Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Material: Appendix

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1. Methods

1.1. Study design

Retrospective programmatic observational study of an optional premarital genetic screening program implemented in Abu Dhabi between 1 October 2022 and 30 September 2024 across 22 clinics. The study evaluated implementation processes, program uptake, diagnostic yield, turnaround time, and downstream actions including confirmatory testing and genetic counselling.

1.2. Implementation of an Optional Genetic Screening Program

The premarital genetic screening program was designed to identify significant reproductive genetic risks while respecting autonomy and public health priorities. Participation was voluntary and limited to consenting Emirati couples planning marriage in Abu Dhabi at this phase. The program integrated scientific rigor, ethical governance, and public health alignment through four pillars: workforce upskilling, ethical safeguards, targeted gene selection, and continuous quality improvement (Figure S1).

1.3. Sequencing and Confirmatory Testing

Whole-genome sequencing was conducted using the NovaSeq platform (Illumina), producing 150 bp paired-end reads (2×150 bp). Genomic DNA libraries were prepared in accordance with the manufacturer's instructions. Sequencing data were processed using the DRAGEN Bio-IT Platform (version 4.4.4, Illumina) for alignment to the GRCh38 human reference genome and for variant calling. The DRAGEN germline pipeline was applied to detect single nucleotide variants, insertions and deletions, structural variants, copy number variants, and short tandem repeats. Variant calls were generated in standard formats for downstream analysis. Subsequent variant annotation, filtering, prioritization, and clinical interpretation were performed using the Orion Platform (M42 Engineering, Clinical Genomics). All cases underwent a standardized review and approval workflow prior to integration into the laboratory information management system (LIMS). Variants were classified in accordance with American College of Medical Genetics and Genomics (ACMG)/AMP guidelines, supported by integrated genomic databases and curated evidence. Quality control metrics, including read quality, alignment statistics, and sequencing depth, were evaluated for each sample to ensure sufficient coverage and the reliability of variant detection.

1.4. Upskilling Healthcare Providers

To address the shortage of genetic specialists, the DOH upskilled family physicians to provide genetic counseling through three tailored training pathways. This initiative includes an intensive UAE University led course, a scalable self-guided assessment program, and an advanced six-month clinical genomics course delivered with Mass General Brigham, Harvard Medical School, and Khalifa University. Over 300 physicians were trained, ensuring consistent counseling quality and system sustainability.

1.5. Ethical Framework

A robust ethical and legal framework underpinned the implementation of the program, ensuring privacy, informed consent, and protection against genetic discrimination. UAE Federal Law by Decree No. 49 of 2023 formally regulates human genome use and mandates genetic counseling and consent for premarital genetic screening. This framework strengthened public trust and aligned the program with international ethical standards.

1.6. Genetic Conditions and Gene Panel Selection Criteria

1.6.1. Rationale for Autosomal Recessive Focus

Given high consanguinity rates, the program focused exclusively on autosomal recessive conditions, reporting results only when both partners carried pathogenic or likely pathogenic variants in the same gene. Variants of uncertain significance, autosomal dominant, X-linked, and mitochondrial conditions were excluded to reduce stigma and maintain reproductive relevance.

1.6.2. Gene Selection and Variant Interpretation

Gene selection was guided by disease severity classifications and ACMG standards. Variant interpretation followed ACMG 2015 guidelines and underwent multidisciplinary review to ensure consistency and clinical relevance.

1.6.3. Sequencing and Confirmatory Testing

WGS was performed at the Biogenix–G42 laboratory. Virtual gene panels were derived bioinformatically, with confirmatory testing mandated for technically complex genes such as CYP21A2 using Sanger sequencing and MLPA. Results were reported within 14 days, and lifetime reanalysis was enabled through a single WGS per participant.

1.7. Panel Review and Continuous Improvement

The gene panel underwent biannual expert review to incorporate emerging evidence and local population data. Adjustments included gene additions and removals, variant reclassification, and workflow enhancements such as integration of validated HBA callers. This dynamic process ensured clinical accuracy and population relevance. (Figure S2)

1.8. Phase One Implementation

Phase one employed a structured rollout to validate workflows, laboratory integration, and provider readiness. It enabled early identification of logistical challenges and informed the development of standardized operating procedures, supporting future expansion without compromising quality.

1.9. Genomic Literacy

Patient-friendly gene cards were developed to enhance genomic literacy among couples with positive findings. These resources explained inheritance patterns, disease features, and reproductive options, reinforcing informed decision-making.

1.10. Premarital Screening Unit

A centralized Premarital Screening Unit was established to coordinate between stakeholders, manage follow-up of positive cases, ensure digital integration, and support couples throughout counseling and family planning decisions. The unit enabled real-time monitoring, digital certification, and complaint resolution.

1.11. Reproductive Assistance

The program emphasized informed choice rather than marriage prevention. Couples identified as genetically at-risk who chose to marry were referred for fully covered reproductive services, including IVF and pre-implantation genetic testing when clinically indicated, guided by DOH-issued evidence-based standards.

1.12. Counseling Challenges

Challenges in implementation included parental influence minimizing perceived risk, variability in counseling between clinics, religious considerations, and differences in emotional maturity. These findings highlight the need for further standardization, culturally tailored communication, and continued physician training.

2. Results

2.1. Phase one results

Among 1,094 couples screened, 13% were genetically at-risk. The most frequently implicated genes were *CYP21A2, USH2A, MEFV*, and *ABCA4*. Genetic heterogeneity was substantial, with 39% of variants classified as “Other.” (Figure S3).

2.2. Marriage Decisions

Of at-risk couples, 31% chose not to proceed with marriage, while 59% proceeded and were referred for reproductive counseling. Long-term reproductive outcomes are still being monitored. The remaining 10% at the time of the study either did not decide or did not respond to follow-up calls

2.3. Emirati Genome Program Findings

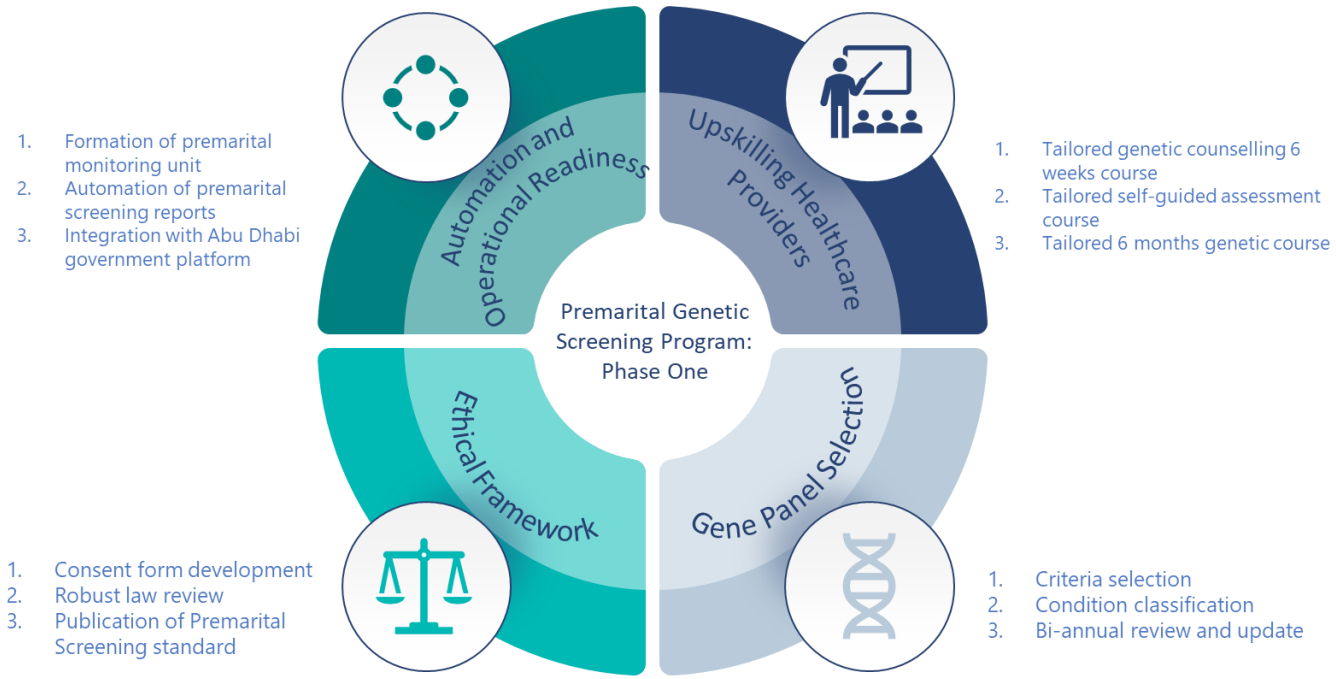
Analysis of 43,611 EGP genomes identified 120 pathogenic or likely pathogenic variants across the 48 most relevant genes. Severe recessive-lethal disorders and congenital anomalies represented the highest cumulative allele frequencies. The findings support the inclusion of these gene categories in premarital screening and underscore population-specific variant enrichment. (Figure S4 & S5).

2.4. Phase One Satisfaction Survey

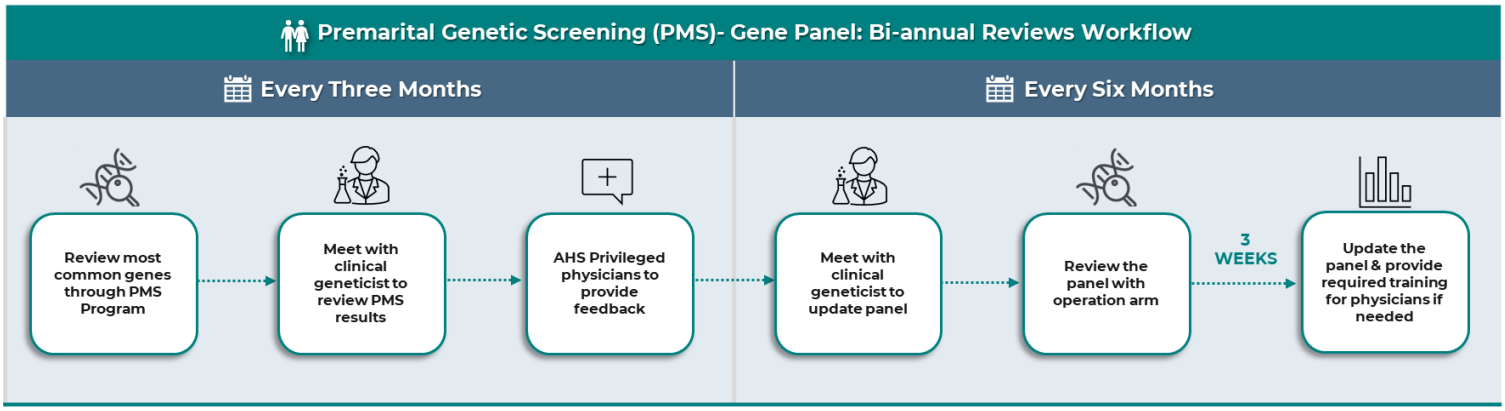
Survey feedback from 54 participants showed high overall satisfaction (average score 4/5), with strengths in staff courtesy, clarity of information, and privacy. Waiting time was the main area identified for improvement.

3. Figures

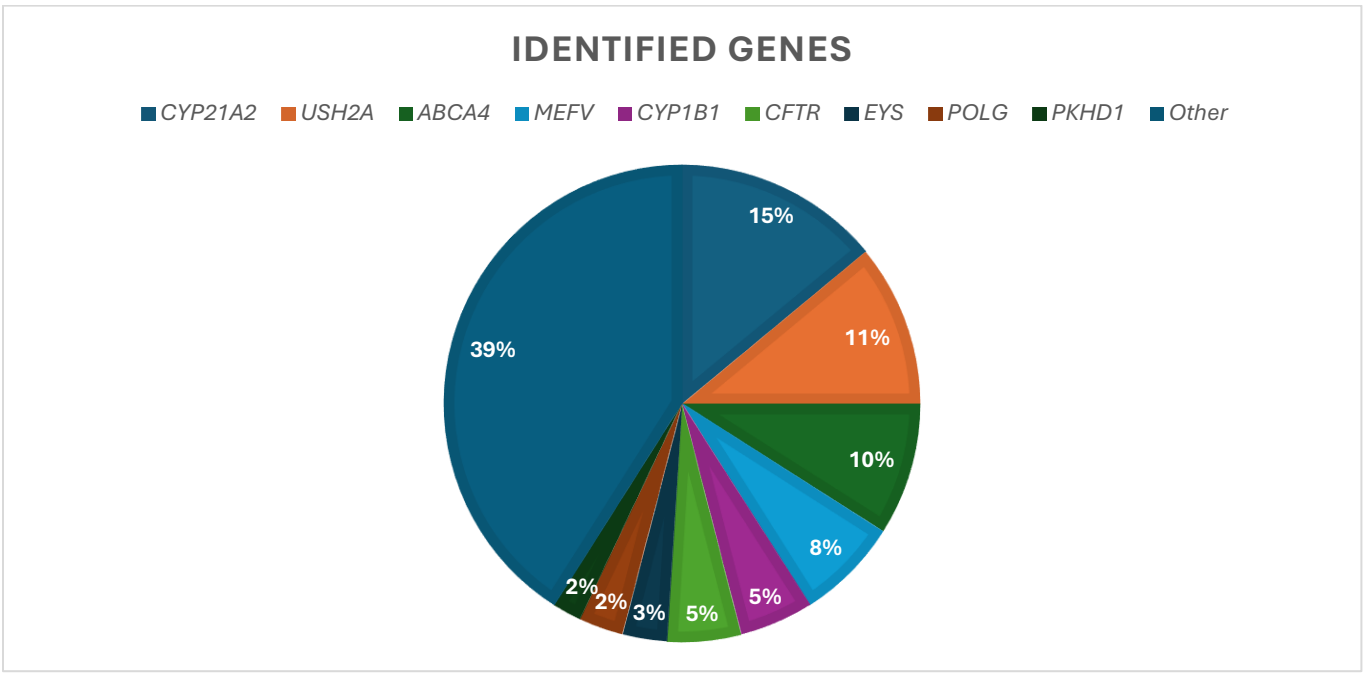
3.1. Figure S1: Four pillars of the Premarital Genetic Screening Program



3.2. Figure S2: Gene Panel review workflow

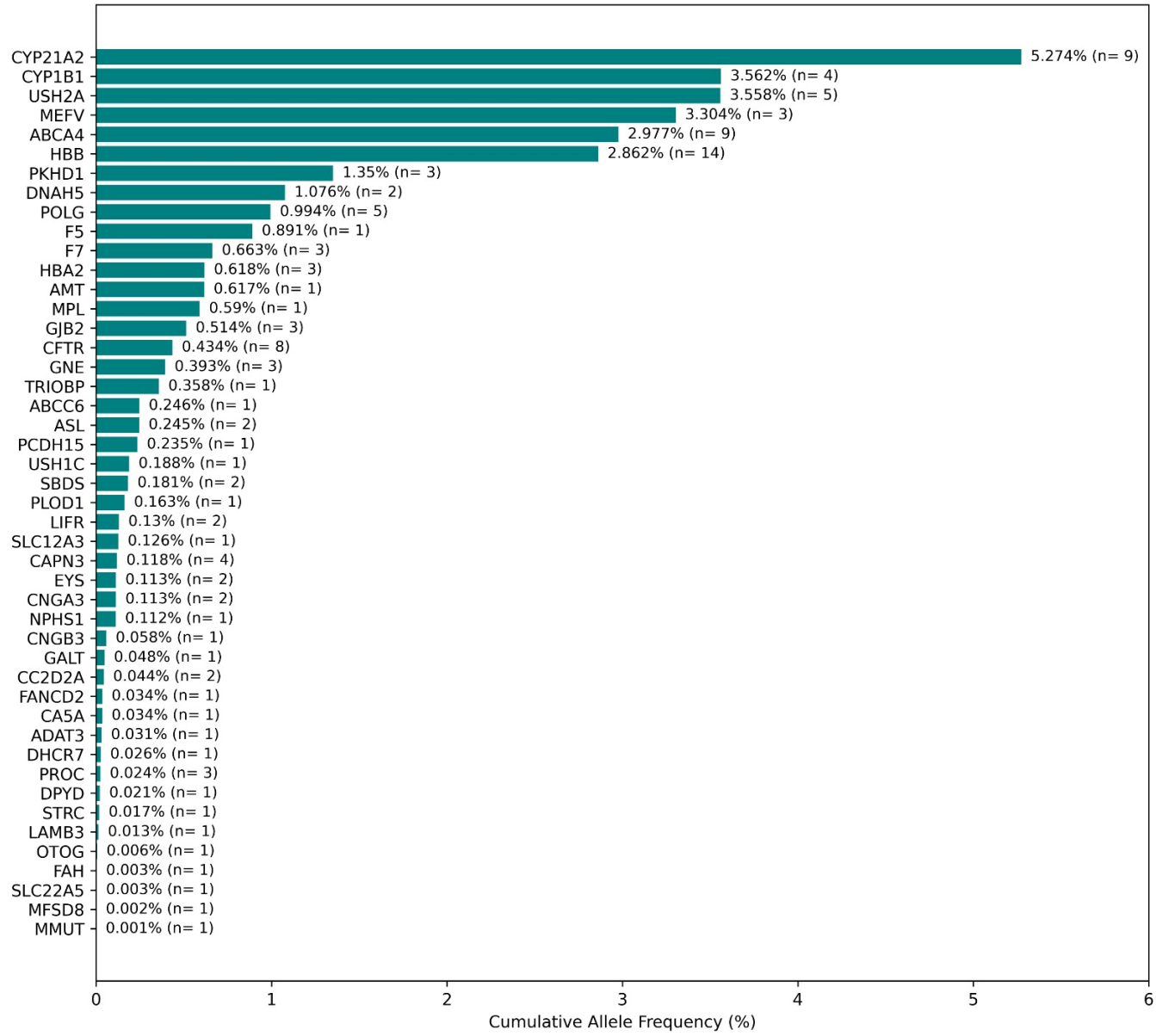


3.3. Figure S3: Distribution of identified gene variants among participants in the premarital genetic screening program.



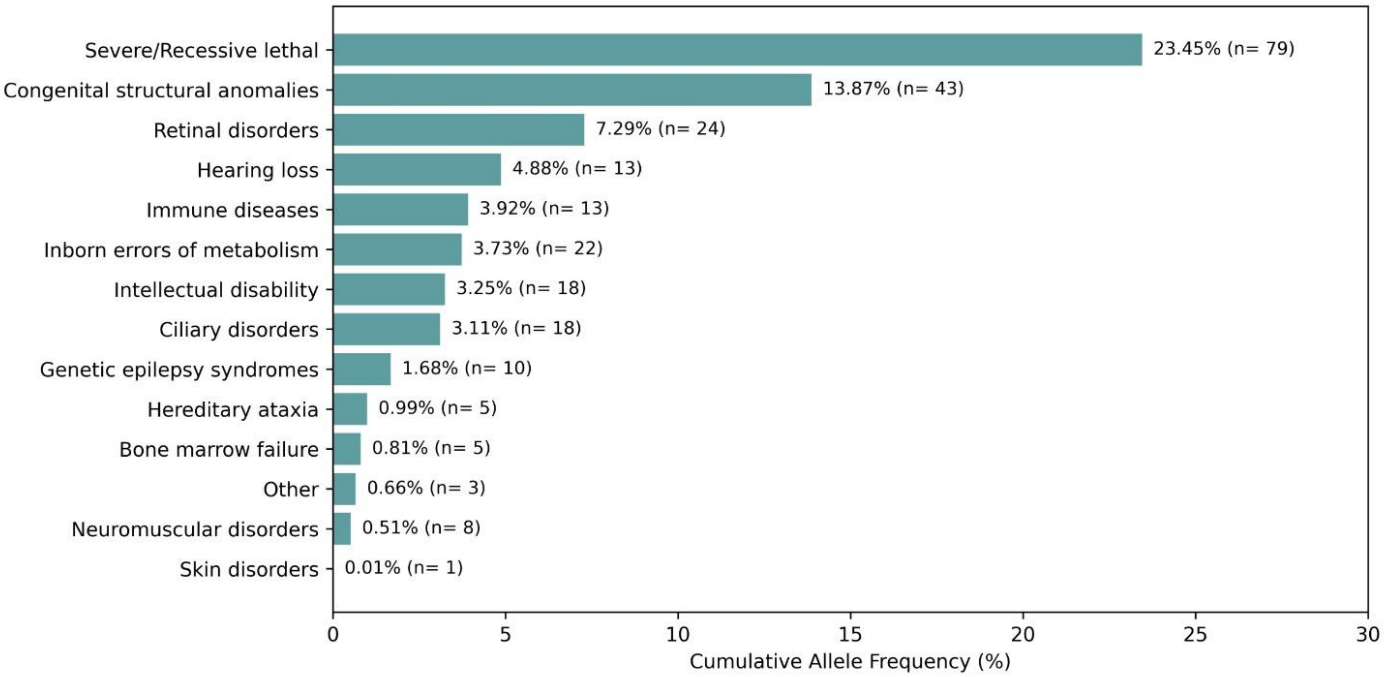
The majority of variants are spread across a range of genes, with the ten most frequent shown individually. variants classified as “Other” account for 39% of cases, reflecting considerable genetic diversity beyond the most common disease-associated genes.

3.4. Figure S4: Cumulative allele frequency (%) of pathogenic or likely pathogenic variants detected in the premarital genetic screening cohort, grouped by gene.



The number of pathogenic alleles observed for each gene (n) is indicated on the chart, underscoring the genetic heterogeneity among screened individuals.

3.5. Figure S5: Cumulative allele frequency (%) of pathogenic or likely pathogenic variants grouped by clinical disorder category among screened individuals.



Severe/recessive lethal disorders and congenital structural anomalies represent the highest cumulative allele frequencies, indicating their predominance among identified variants. The chart underscores the clinical diversity of pathogenic alleles in the cohort, with a long tail of lower-frequency categories contributing to the genetic disease spectrum. The number of observed pathogenic alleles (n) is shown for each category.

4. Tables

4.1. Table S1. Gene Panel Update: Lists genes added or removed, in the premarital genetic screening gene panel, along with the rationale for each update.

Gene	Addition/Removal	Justification
CDKN2A	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
PTEN	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
PRNP	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
ELN	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
PIK3CD	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
HBG2	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
KCNQ1	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
SCN1A	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
SCNAI2	Removal	Autosomal Dominant Conditions or Unclear Pattern of Inheritance
MEFV	Removal	Causes Mild Disease
SLC2A9	Removal	Causes Mild Disease
ACADS	Removal	Causes Mild Disease
ACADSB	Removal	Causes Mild Disease
TAB1	Removal	Causes Mild Disease
GALE	Removal	Causes Mild Disease
F12	Removal	Causes Mild Disease
ACADM	Removal	Treatment Available
BTD	Removal	Treatment Available
SURF1	Addition	Severe Condition Found in UAE population
ZNF699	Addition	Severe Condition Found in UAE population
FBXO22	Addition	Severe Condition Found in UAE population
FREM1	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
MPDZ	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
BCAS3	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
SLC25A46	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
MED11	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
MED27	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
TMEM94	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children

UNC80	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
OCLN	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
GJC2	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
SLC39A14	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
ANKLE2	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children
FKBP10	Addition	Causes severe disease with early onset, inclusion would allow for comprehensive screening of possible risk of passing on to their children

4.2. Table S2. Variant Reclassified: Details all genetic variants that were reclassified based on updated evidence.

Gene	Variant	Previous Classification	ACMG Criteria Reclassification Justification
USH2A	c.784+14389G>T	Likely pathogenic	**Reclassified** to VUS-PS3,PM3,PP5,BS2
CYP1B1	NM_000104.4:c.1103G>A (p.Arg368His)	Likely pathogenic	**Reclassified** to VUS-PS3,PM1,PM3,BS2
ABCA4	NM_000350.3: c.5882 G>A (p.Gly1961Glu)	Pathogenic	**Reclassified** to VUS: Is a low penetrant variant. Not to be reported as common carrier.

4.3. Table S3. Pathogenicity of Couples Identified as Genetically at Risk: Summarizes couples in the screening cohort who were identified as genetically incompatible, including the pathogenic or likely pathogenic variants detected and associated clinical significance.

5. References

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