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Recurrent Pregnancy loss in Consanguineous family with two different variant identifications by Couple carrier screening

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Abstract

We present a rare case of recurrent pregnancy loss associated with autosomal recessive mutation identified by Clinical Exome sequencing (Couple carrier testing Method). The Consanguineous Couple were facing recurrent pregnancy loss before 20 weeks of gestation since last 7 years of marriage. This type of pregnancy loss occurs in approximately 5% of reproductive-aged women, her hormone level, ultrasound, and the biochemical test report were normal. We report two autosomal recessive mutations in two different genes responsible for fetus growth during pregnancy identified in couple and this mutation has been confirmed by Sanger validation method. Study showed the utility of Clinical Exome sequencing method in couple carrier screening to take proper decision in future family planning. Ultimately, the consanguineous marriages are really stigma in our society as a mother of rare disease and responsible for the pregnancy losses as well.

Keywords: Recurrent Pregnancy loss; Abortions; Mutation; Carrier Screening

Abbreviation: RPL: Recurrent Pregnancy Loss; ACOG: American College of Obstetrics and Gynaecology; ACMG: American College of Medical Genetics; SMA: Spinal Muscular Atrophy; ASRM: American Society for Reproductive Medicine; CMA: Chromosomal Microarray; PCS: Preconception Carrier Screening; CF: Cystic Fibrosis; FXS: Fragile X Syndrome; ECS: Expanded Carrier Screening; NGS: Next-Generation Sequencing; PKD: Polycystic kidney disease

Introduction

Spontaneous pregnancy loss is the very common problem of pregnancy. Almost 70% of human conceptions fail to achieve the viability, with almost 50% of all the pregnancies ending in the miscarriage before the clinical acknowledgement of a missed period or the presence of embryonal heart activity [1,2]. Recurrent pregnancy loss (RPL) is less common, taking place in about one out of 100 pregnant women [3]. it has been over all defined as the three or more consecutive pregnancy losses before 20 weeks of the gestational age [2].

An estimated 1% of the couples attempting pregnancy suffer three or more consecutive losses, and as many as 5% have two or more consecutive losses [4]. Causes of RPL can be categorized as genetic abnormalities, hormonal and metabolic disorders, uterine anatomical aberrations, infectious causes, autoimmune disorders, thrombophilic disorders, autoimmune causes, and idiopathic. This latter group accounts for over 50% of the cases [5].

Approximately 50% of the first trimester miscarriages are due to the chromosomal abnormalities in the foetus. Till date, the Trisomies are the most detected abnormalities it is reported approx. 61.2%, followed by triploidies approximately 12.4% cases, monosomy X (10.5%), tetra ploidies (9.2%) and the structural chromosomal abnormalities (4.7%). Most aneuploidies are lethal (Death causing) and the viable trisomies are constrained to only a few human chromosomes.

The most common human trisomy is the chromosome 21 (Down Syndrome). Humans are much abler to tolerate the extra sex chromosomes than extra autosomes. After Down Syndrome the most common human aneuploidy is Klinefelter's syndrome (47, XXY). On the other hand, cells seem to be particularly sensitive to losing chromosomes, since the only viable human monosomy involves the X chromosome (Turner's syndrome).

Most often the chromosomal rearrangements in either carrier are a major clinically recognized cause of the miscarriage and these studies are published in a different journal have shown the prevalence of the chromosomal incongruities that varies from 4% to 8% of the couples who are affected by at least two or three pregnancy damages [6-8] Recent recommendations supporting clinical intervention after only two consecutive spontaneous abortions when other features of pregnancy loss are present define a higher prevalence of one in 100 women.

These additional features include detectible fetal heart activity preloss; normal fetal chromosomal content; advanced maternal age; or couple subfertility (Practice Committee of the American Society for Reproductive Medicine 2008a) [9]. Uterine structural abnormalities, endocrinal abnormalities, infections, immunologic factors, metabolic or hormonal disorders, environmental factors, sperm quality, and maternal and paternal age have each been linked to RPL.

The standard RPL estimation presently incorporates the testing for the chromosomal translocations in each of the parent as well as the several maternal testing for endocrine (thyroid), autoimmune (lupus anticoagulant and antiphospholipid antibodies), anatomic (endometrial or uterine abnormalities), and, in some cases, single gene disorders (such as inherited thrombophilias) [10,11].

Despite the number of proposed etiologies, parental chromosomal abnormalities and complications resulting from the antiphospholipid antibody syndrome continue to be the only undisputed causes of RPL. It's reported in several literatures, that RPL is remains unexplained in 45% to 50% of patients [12]. In most of the cases, there is a poor prognosis that is far from bleak; researchers have shown that the overall possibility of live birth after RPL is 70% –75%, even in women with advanced maternal age [13, 14].

To the cause of these losses, Carrier screening programs were announced in the year 1970s to offer individuals for the opportunity to learn the likelihood that they could pass on an autosomal or X-linked condition to their offspring. Firstly, the carrier screening programs were used only with the ethnic groups who had relatively high incidence of certain conditions, such as ancestry-based screening for Tay–Sachs's disease in Ashkenazi Jewish communities and βthalassemia in Mediterranean populations [15,16].

The carrier screening testing in the prenatal or at the timing of preconception is suggested for a variety of the conditions based upon the ethnic background and family history. Certain autosomal recessive disease conditions are the more prevalent and reported in the individuals with the specific ancestry or specific to the certain population with their percentage of risk levels. Thus, the couples of the certain populations are at the increased risk for having the offspring with one of such type of conditions. Some of these conditions may be lethal in childhood or are related with significant morbidity.

For Cystic fibrosis the carrier screening is acclaimed by the American College of Obstetrics and Gynaecology (ACOG) for individuals at the stage of preconception and the prenatal periods regardless of ethnic background or the family history. ACOG's current recommendations indicates that the complete sequencing of the CFTR gene is not appropriate for the routine carrier screening, but carrier screening panels should include at least minimum of 23 most common mutations (ACOG 2017) [17].

It has been recommended by the American College of Medical Genetics (ACMG) and ACOG for the prenatal screening of spinal muscular atrophy (SMA) regardless of family history. Fragile X carrier screening is suggested for women with a family history of fragile X-related disorders, unexplained mental retardation or developmental delay, autism, or premature ovarian insufficiency [18]. Currently Fragile X carrier screening in the general population is not routinely recommended. Individuals of Ashkenazi Jewish descent have an increased risk to have a child with certain autosomal recessive conditions.

The American College of Medical Genetics (ACMG) recommends for the carrier screening for cystic fibrosis, Canavan disease, familial dysautonomia, Tay-Sachs's disease, Fanconi anemia (Group C), Niemann-Pick (Type A), Bloom syndrome, mucolipidosis IV, and Gaucher disease for all Ashkenazi Jews who are pregnant or considering pregnancy. These disorders all have significant health impact on an affected infant.

RPL testing the American College of Obstetricians and Gynaecologists (ACOG) and the American Society for Reproductive Medicine (ASRM) both are suggested for the chromosomal analysis via karyotyping when a couple has a history of RPL. Karyotype analysis can be performed on either the products of conception or on both parents when a history of RPL is identified. ACMG stated chromosomal microarray (CMA) should not be used to evaluate the parents with the history of RPL, as this technology cannot detect the stable chromosomal rearrangements.

Developing evidence shows that the several advantages of the increasing clinical sensitivity to the Mendelian recessive diseases in the genetic screening of the approaching parents (Preconception carrier screening, PCS). Notably, population-based incorporation of parallel screening for cystic fibrosis [CF], fragile X syndrome [FXS], and spinal muscular atrophy [SMA] in routine preconception and early pregnancy programs results in a combined affected pregnancy risk comparable to the risk for Down syndrome [19].

Advancement in the sequencing technology and decreases in the cost [20] have made the expanded carrier screening (ECS) reasonable and inexpensive. In 2011, after 14 years of cumulative experience in gene-by-gene carrier screening, screening tests were first expanded to simultaneously test for 448 Mendelian recessive diseases using next-generation sequencing (NGS) technology [21]. Subsequently, ECS has been implemented in the several populations, and the power of the NGS and expanded

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panels increases detection rates compared with traditional tests [22–25]. Expanded carrier screening does influence reproductive decisions for a high percentage of at-risk couples.

Current documents of guidance do not specify that which conditions should be involved on an expanded panel, but most of them recommended at least some specific conditions such as CF and spinal muscular atrophy [26-28]. There is also consensus among the professional societies that expanded carrier screening panels should focus on the childhood-onset situations that are likely to have a significant impact on the child's quality of life [29-33].

In addition to age of onset and clinical impact, most guidance documents also include criteria related to the scope of the condition (including frequency of the gene and penetrance of the phenotype) and the extent to which parents and/or providers can act in response to a positive finding. However, professional societies vary in terms of the specificity of their lists of considerations and/or criteria, as well as the details of their guidance.

Case Report

Genomic DNA is extracted from the blood samples of the couple presented with the history of recurrent pregnancy loss. who presented for genetic counselling because of three recurrent miscarriages, and they have been married since 7 years. It is the first study in our laboratory. Informed consent was obtained from couple. For NGS, patient DNA corresponding to exonic regions is captured using Agilent targeted Exome hybridization probes. Captured DNA is sequenced by using the Thermofisher's semi-conductor sequencing platform Ion-S5 using 200 bp reads. The following quality control metrics are generally achieved in >97% of target bases are covered at >20x, mean coverage of target bases ~100x.

Data analysis and the variant interpretation has been completed by the grouping of torrent suite software and our internal bioinformatics pipeline. Variants are filtered and interpreted by using the curated databases such as Clinvar, OMIM, dbSNP etc. and common, benign, and low-quality variants are filtered from analysis. All differences from the reference sequences (sequence variants) are assigned to one of five interpretation types (Pathogenic, Likely Pathogenic, Variant of Uncertain Significance, Likely Benign and Benign) as per ACMG Guidelines [34].

All sequence variants in apposite gene regions will be detected and interpreted, but only Pathogenic and Likely Pathogenic variants will be included in the test report. Rare and undocumented synonymous variants are nearly always classified as likely benign if there is no indication that they alter protein sequence or disrupt splicing. Likely benign and benign variants are not included for any sections in report.

Table 1: List of genes analysed in Couple carrier screening test.

ABCB11	ASL	CLN8	DPYD	GALE	HEPACAM	LMF1	NEB	PRPS1	SLC45A2
ABCC2	ASPA	CLRN1	DUOX2	GALK1	HEXA	LRPPRC	NPC1	PTS	SLC4A11
ABCC6	ASS1	CNGB3	DUOXA2	GALT	HEXB	MAN2B1	NPC2	PYGM	SLC5A5
ABCD1	ATM	COL4A3	DYSF	GAMT	HFE	MAT1A	NPHS1	RAB23	SLC7A7
ACADM	ATP7A	COL4A4	EDA	GBA	HFE2	MCCC1	NPHS2	RAPSN	SLC7A9
ACADS	ATP7B	COL4A5	EIF2B5	GBE1	HGD	MCCC2	NR2E3	RDH12	SMPD1
ACADVL	AVP	COL7A1	EMD	GCDH	HGSNAT	MCEE	OPA3	RFX5	SRD5A2
ACAT1	BBS1	CPT1A	ETFA	GCK	HLCS	MCOLN1	OTC	RFXANK	STAR
ACOX1	BBS10	CPT2	ETFB	GDF5	HMGCL	MEFV	PAH	RFXAP	SUMF1
ACTA1	BBS12	CRB1	ETFDH	GJB1	HOGA1	MFSD8	PC	RLBP1	TFR2
ADA	BBS2	CTH	ETHE1	GJB2	HPS1	MKS1	PCCA	RS1	TG
ADAMTS2	BCKDHA	CTNS	EVC	GLA	HPS3	MLC1	PCCB	RTEL1	TGM1
AGA	BCKDHB	CTSK	EVC2	GLB1	HSD17B3	MMAA	PDHA1	SACS	TH
AGL	BCS1L	CYBB	EYS	GLDC	HSD17B4	MMAB	PDHB	SEPSECS	TMEM216
AGXT	BLM	CYP11B1	F11	GLIS3	HSD3B2	MMACHC	PEPD	SERPINA1	TPO
AHCY	BRIP1	CYP11B2	F2	GM2A	IDS	MMADHC	PEX1	SGCA	TPP1
AIRE	BTD	CYP17A1	F5	GNE	IDUA	MMP1	PEX10	SGCB	TRIM32
ALDH3A2	CAPN3	CYP19A1	F8	GNMT	IKBKAP	MPI	PEX2	SGCG	TSHB
ALDH4A1	CBS	CYP1B1	F9	GNPTAB	IL2RG	MPL	PEX6	SGSH	TSHR
ALDH7A1	CDH23	CYP21A2	FAH	GNS	IVD	MPV17	PEX7	SLC12A3	TTPA
ALDOB	CEP290	CYP27A1	FANCA	GP1BA	IYD	MTHFR	PFKM	SLC12A6	TYR
ALG6	CFTR	CYP27B1	FANCC	GP9	KCNJ11	MTM1	PHGDH	SLC17A5	UGT1A1
ALPL	CHM	DBT	FANCG	GPR56	LAMA2	MTRR	PKHD1	SLC22A5	USH1C
AMH	CHRNA1	DCLRE1C	FH	GRHPR	LAMA3	MTTP	PMM2	SLC25A13	USH2A

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AMHR2	CHRND	DDAH1	FKRP	GUCY2D	LAMC2	MUT	POLG	SLC25A15	VPS13A
AMPD1	CHRNE	DHCR7	FKTN	HADHA	LCA5	MVK	POMGNT1	SLC26A2	VPS13B
AMT	CHRNG	DHDDS	FMR1	HAL	LDLR	MYO15A	POMT1	SLC26A3	VPS45
AR	CIITA	DLD	G6PC	HAX1	LDLRAP1	MYO7A	POR	SLC26A4	WISP3
ARG1	CLN3	DMD	G6PD	HBA1	LHCGR	NAGLU	PPT1	SLC37A4	WNT10A
ARL13B	CLN5	DNAH5	GAA	HBA2	LIAS	NBN	PROM1	SLC39A4	WRN
ARSA	CLN6	DNAI1	GALC	HBB	LIFR	NDRG1	PROP1	SLC3A1	

In this study, we tested a panel of over ~300 genes that are associated with around 400 disorders inherited in an autosomal recessive (some X-linked recessive) manner and are mostly very severe and are childhood onset diseases (Table 1). Carrier screening is envisioned for an individual at a reproductive age as a preconception or the prenatal screening to determine if he/she carries one or more mutations for the diseases.

These mutations were designated based on the current American College of Medical Genetics (ACMG) and American College of Obstetrics and Gynaecology (ACOG) commendations, as well as a thorough review of scientific literature and the assessment of their clinical utility. This test is not intended for diagnostic testing of children suspected of having any of the diseases in the panel. Rare false negatives may occur in the setting of bone marrow transplantation, blood transfusion, and genetic variants such as other point mutations and deletions.

The studied couple had the previous history of three recurring abortions with the missing heartbeat in fetus. These couple married for 7 years in the same family (Consanguineous marriage) (Figure 1a). Pedigree of the family showed the 1st degree of consanguinity. After enrollment of this couple, we have performed several hormonal and biochemical tests. Result of the biochemical test has been mentioned in Figure 1b.

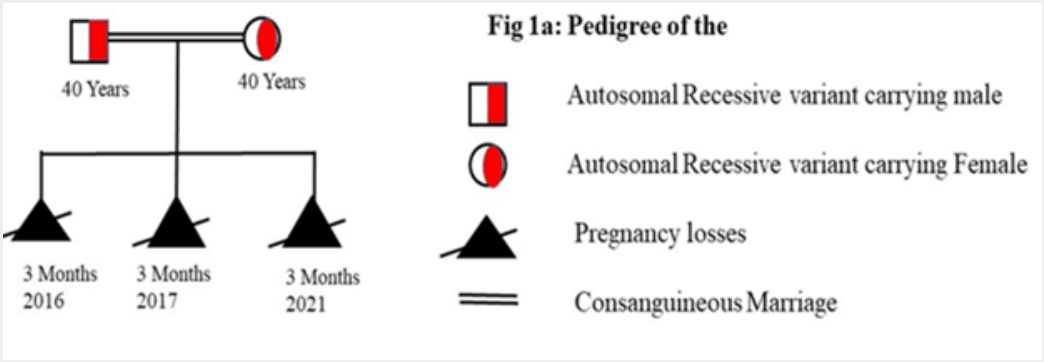

Figure 1a: Pedigree of the

- **Married for 7 Years**
- **Case of Recurrent abortion**
- **Conceived three times all the time cardiac activity missing**
- **Consanguinity Marriage**

Other Test Parameters
USG : Normal
EMV : 1ge (113.30 U/ml)
AMH : 1.00 ng/ml
T3 : 1.45 ng/ml
T4 : 5.7 ng/ml
TSH : 7.73 ng/ml
FSH : 7.90 MIU/ml
LH : 8.00 MIU/ml
PRL : 10.30 MIU/ml
Vit D : 9.00 ng/ml
c-ANCA : Negative
p-ANCA : Negative
Anti-cardiolipin antibody: 9.33 u/ml
Antiphospholipid antibody: 8.95 u/ml

Figure 1b: Hormone levels and other test parameters of the female patient.

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All the test reports were normal, and the ultrasound report was also normal. But all the time this couple faced the pregnancy losses at time of first trimester (3rd month) (Figure 1a). After getting done all the tests, we have enrolled this couple for the couple carrier screening test to know the cause of pregnancy loss.

The genes we included in this couple carrier screening test is mentioned in the Table 1. The result of this test indicated this couple is carrier for the two different gene in the two different variants (Table 2&3). The couple found to be carrier of variant c.997A>G; p. Lys333Glu (ACADM gene) and c.732G>C; p. Trp244Cys (PKHD1 gene) (Table 3). All the variant details of identified mutation in couple is mentioned in the table 3.

Table 2: Disease information and their risk factors reported in different population.

Gene	Disease Name	Ethnicity	Detection Rate	Carrier Frequency	Residual Risk
ACADM	Acyl-CoA dehydrogenase,medium chain, deficiency of	European Caucasian Saudi Arabian	>80% 95%	1 in 50 1 in 68	< 1 in 250 < 1 in 1300
ACADVL	Acyl-CoA dehydrogenase, very long-chain, deficiency of	General Population	> 18%	< 1 in 87	< 1 in 100
ADA	Severe combined immunodeficiency due to ADA deficiency	General Population	5%	1 in 500	< 1 in 525
AGA	Aspartylglucosaminuria	Finnish	98%	1 in 69	< 1 in 3000
AGL	Glycogen storagedisease IIIa, IIb	Caucasian North African Jewish	19% all GSD III, 51% GSD IIIb >99%	1 in 159 1 in 37	1 in 196 allGSD III, < 1 in 300 GSDIIIb < 1 in 3500
AGXT	Hyperoxaluria,primary, type 1	General Population	>33%	< 1 in 159	< 1 in 236
AIRE	Autoimmune polyendocrinopathy syndrome, type I, withor without reversible metaphyseal dysplasia	Finnish Iranian Jewish	89% >99%	1 in 80 ~ 1 in 48	1 in 715 < 1 in 4500
ALPL	Hypophosphatasia	JapaneseManitoba Mennonite	52% >90%	< 1 in 159 1 in 25	< 1 in 300 < 1 in 246
ARSA	Metachromaticleukodystrophy	Austrian European Caucasian Habbanite Jewish	>70% 44% >50%	1 in 100 1 in 100 1 in 5	<1 in 333 1 in 179 < 1 in 9
ASL	Argininosuccinicaciduria	Dutch Saudi Arabian	56% 52%	1 in 133 1 in 80	1 in 300 1 in 165
ASPA	Canavan disease	Ashkenazi Jewish General Population	98% 50%	1 in 55 < 1 in 100	1 in 2715 < 1 in 200
ATM	Ataxia-telangiectasia	Amish Costa Rican North African Jewish Norwegian	99% 56% 97% 57%	Unknown 1 in 100 1 in 82 1 in 100	< 1 in 500 1 in 227 1 in 2700 1 in 232
ATP7B	Wilson disease	Ashkenazi Jewish European Caucasian	67% 40%	1 in 100 1 in 87	1 in 300 1 in 145

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BBS1	Bardet-Biedl syndrome 1	General Population	65%	< 1 in 250 (BBS1 only)	< 1 in 700
BBS10	Bardet-Biedl syndrome 10	General Population	48%	< 1 in 250 (BBS10 only)	< 1 in 500
BBS12	Bardet-Biedl syndrome 12	Caucasian General Population	27% 19%	< 1 in 500 (BBS12 only) < 1 in 500 (BBS12 only)	< 1 in 680 < 1 in 600
BCKDHA	Maple syrup urine disease, type Ia	Mennonite	99%	< 1 in 7	< 1 in 568
BCKDHB	Maple syrup urine disease, type Ib	Ashkenazi Jewish	99%	1 in 80	1 in 7900
BCS1L	Bjornstad syndrome	Finnish	>99%	1 in 109	< 1 in 10,000
BLM	Bloom syndrome	Ashkenazi Jewish European Japanese	97% 40% 44%	1 in 107 Unknown Unknown	1 in 3520 < 1 in 250 < 1 in 250
CAPN3	Muscular dystrophy, limb-girdle, type 2A	Bulgarian Croatian Italian (Northeastern) Russian Turkish	58% 76% 38% 45% 35%	1 in 100 1 in 133 1 in 163 < 1 in 100 1 in 100	1 in 246 1 in 550 1 in 263 < 1 in 180 1 in 160
CBS	Homocystinuria, B6- responsive and nonresponsive types	Irish Norwegian Qatari	70% 75% >92%	1 in 128 1 in 41 < 1 in 22	< 1 in 400 < 1 in 150 < 1 in 260
CDH23	Deafness	General Population	9%	~1 in 134	< 1 in 147
CEP290	Bardet-Biedl syndrome 14	Northern European	48%	~ 1 in 224	1 in 430
CFTR	Cystic Fibrosis	African American Ashkenazi Jewish Asian Caucasian Hispanic	77% 99% 55% 92% 83%	1 in 61 1 in 24 1 in 94 1 in 25 1 in 58	1 in 262 1 in 2301 1 in 205 1 in 301 1 in 336
CHM	Choroideremia	Finnish	90%	< 1 in 5000	< 1 in 57000
CLN5	Ceroid lipofuscinosis, neuronal, 5	Finnish	94%	1 in 100	< 1 in 1700
CLN6	Ceroid lipofuscinosis, neuronal, 6	Portuguese	80%	1 in 139	< 1 in 600

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CLN8	Ceroid lipofuscinosis, neuronal, 8	Finnish	99%	1 in 135	< 1 in 13,000
CLRN1	Retinitis pigmentosa 61	Ashkenazi Jewish Finnish	92% 95%	1 in 140 1 in 100	< 1 in 13000 1 in 1981
CNGB3	Achromatopsia 3	European Pingelapese (Micronesian)	83% 99%	1 in 123 1 in 3	< 1 in 700 < 1 in 189
CPT1A	CPT deficiency, hepatic, type IA	Hutterite	95%	1 in 16	< 1 in 300
CPT2	Carnitinepalmitoyltransferase II deficiency	General Population	>50%	Unknown	< 1 in 500
CTNS	Cystinosis, nephropathic	French Canadian General Population (US) Italian	54% 62% 17%	1 in 39 1 in 159 1 in 159	1 in 84 1 in 416 1 in 191
CTSK	Pycnodysostosis	General Population	Unknown	Rare	< 1 in 380
CYP17A1	17,20-lyase deficiency	Brazilian Canadian Mennonite and Dutch Freislander Chinese	87% 92% 32%	< 1 in 112 < 1 in 112 < 1 in 112	< 1 in 850 < 1 in 1300 < 1 in 165
CYP27A1	Cerebrotendinousxanthomatosis	Caucasian	9%	1 in 115	1 in 127
DCLRE1C	Omenn syndrome	Navajo and Apache (Athabascan-speaking)	98%	1 in 23	< 1 in 1000
DLD	Dihydrolipoamide dehydrogenase deficiency	Ashkenazi Jewish	95%	< 1 in 80	< 1 in 1500
DPYD	Dihydropyrimidine dehydrogenasedeficiency	General Population	52%	~ 1 in 51	~1 in 104
ETFA	Glutaricaciduria, type IA	European Caucasian	25%	Very rare	< 1 in 500
ETFDH	Glutaricaciduria, type IC	European Caucasian	17%	Very rare	< 1 in 500
ETHE1	Ethylmalonic encephalopathy	General Population	11%	Very rare	< 1 in 500
F11	Factor XI deficiency	Ashkenazi Jewish General Population	95% 12%	1 in 11 1 in 500	< 1 in 200 1 in 569
FANCC	Fanconi anemia, complementationgroup C	Ashkenazi Jewish	99%	1 in 89	1 in 8801

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FANCG	Fanconianemia, complementationgroup G	BrazilianJapanese	99% 65%	Very rareVery rare	< 1 in 1000 < 1 in 1000
FKTN	Cardiomyopathy, dilated, 1L	Ashkenazi Jewish	99%	1 in 144	1 in 14179
G6PC	Glycogen storagedisease Ia	Ashkenazi JewishCaucasian Chinese Hispanic Japanese Korean	99% 60% 80% <54% 90% 75%	1 in 71 1 in 159 1 in 159 1 in 159 1 in 159 1 in 159	1 in 7022 1 in 395 1 in 789 < 1 in 344 < 1 in 1577 1 in 631
GAA	Glycogen storage disease II	African American Dutch	43% 32%	1 in 60 1 in 100	1 in 104 1 in 147
GALC	Krabe disease	EuropeanCaucasian Japanese	22% 57%	1 in 159 Unknown	1 in 191 < 1 in 350
GALT	Galactosemia	Ashkenazi JewishGeneral Population	87.5% ~84%	1 in 127 1 in 87	< 1 in 1000 < 1 in 500
GBA	Gaucher disease	Ashkenazi Jewish General Population (non-Jewish)	96% 70%	1 in 15 < 1 in 100	1 in 354 < 1 in 331
GCDH	Glutaricaciduria, type I	Amish Caucasian	99% >40%	1 in 12 1 in 112	< 1 in 1000 < 1 in 187
GNE	Nonaka myopathy	Iranian Jewish Japanese Korean	99% 73% 80%	1 in 20 Unknown Unknown	< 1 in 1800 < 1 in 500 < 1 in 500
GRHPR	Hyperoxaluria, primary, type II	European Caucasian	30%	1 in 500	< 1 in 715
HADHA	Trifunctional protein deficiency	Northern European	71%	1 in 177	1 in 602
HBB	Sickle cell anemia	African American Indian Mediterranean Northern Spain (Seville)	80% >45% >75% 80%	< 1 in 8 1 in 20 1 in 7 1 in 8	1 in 38 < 1 in 35 1 in 24 1 in 75
HEXB	Sandhoff disease, infantile, juvenile, and adult forms	Argentinian Creole	97%	1 in 183	< 1 in 6000

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HGSNAT	Mucopolysaccharidosis type IIIC (Sanfilippo C)	European Caucasian	80%	< 1 in 300	< 1 in 1700
HLCS	Holocarboxylasesynthetase deficiency	Faroese General Population Japanese	Unknown 44% 42%	1 in 51 1 in 148 1 in 159	< 1 in 51 1 in 263 1 in 273
HMGCL	HMG-CoA lyase deficiency	Iberian Peninsula Saudi Arabian	84% 94%	Unknown < 1 in 50	< 1 in 500 < 1 in 800
HPS3	Hermansky-Pudlak syndrome 3	Ashkenazi Jewish	89%	1 in 235	< 1 in 2000
IDUA	Mucopolysaccharidosis Ih/s	European Caucasian General PopulationItalian Moroccan Scandinavian	35% 21% 39% 92% 62%	1 in 159 1 in 159 1 in 159 1 in 159 1 in 159	1 in 243 1 in 200 1 in 259 < 1 in 2000 1 in 416
IKBKAP	Dysautonomia, familial	Ashkenazi Jewish	>99%	1 in 30	1 in 3000
IL2RG	Combined immunodeficiency, X-linked, moderate	General Population	19%	1 in 25,000	1 in 30,000
LAMA3	Epidermolysis bullosa, generalized atrophic benign	Pakistani	99%	Unknown	< 1 in 500
LAMC2	Epidermolysisbullosa, junctional, Herlitz type	Italian	33%	Unknown	< 1 in 500
LRPPRC	Leigh syndrome, French-Canadian type	French Canadian	95%	1 in 23	< 1 in 400
MCOLN1	Mucolipidosis IV	Ashkenazi Jewish	95%	1 in 96	<1 in 1900
MEFV	Familial Mediterranean fever	Armenian Ashkenazi Jewish Mediterranean North African Jewish Turkish	69%	< 1 in 5	< 1 in 14
MKS1	Bardet-Biedl syndrome 13	European Finnish German	12% 55% 47%	1 in 188 1 in 48 1 in 184	1 in 212 1 in 106 1 in 344
MLC1	Megalencephalic leukoencephalopathy with subcortical cysts	Libyan Jewish	>99%	1 in 40	< 1 in 4000
MMAA	Methylmalonic aciduria, vitamin B12- responsive	Caucasian	45%	Unknown	< 1 in 400

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MMACHC	Methylmalonicaciduria and homocystinuria, cblC type	Chinese General Population Italian Portuguese	54% 65% 75% 91%	Very rare Very rare Very rare Very rare	< 1 in 500 < 1 in 500 < 1 in 500 < 1 in 500
MPI	Congenital disorder of glycosylation, type Ib	General Population	Unknown	Very rare	< 1 in 400
MPL	Thrombocytopenia,congenital amegakaryocytic	EuropeanCaucasian	~30%	Unknown	< 1 in 500
MPV17	Mitochondrial DNA depletion syndrome 6 (hepatocerebral type)	Navajo	99%	1 in 20	1 in 1950
MTTP	Abetalipoproteinemia	Ashkenazi Jewish	75%	1 in 131	< 1 in 500
MUT	Methylmalonic aciduria	African American European	34% 20%	Unknown Unknown	Unknown Unknown
		Caucasian Hispanic Japanese	55% 26%	Unknown Unknown	Unknown Unknown
MYO7A	Deafness	General Population Moroccan	Unknown 85%	Unknown Unknown	Unknown Unknown
NAGLU	Mucopolysaccharidosis type IIIB (Sanfilippo B)	Japanese Spanish Portuguese	42% 38%	1 in 200 1 in 187	1 in 345 1 in 300
NBN	Nijmegen breakage syndrome	Eastern European	85%	1 in 155	< 1 in 1000
NEB	Nemaline myopathy 2, autosomal recessive	Ashkenazi Jewish	99%	< 1 in 108	< 1 in 10000
NPC1	Niemann-Pick disease, type C1, D	General Population	>15%	>1 in 174	<1 in 200
NPHS1	Nephrotic syndrome, type 1	Finnish	16%	1 in 46	1 in 54
NPHS2	Nephrotic syndrome, type 2	European Israeli-Arab	< 20% 55%	Unknown Unknown	< 1 in 300 < 1 in 500
PAH	Phenylketonuria	Caucasian Irish	47% 68%	1 in 50 1 in 34	1 in 94 1 in 104
PCCA	Propionicacidemia	Japanese	15%	1 in 66	1 in 78
PCCB	Propionicacidemia	Japanese Spanish/Latin American	32% 50%	< 1 in 66 < 1 in 159	< 1 in 97 < 1 in 316
PEX1	Heimler syndrome 1	General Population	>80%	1 in 140	< 1 in 700
PEX7	Peroxisome biogenesis disorder 9B	European Caucasian	72%	< 1 in 159	< 1 in 550

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PKHD1	Polycystic kidney disease 4, with or without hepatic disease	Caucasian Finnish	>20% 75%	1 in 71 1 in 71	< 1 in 89 1 in 282
PMM2	Congenital disorder of glycosylation, type Ia	European Caucasian	53%	1 in 71	1 in 150
POLG	Mitochondrial recessive ataxia syndrome	Scandinavian	59%	1 in 100	1 in 244
POR	Antley-Bixler syndrome	European Caucasian General	40% 50% 60%	Unknown Unknown Unknown	< 1 in 500 < 1 in 500 < 1 in 500
PPT1	Ceroid lipofuscinosis, neuronal, 1	Finnish General Population (US)	98% 59%	1 in 70 < 1 in 139	< 1 in 3000 < 1 in 300
PTS	Hyperphenylalaninemia, BH4-deficient, A	Chinese	70%	1 in 180	< 1 in 600
PYGM	McArdle disease	Caucasian Japanese	>62% 71%	1 in 159 Unknown	< 1 in 400 Unknown
RAB23	Carpenter syndrome	General Population Northern European	67% 75%	< 1 in 500 < 1 in 500	< 1 in 1500 < 1 in 2000
RDH12	Leber congenital amaurosis 13	General Population	40%	1 in 500	< 1 in 800
RLBP1	Bothnia retinal dystrophy, Retinitis punctataal-bescens	Newfoundland, Northern Swedish	99% 94%	Unknown 1 in 60 (Bothnia dystrophy)	< 1 in 500 < 1 in 900
RS1	Retinoschisis	European Caucasian Finnish	35% 95%	< 1 in 2500 < 1 in 7500	< 1 in 3800 < 1 in 150,000
SGCA	Muscular dystrophy, limb-girdle, type 2D	Brazilian European Caucasian	64% 23%	1 in 250 1 in 250	1 in 694 1 in 325
SGCB	Muscular dystrophy, limb-girdle, type 2E	Amish General Population	99% (Indiana) Unknown	Unknown Unknown	< 1 in 500 < 1 in 500
SGCG	Muscular dystrophy, limb-girdle, type 2C	General Population Gypsy/Romani	Unknown 99%	~ 1 in 350 < 1 in 50	1 in 350 < 1 in 5000
SGSH	Mucopolysaccharidosis type IIIA (Sanfilippo A)	Italian	29%	1 in 126	1 in 176
SLC12A6	Agenesis of the corpus callosum with peripheral Neuropathy	French Canadian	99%	1 in 23	1 in 2200
SLC17A5	Sialic acid storage disorder, infantile	Finnish	97%	1 in 100 to 1 in 200	< 1 in 3000

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SLC25A15	Hyperornithinemia- hyperammonemia- homocitrullinemia syndrome	French Canadian	96%	1 in 20	1 in 472
SLC26A4	Deafness	European Caucasian	~20%	~1 in 58	~1 in 73
SLC37A4	Glycogen storage disease Ib	Caucasian	46%	1 in 350	< 1 in 650
SLC45A2	Albinism, oculocutaneous, type IV	Japanese	39%	1 in 146	1 in 239
SLC7A7	Lysinuric proteinintolerance	Finnish Italian Japanese	99% 44% 64%	1 in 138 < 1 in 120 1 in 120	< 1 in 10,000 < 1 in 200 1 in 330
SMPD1	Niemann-Pick disease,type A	Ashkenazi JewishGeneral Population North African Saudi Arabian	95% 20% 87% 85%	1 in 90 (TypeA) 1 in 159 (TypeB) Unknown(Type B) 1 in 100 (Type B)	1 in 1780 1 in 200 < 1 in 500 < 1 in 650
TGM1	Ichthyosis, congenital	General Population Norwegian	28% 80%	1 in 224 1 in 151	< 1 in 300 < 1 in 750
TMEM216	Joubert syndrome 2	Ashkenazi Jewish	99%	1 in 92	1 in 9122
TPP1	Ceroid lipofuscinosis,neuronal, 2	European Caucasian Newfoundland	63% 67%	1 in 139 1 in 53	< 1 in 350 1 in 159
TTPA	Ataxia with isolatedvitamin E deficiency	Italian North African	>50% >80%	1 in 268 1 in 159	< 1 in 535 <1 in 789
TYR	Albinism, oculocutaneous, typeIA	Chinese	11%	1 in 100	1 in 113
UGT1A1	Crigler-Najjar syndrome, type I	Dutch Tunisian	34% 84%	1 in 500 1 in 500	1 in 750 < 1 in 3000
USH1C	Deafness 18A	Acadian French Canadian	99% 40%	Unknown < 1 in 100	< 1 in 500 < 1 in 280
USH2A	Usher syndrome, type2A	French Canadian General Population	>55% >20%	~ 1 in 125 ~ 1 in 125	< 1 in 275 < 1 in 150
VPS13B	Cohen syndrome	Amish (Ohio)Finnish	> 99% 75%	1 in 12 1 in 120 - 1 in 160	< 1 in 1000 < 1 in 480

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WRN	Werner syndrome	Caucasian Japanese	29% 78%	1 in 224 < 1 in 71	< 1 in 315 < 1 in 315
ABCC6	Pseudoxanthoma Elasticum	European	28%	1/80 to 1/160	< 1 in 110
ALDH7A1	Pyridoxine-Dependent Epilepsy	Dutch European Caucasian	64% 33%	< 1 in 260 < 1 in 260	< 1 in 725 < 1 in 390
CHRNE	Congenital Myasthenic Syndrome, CHRNE- associated	European/Gypsy North African	>50% >44%	< 1 in 20 Unknown	< 1 in 39 < 1 in 400
CRB1	CRB1-associated Retinal Dystrophies	European Caucasian	~20%	~1 in 175	~ 1 in 220
CYP1B1	Primary CongenitalGlaucoma	CaucasianIndian Saudi Arabian Slovakian Gypsy(Rom)	19% 8% North, 17% South 10% 99%	1 in 51 < 1 in 29 1 in 26 < 1 in 9	1 in 62 < 1 in 32 1 in 28 < 1 in 800
CYP27B1	Vitamin D-dependentRickets, Type I	French Canadian	>89%	1 in 26	< 1 in 228
DNAH5	Primary Ciliary Dyskinesia, DNAH5-associated	Caucasian	15%	~1 in 120	~1 in 141
DNAI1	Primary Ciliary Dyskinesia, DNAI1-associated	CaucasianPolish	17% 33%	~ 1 in 200 ~ 1 in 200	~ 1 in 240 ~1 in 300
EIF2B5	Leukoencephalopathywith Vanishing White Matter	General Population	34%	Unknown	< 1 in 500
EYS	Retinitis Pigmentosa,EYS-associated	Moroccan Jewish	Unknown	Unknown	< 1 in 34
GP1BA	Bernard-Soulier Syndrome, Type A1	General Population	Unknown	Very rare	< 1 in 500
GP9	Bernard-Soulier Syndrome, Type C	General Population	Unknown	Very rare	< 1 in 500
GPR56	Bilateral Frontoparietal Polymicrogyria (BFPP)	General Population	Unknown	Unknown	< 1 in 500

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LDLRAP1	Familial Hypercholesterolemia, LDLRAP1 associated	Sardinian	54%	< 1 in 100	< 1 in 200
MTRR	Homocystinuria, cblE type	European	60%	Very rare	< 1 in 500
NDRG1	Charcot-Marie-Tooth Disease, Type 4D (CMT4D)	Gypsy/Romani	>99%	1 in 11	< 1 in 989
PC	Pyruvate Carboxylase Deficiency	Canadian Indian General Population	> 99% 13%	1 in 10 1 in 250	< 1 in 850 1 in 288
PEPD	Prolidase Deficiency	Druze	67%	1 in 21	1 in 62
RAPSN	Congenital Myasthenic Syndrome, RAPSN-associated	General Population	70%	Unknown	< 1 in 500
SACS	Autosomal Recessive Spastic Ataxia	Northeastern Quebec	95%	1 in 22	1 in 431
SLC25A13	Citrin Deficiency	Japanese	>30%	1 in 70	< 1 in 100
WISP3	Progressive PseudorheumatoidDysplasia (PPD)	Middle Eastern	~57%	Unknown	< 1 in 500
WNT10A	Odonto-onycho- dermal dysplasia/Schopf-Schulz-Passarge Syndrome	General Population	>36%	Unknown	< 1 in 500

Table 3: Carrier screening finding (Variant Details) of the couple is mentioned in the below table.

Disease	Male	Female
Acyl-CoA dehydrogenase, medium chain, deficiency of (OMIM: 201450)	CARRIER Gene: ACADM Variant Location: chr1:76226846: A: G c.997A>G p.Lys333Glu Classification: Pathogenic	CARRIER Gene: ACADM Variant Location: chr1:76226846: A: G c.997A>G p.Lys333Glu Classification: Pathogenic
Polycystic kidney disease 4, with or without hepatic disease (OMIM: 263200)	CARRIER Gene: PKHD1 Variant Location: chr6:51934301:C: G c.732G>C p.Trp244Cys Classification: VUS	CARRIER Gene: PKHD1 Variant Location: chr6:51934301:C: G c.732G>C p.Trp244Cys Classification: VUS

Both the patients (Husband and Wife) are the carriers of same condition which follow autosomal recessive mode. Combining these results and keeping in view the clinical history, clinician correlated the findings. Genetic counselling has been given to the couple to discuss the potential clinical or reproductive implications of this carrier screening result.

To validate the couple carrier screening results, we have also done Sanger Sequencing (Figure 1 c, d, e, f).

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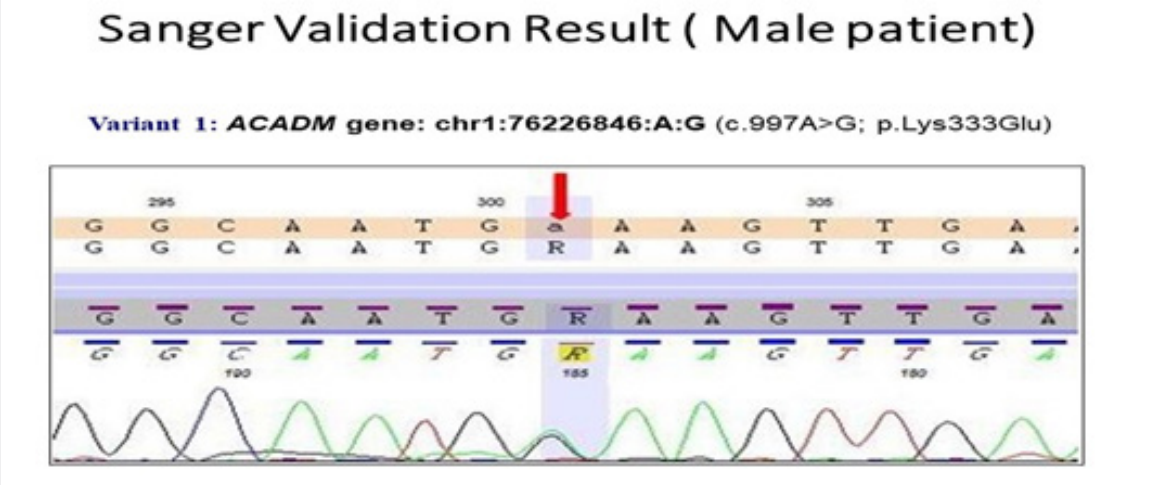

Figure 1c: Sanger Validation Result (Male patient).

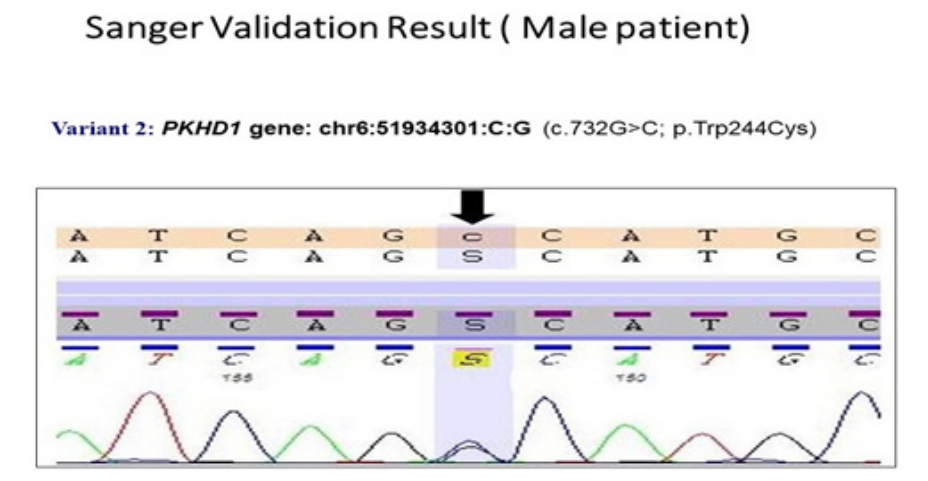

Figure 1d: Sanger Validation Result (Male patient).

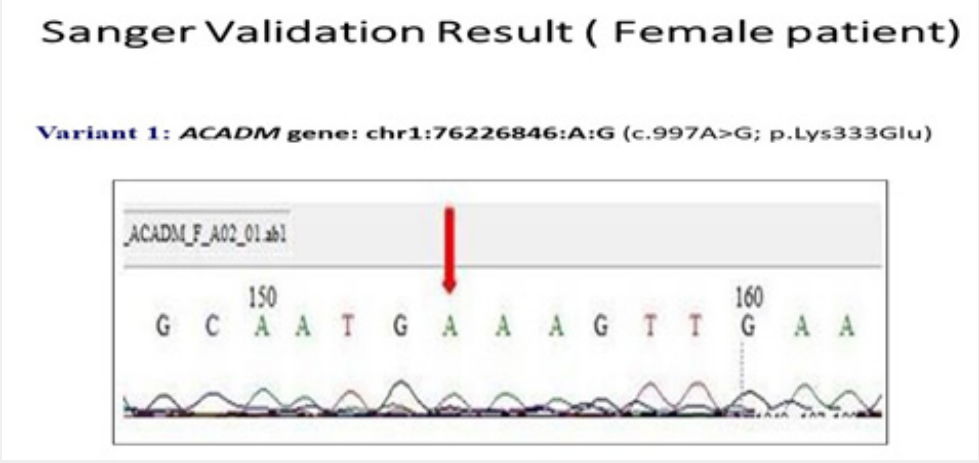

Figure 1e: Sanger Validation Result (Female patient).

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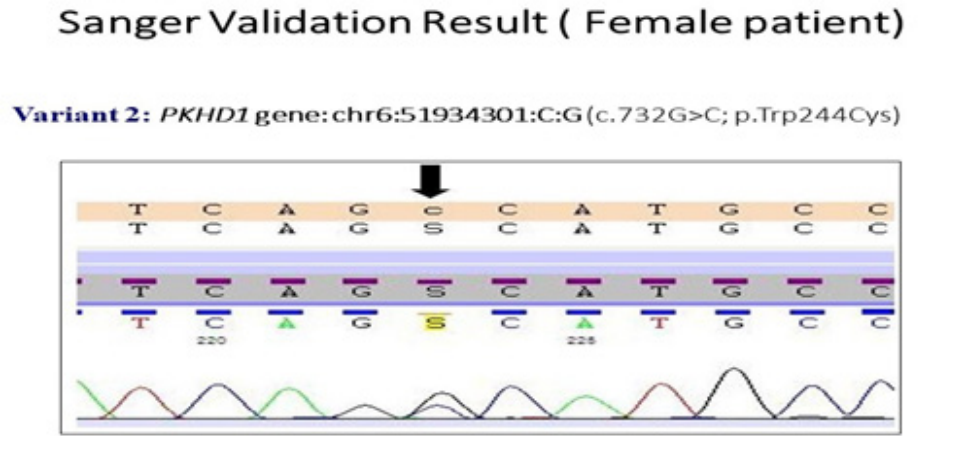

Figure 1f: Sanger Validation Result (Female patient).

Genetic testing is based upon the information, developments and testing techniques that are known today. Forthcoming research may reveal the changes in the interpretation of previously obtained genetic testing results. Certain genes may not be covered completely, and few mutations may be missed.

We sequence coding exons for each given transcript, plus ~10 bp of flanking non -coding DNA for each exon. Unless specifically indicated, test reports contain no information on about other portions of the gene, such as regulatory domains, deep intronic regions, uncharacterized alternative exons, chromosomal rearrangements, repeat expansions, epigenetic effects, and mitochondrial genome variants. Also, this analysis cannot detect single and multi-exon deletions and duplications.

A negative finding does not rule out the genetic diagnosis. These results should be used in the context of the available clinical findings and should not be used as the sole basis for treatment. As with all medical laboratories testing, there is a small chance that the laboratory could report inaccurate information. For example, the laboratory could report that a given genotype is present when in fact it is not. Any kind of laboratory error may lead to incorrect decisions regarding medical treatment and/or diet and fitness recommendations.

Discussion

Clinical Exome sequencing has transformed the molecular diagnosis of postnatal genetic diseases, but so far it has been used less often to study the reproductive related disorders. Here we provided an overview and the outcomes of the genomic sequencing for detecting the causes of RPL in a couple who suffering from recurrent pregnancy losses. This study includes couple carrier screening by clinical exome sequencing to look for the pathogenic sequence changes in the whole exome or in a preselected list of genes measured to be very important for the early embryonic development and the maintenance of pregnancy.

We developed an approach to diagnose rare autosomal recessive lethal disorders in a consanguineous couple with a history of multiple affected fetuses. The aim was to obtain a molecular genetic diagnosis and enable prenatal testing in the future pregnancies. The result showed that the couple detected with the carrier status of two variants in two different genes. These are ACADM and PKHD1 gene's variants causing a severe form of fetal Acyl-CoA dehydrogenase, medium chain, deficiency, and Polycystic kidney disease 4, with or without hepatic disease respectively.

These two genes (ACADM & PKDH1) different variants studies have already been reported in the different populations and ethnic groups [35-39]. For the gene ACADM the variants have been reported in European, Caucasian and the Saudi Arabian population with 80% to 95% detection rate. And the carrier frequency rate of this gene is 1 out of 50 cases (Table 2). The ACADM gene delivers the directions for the making an enzyme called medium-chain Acyl-CoA dehydrogenase (MCAD). This enzyme's function is inside the mitochondria (energy-producing center in cells). MCAD is very important for the fatty acid oxidation, which is the multistep process that breaks down (metabolizes) fats and converts them into the energy.

This MCAD is mandatory to metabolize a group of fats named the medium-chain fatty acids. These fatty acids are found in foods and body fat and are produced when larger fatty acids are metabolized. Fatty acids are a major source of energy for the heart and muscles. During periods without food (fasting), fatty acids are also an important energy source for the liver and other tissues.

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For the gene PKDH1 the variant has been reported mostly in the Caucasian and finish population with 20% to 75% detection rate. And the carrier frequency rate of this gene is 1 out of 71 case (Table 2). Polycystic kidney disease (PKHD1 related) causes cysts (fluid-filled sacs) to develop on the kidneys and restrict their ability to filter waste from the blood. PKD causes enlarged kidneys, which can lead to kidney failure. Cysts may also develop in other organs, including the liver, and other symptoms include underdeveloped lungs, heart valve problems and high blood pressure.

Symptoms are usually present from birth, though some people are more mildly affected than others. Treatment through dialysis and kidney transplant can reduce the seriousness of the condition. We conclude that these variants are highly responsible for the disease causing. Diagnosing the lethal foetal disorders has previously been very difficult because of the presence of the large number of potential genes, the phenotypic variability associated with many known genetic causes and the challenges of defining phenotype and pathology in a mid-gestation foetus.

Sequencing of the parental samples overcomes issues of limited quality or the quantity of foetal samples. A genetic diagnosis is must to confirms or identify the risk for future offspring and to get permission in the early prenatal diagnosis or preimplantation genetic diagnosis in future pregnancies.

This in turn reduces the anxiety associated with the waiting until mid-pregnancy for an ultrasound diagnosis and avoids the added suffering of a late cessation of the pregnancy period. This strategy is also valid to those disorders not detectable by the ultrasound diagnosis where late foetal demise or a neonatal death could not otherwise be predicted.

Conclusion

RPL is a condition which has both the psychological and the economical adverse effects on both for the couples and scientific experts dealing with these patients. Emphasizing the real reason behind these cases will be beneficial for both patients and the experts. This is very important to emphasize that the consanguineous marriages are so much responsible for these types of genetic disorders.

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