of ≥5 cumulative of both ovaries or Anti-Mullerian Hormone levels (AMH) of ≥1.2 ng/mL
- BMI ≤ 30 kg/m^2 at diagnosis

Women diagnosed with unexplained infertility and conceived only through IVF/IUI were also recruited.

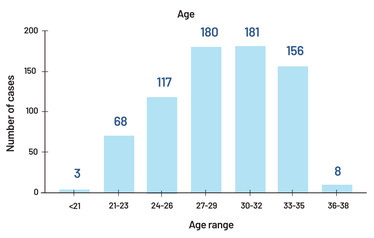
Parents and sisters of subjects, wherever possible

Summary	
Subjects recruited	1009
Proband	713
Mother	211
Father	60
Sister	25

Subject distribution

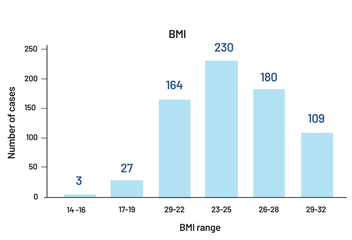
Kolkata	308
Bengaluru	139
Cuttack	121
Chennai	99
Kolhapur	61
Siliguri	56
Agra	53
Salem	41
Pune	31
Tambaram	25
Lucknow	23
Prayagraj	18
Delhi	12
Patna	8
Aurangabad	7
Mumbai	7

Age distribution at the time of diagnosis (probands =713)



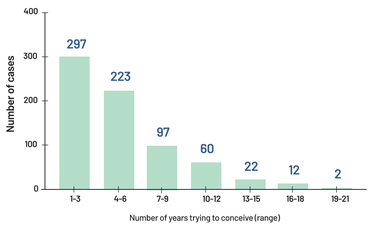
98.5% of all probands were in the 21-35 age at diagnosis

BMI distribution (probands =713)



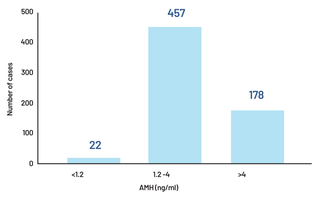
- All these recruitments are as per the accepted BMI range for the proband
- The depiction of different bar is only to show the distribution of BMI among the recruited probands

Number of years trying to conceive (probands =713)

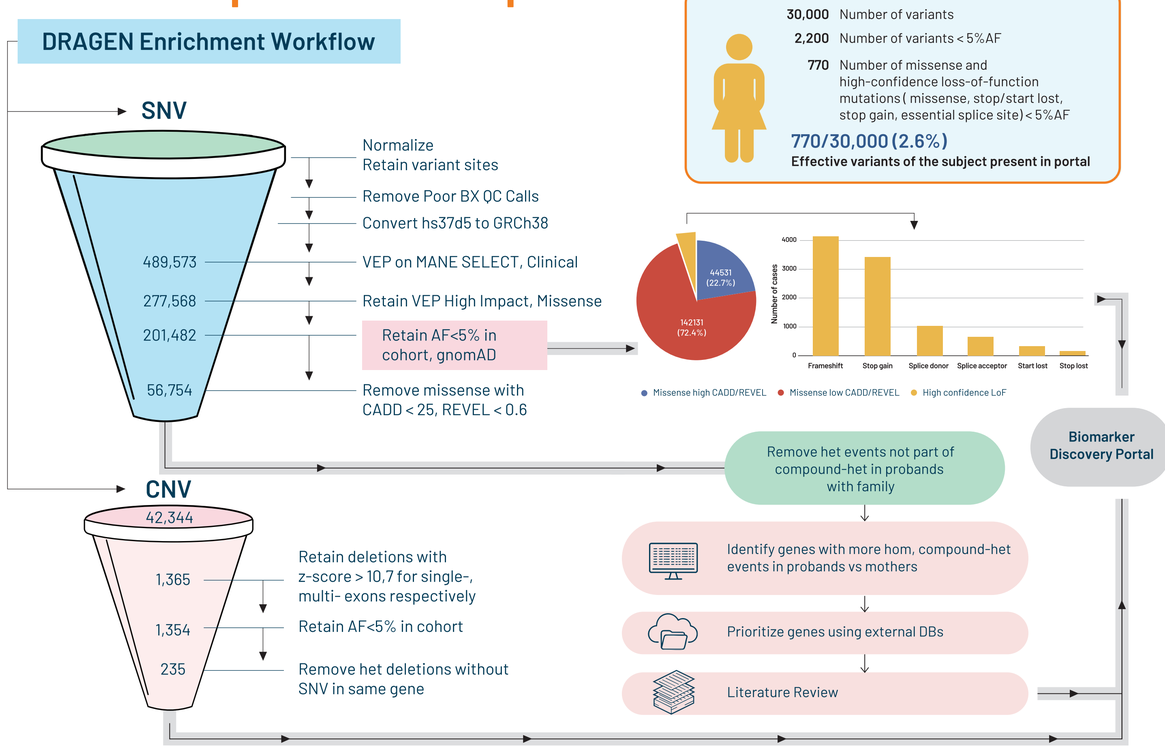


All the probands recruited are primary infertile cases

Ovarian reserve indicated by AMH



Custom pLoF set up



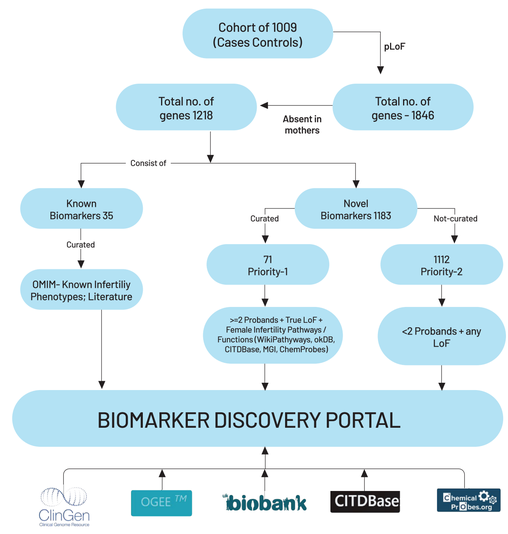
Study Highlights

1. Largest Indian genomic study on idiopathic female infertility.
2. 35 known genes, 1183 novel genes of which a total of 106 highlighted as candidate genes carrying rare, high-impact LoF and strong missense variants.
3. All rare variant data available via an interactive portal for further discoveries.

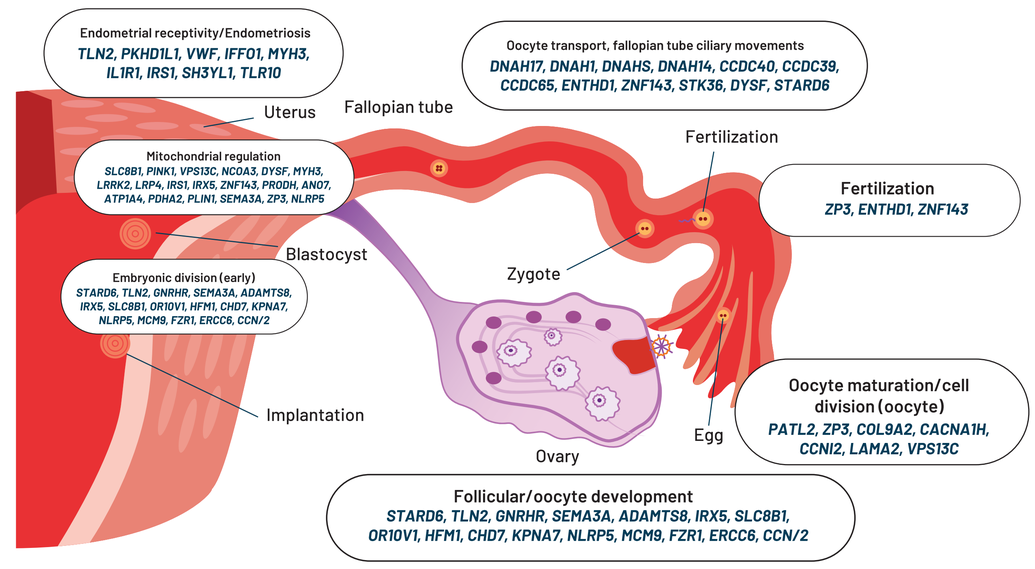
Infrastructure

1. Robust pLoF analysis workflow.
2. Expandable portal integrating public datasets and computational insights from UKBB.
3. Interactive workflows for candidate gene discovery.
4. Scalable, secure platform supporting multi-study integration with role-based access.

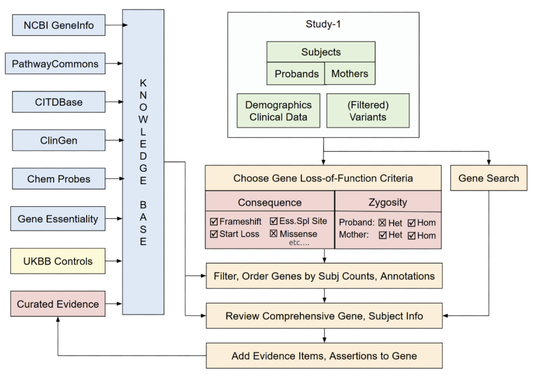
Curation process and knowledgebase creation



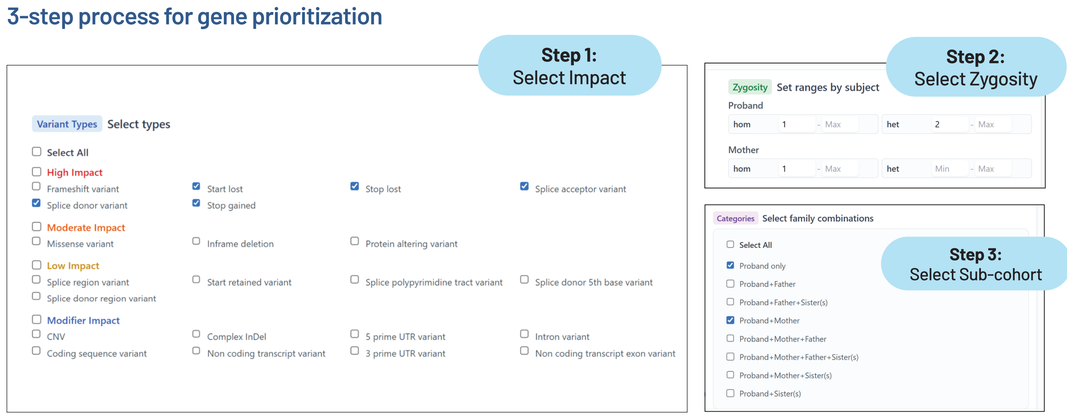
pLoF genes mapped to different function



Architecture for Biomarker Discovery Portal (BDP)

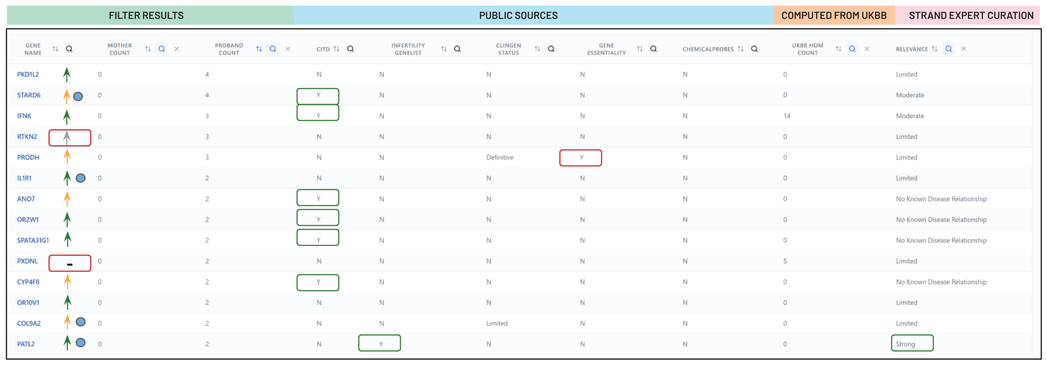


3-step process for gene prioritization



Gene Based Search

Prioritized LoF genes using BDP



Gene details

Acknowledgements

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