STUDENT ID: - 21476600.

Full Name: - Aniket Ashok Kuhikar.

Part 1

A. Critically discuss the types and significance key information collected from the family as part of the history taking and discuss the significance of each piece of information.

Answer (A). Roger who is 15 years old boy was diagnosed by his genomics counsellor that he has Oculomotor apraxia. Oculomotor apraxia is a disorder that involves brain, especially the frontal lobe (mediocre parietal lobule) of the left side of the equator of the cerebrum. The symptoms of Oculomotor apraxia were seen from his childhood as he was not able to walk independently until he was 3 years old. People with this condition have problem in the eye movements they cannot move eye horizontally and quickly. Roger's father who died due to pancreatic cancer at the age of 47. Roger's mother (Lousia) who is 48years old moved to Utah from UK after his father's death. Louisa and Roger's sister (Emiley) who is 26 are both healthy. Emiley who is married to her maternal uncle's son has 2 daughters, first-born is 22 months old and the second-born named Lily is 6 months old is Polydactyly. Polydactyly is a little, raised piece of delicate tissue, containing no bones called a nubbin.

B. Draw the family tree (Pedigree) and critically discuss its significance.

Answer. (B)

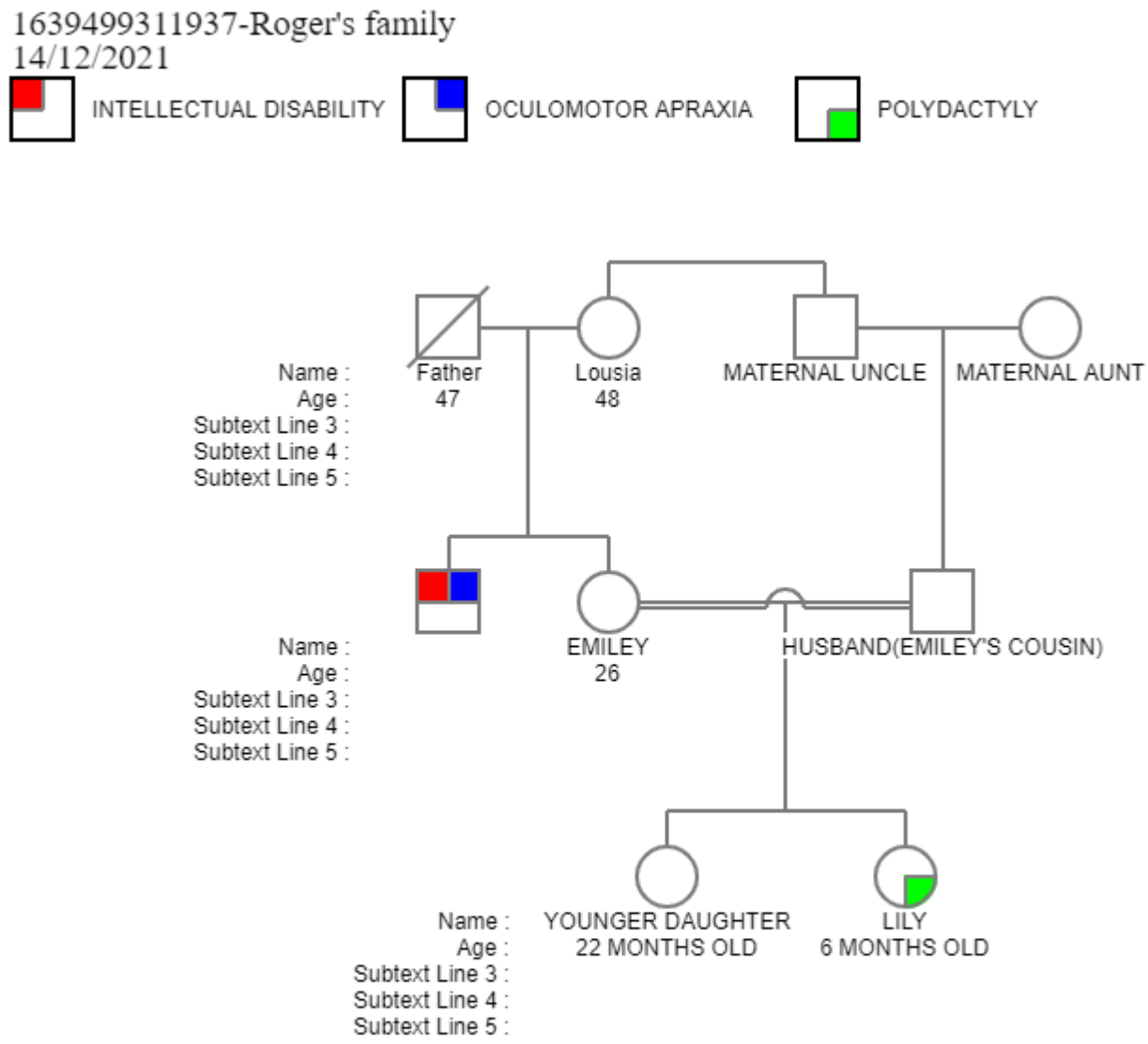

Figure 1: The family tree of Roger.

The figure depicts the pedigree of Roger's family. Pedigree analysis helps to get information about with distinguishing patients and families who have an expanded danger for hereditary problems. The proband Roger has Oculomotor apraxia (OMA). OMA is autosomal recessive disorder. Roger's father died from a Pancreatic cancer. There are two large classification of pancreatic cancer which are Exocrine pancreatic cancer, which as adenocarcinoma in it and Neuroendocrine pancreatic cancer. However, they have several cancer types which can vary from symptoms to prognosis. Moreover, this pancreatic cancer can be familial pancreatic cancer passed down from the hereditary.

	Gene*	Chromosome	Risk ratio
Familial breast and ovarian cancer	*BRCA2*	13	3·5–10
Familial atypical multiple mole melanoma syndrome	*CDKN2A (P16)*	9	9–47
Peutz-Jeghers syndrome	*STK11 (LKB1)*	19	132
Hereditary pancreatitis	*PRSS1; SPINK1*	7; 5	50–80
Hereditary non-polyposis colorectal cancer (Lynch syndrome)	Multiple	Multiple	9
Familial pancreatic cancer	*PALB2*	16	6
Familial pancreatic cancer (monoallelic); ataxia-telangiectasia (biallelic)	*ATM*	11	Unknown

Figure 2: - Inherited disorder with increased risk of pancreatic ductal adenocarcinoma.

The table depicts the morphology of pancreatic ductal adenocarcinoma. The patient with the familial pancreatic cancer associates with the germline mutations in PALB2, as likely whose protein interacts with BRCA2. Furthermore, heterozygous mutations in ATM can also cause the subset for the familial pancreatic cancer. Apart from family history the patients with pancreatic cancer can also suffer due to excessive smoking.

Louisa, Emiley and Emileys's first born they are healthy but Lily is polydactyly. There are three major types of polydactyly.

1. Ulnar or postaxial polydactyly: - When finger grows on the ulnar side of hand, besides the little finger. Furthermore, the extra finger is not fully developed with the end of phalanx with a nail which is connected to hand with a small skin pedicle.
2. Radial polydactyly: - When a finger grows on the radial side of the hand, besides the thumb. Radial. Radial polydactyly varies from the incomplete growth of duplicate thumb including the first metacarpal.

3. Central polydactyly: - In very few cases, when the finger is attached to the middle or the index finger. Moreover, the index finger is most affected.

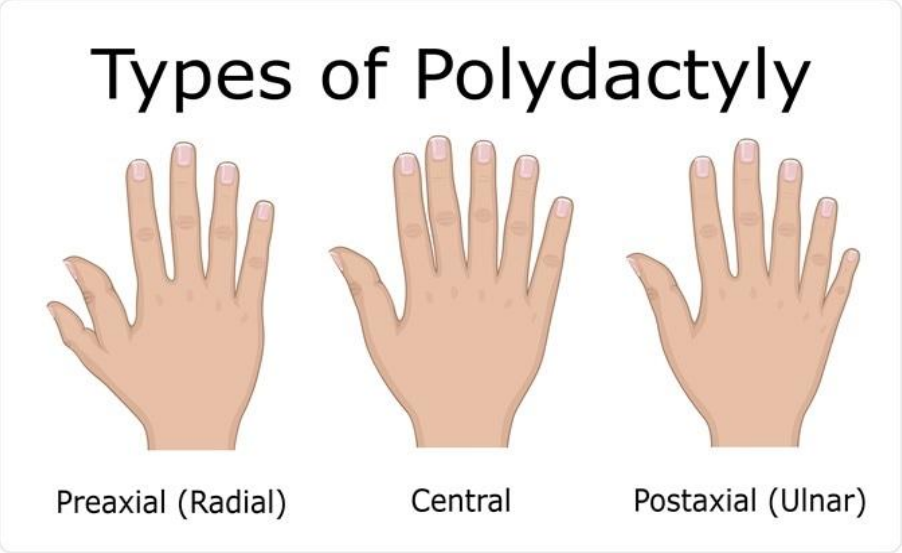

Figure 3: - Types of Polydactyly. ©News Medical Life Science

The polydactyly can be passed down to Lily from one of her parents, if that's the case than it is familial polydactyly. However, if polydactyly is not passed down from parents it can occur due to the change in the baby's gene while in the womb.

C. State and critically explain the likely mode of inheritance of Roger's condition.

Answer (C). Roger possesses Autosomal recessive disorder. Roger's father died due to the pancreatic cancer. Oculomotor apraxia is caused by recessive mutations in *APTX* coding for Aprataxin on chromosome 9p13.3 (Moreira et al., 2001). However, this protein involves in the mending the fragments of DNA single strand. Moreover, it's a key player in detection of DNA single strand fragments. Roger is suffering from deficiency of coenzyme Q10, which is linked to the chromosome 9p13.

D. Critically explain why genome sequencing might be appropriate in this situation.

Answer (D). Genome sequencing is important in this case because I believe if the pancreatic cancer is from hereditary(familial) then Roger's father is Homozygous Dominant with [AA] but if the pancreatic cancer is not familial and is due excessive smoking or some other reason than

his genotype will be Homozygous Recessive with [aa]. Moreover, if roger's father and mother had Consanguineous marriage than the roger's disorder is passed down from his parents.

In addition, If the pancreatic cancer is familial than there are 50% chances where roger is affected to the FPC linked genes like *BRCA1*, *BRCA2*, *PALB2*, *CDKN2A*, and *ATM*(This are genes which are linked to FPC know as Germline mutations)

Familial pancreatic cancer (2 or more first-degree relatives)	9 – 32	Unknown

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Figure 4: - Risk for Pancreatic cancer.

By performing the genome sequencing we slow down or we can stop the outcomes. We can also look out for the mutations which can be more beneficial for the roger. We could have more treatment options for roger. Furthermore, we can also predict about the diseases. The importance of the genome sequencing is not only to the induvial undertaking to the process but for the family members and the direct descendants too.

Part 2

• Variant 1 Location (GRCh37): chr12:88483128C>T

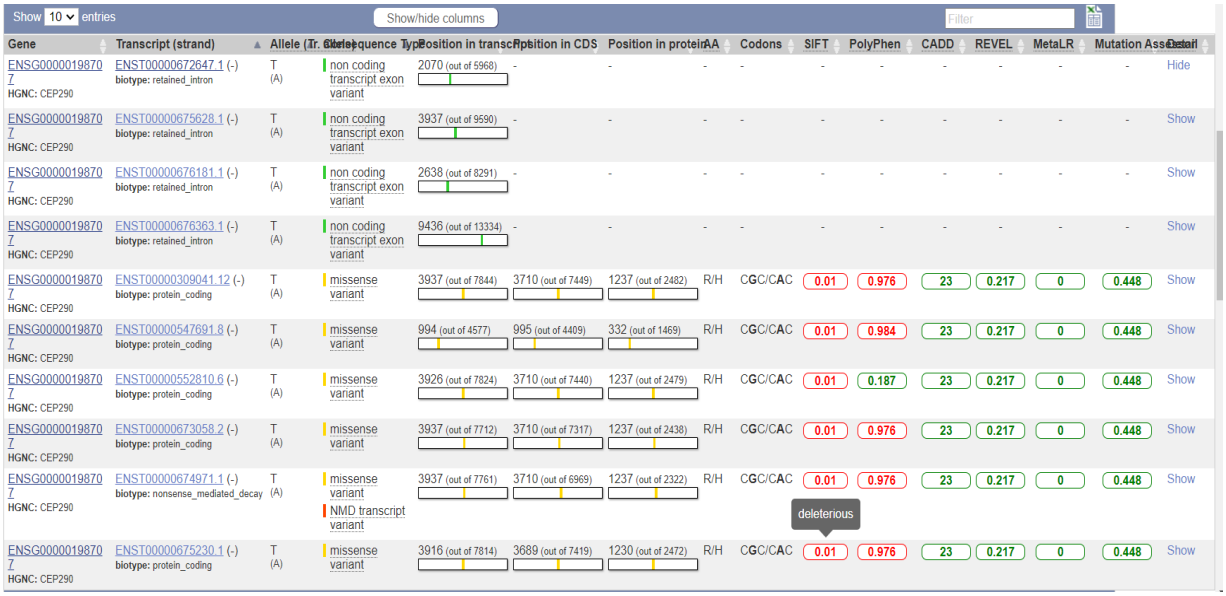
Location (GRCh38): chr12:88089351C>T

Gene: CEP290

Variant: homozygous missense variant

A. Molecular biological consequence of the variants

Answer (A). Centrosomal protein of 290kDa also known as CEP290. CEP290 they are Autosomal recessive. CEP290, a significant TZ part, is developmentally rationed from unicellular Chlamydomonas to people and is perhaps the most captivating cilia gene. CEP290 are strongly expressed in the placenta and they are weaker in brain.



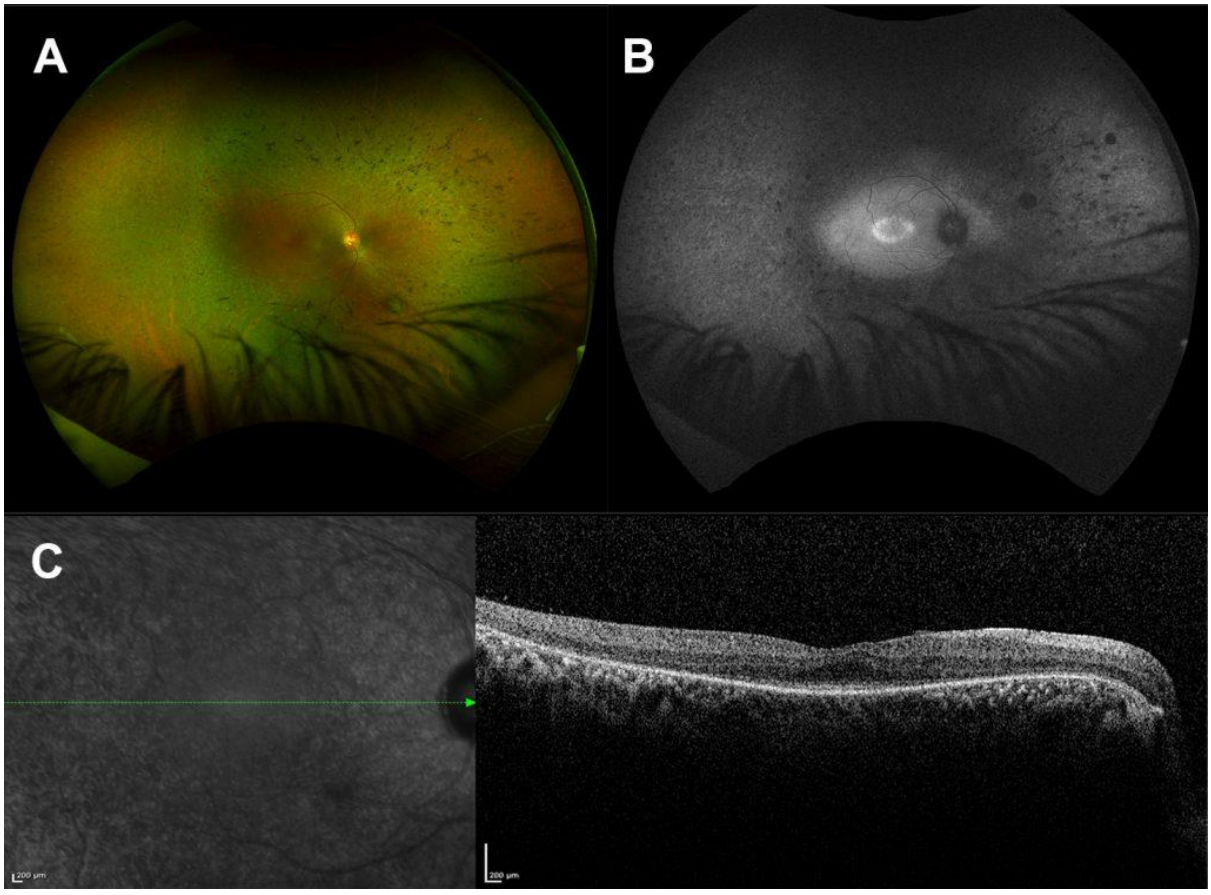
Gene	Transcript (strand)	Allele	Consequence	Position in transcript	Position in CDS	Position in protein	AA	Codons	SIFT	PolyPhen	CADD	REVEL	MetaLR	Mutation Assessor	Detail
ENSG00000198707 HGNC: CEP290	ENST00000672647.1 (-) biotype: retained_intron	T (A)	non coding transcript exon variant	2070 (out of 5968)	-	-	-	-	-	-	-	-	-	-	Hide
ENSG00000198707 HGNC: CEP290	ENST00000675628.1 (-) biotype: retained_intron	T (A)	non coding transcript exon variant	3937 (out of 9590)	-	-	-	-	-	-	-	-	-	-	Show
ENSG00000198707 HGNC: CEP290	ENST00000676181.1 (-) biotype: retained_intron	T (A)	non coding transcript exon variant	2638 (out of 8291)	-	-	-	-	-	-	-	-	-	-	Show
ENSG00000198707 HGNC: CEP290	ENST00000676363.1 (-) biotype: retained_intron	T (A)	non coding transcript exon variant	9436 (out of 13334)	-	-	-	-	-	-	-	-	-	-	Show
ENSG00000198707 HGNC: CEP290	ENST00000309041.12 (-) biotype: protein_coding	T (A)	missense variant	3937 (out of 7844)	3710 (out of 7449)	1237 (out of 2482)	R/H	CGC/CAC	0.01	0.976	23	0.217	0	0.448	Show
ENSG00000198707 HGNC: CEP290	ENST00000547691.8 (-) biotype: protein_coding	T (A)	missense variant	994 (out of 4577)	995 (out of 4409)	332 (out of 1469)	R/H	CGC/CAC	0.01	0.984	23	0.217	0	0.448	Show
ENSG00000198707 HGNC: CEP290	ENST00000552810.6 (-) biotype: protein_coding	T (A)	missense variant	3926 (out of 7824)	3710 (out of 7440)	1237 (out of 2479)	R/H	CGC/CAC	0.01	0.187	23	0.217	0	0.448	Show
ENSG00000198707 HGNC: CEP290	ENST00000673058.2 (-) biotype: protein_coding	T (A)	missense variant	3937 (out of 7712)	3710 (out of 7317)	1237 (out of 2438)	R/H	CGC/CAC	0.01	0.976	23	0.217	0	0.448	Show
ENSG00000198707 HGNC: CEP290	ENST00000674971.1 (-) biotype: nonsense_mediated_decay	T (A)	missense variant, NMD transcript variant	3937 (out of 7761)	3710 (out of 6969)	1237 (out of 2322)	R/H	CGC/CAC	0.01 deleterious	0.976	23	0.217	0	0.448	Show
ENSG00000198707 HGNC: CEP290	ENST00000675230.1 (-) biotype: protein_coding	T (A)	missense variant	3916 (out of 7814)	3689 (out of 7419)	1230 (out of 2472)	R/H	CGC/CAC	0.01	0.976	23	0.217	0	0.448	Show

©NCBI

Figure 5: - This are the 10 gene entries of gene and regulations.

Figure shows the consequences of gene and transcript. The most acute effect is by the missense variant. The gene ENSG00000198707 has 34 transcripts, the non coding transcript exon variant is located on 2070th position out of 5968. In addition, the gene ENSG00000198707 which is located on the reverse transcript strand (ENST00000309041.12 (-)) possesses a missense variant. The variant position is on 3937th whereas the transcript length is 7844. The variant position in CDS is on 3710th while the length of CDS is 7449. Meanwhile the position of variant in protein is on 1237th with the length of 2482. The location of the codons is highlighted as follows CGC/CAC. Moreover, the substitution of an amino acid is affecting the protein function by 0.01(SIFT). Meanwhile the mutation arising in this gene is likely to be very less which is 0.448.

Overall, the mutation chances are very low. The mutation chances are not more than 0.448.The most common variant is missense variant.



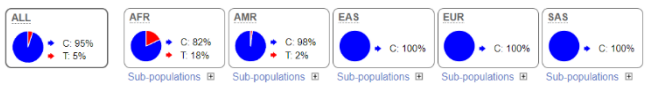
©Gene Vision

Figure6: - Multimodal Imaging

Figure 6 depicts Multimodal imaging of a 34-year elderly person with CEP290-LCA. Shading fundus photo (A) shows some bone-spicule RPE hyperpigmentation and retinal decay in the mid-outskirts. FAF (B) shows a focal hyper-AF ring and the back shaft has ordinary AF. There is hypo-AF with discrete spaces of RPE decay in the outskirts. OCT of the macula (C) shows saved external retinal layers midway and decay with expanding unusualness.

B. Allele frequency

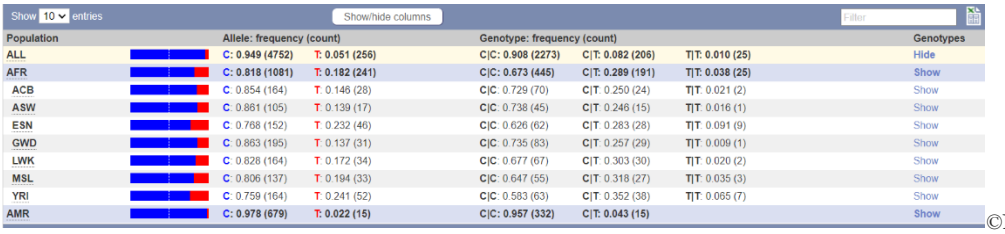
Answer(B). This are some countries where the allele frequency of rs7307793 is likely to be more than other countries. However, some alleles are passed down due to hereditary and some by mutations.



©NCBI

Figure 7: - The allele frequency.

As the figure says the percentage of Cytosine is 100% in East Asians, Europeans, South Asians. The percentage of thymine is very low comparatively to the Cytosine. However, thymine is only 2% in Americans and 18% in Africans.



Show 10 entries | Show/hide columns | Filter

Population	Allele: frequency (count)		Genotype: frequency (count)			Genotypes
ALL	C: 0.949 (4752)	T: 0.051 (256)	C|C: 0.908 (2273)	C|T: 0.082 (206)	T|T: 0.010 (25)	Hide
AFR	C: 0.818 (1081)	T: 0.182 (241)	C|C: 0.673 (445)	C|T: 0.289 (191)	T|T: 0.038 (25)	Show
ACB	C: 0.854 (164)	T: 0.146 (28)	C|C: 0.729 (70)	C|T: 0.250 (24)	T|T: 0.021 (2)	Show
ASW	C: 0.861 (105)	T: 0.139 (17)	C|C: 0.738 (45)	C|T: 0.246 (15)	T|T: 0.016 (1)	Show
ESN	C: 0.768 (152)	T: 0.232 (46)	C|C: 0.626 (62)	C|T: 0.283 (28)	T|T: 0.091 (9)	Show
GWD	C: 0.863 (195)	T: 0.137 (31)	C|C: 0.735 (83)	C|T: 0.257 (29)	T|T: 0.009 (1)	Show
LWK	C: 0.828 (164)	T: 0.172 (34)	C|C: 0.677 (67)	C|T: 0.303 (30)	T|T: 0.020 (2)	Show
MSL	C: 0.806 (137)	T: 0.194 (33)	C|C: 0.647 (55)	C|T: 0.318 (27)	T|T: 0.035 (3)	Show
YRI	C: 0.759 (164)	T: 0.241 (52)	C|C: 0.583 (63)	C|T: 0.352 (38)	T|T: 0.065 (7)	Show
AMR	C: 0.978 (679)	T: 0.022 (15)	C|C: 0.957 (332)	C|T: 0.043 (15)		Show

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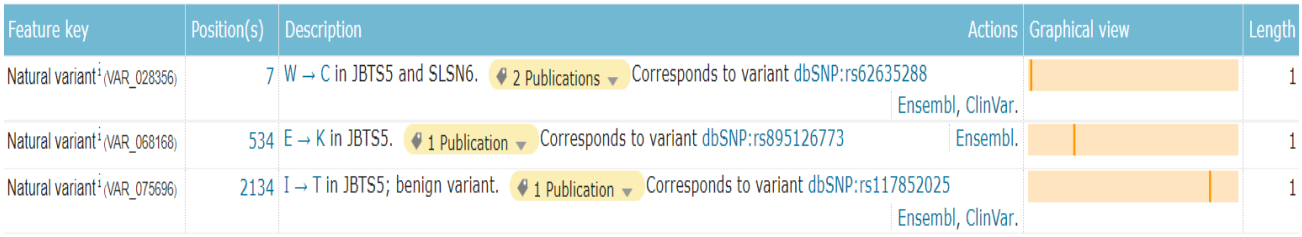
Figure 8: - The allele count of population.

The highest amount of cytosine is in Americans which 00978(679). The maximum amount of thymine is found Yoruba which is in Nigeria which is 0.241(52). However, the allele count of first 10 entries is given in the Figure 8.

C. Likely pathogenicity

Answer(C). Mutations in CEP290, may lead to many diseases in future like LCA/EOSRD: Leber congenital amaurosis 10, which can affect his retina. Joubert syndrome 5 also known JBTS5 which can cause brain abnormalities called the MTS (Molar tooth sign). Senior-Loken syndrome 6, it causes Nephronophthisis, as roger as disorder which is directly connected to his eye movements it is more likely for him to in future to get affected .



Feature key	Position(s)	Description	Actions	Graphical view	Length
Natural variant[1] (VAR_028356)	7	W → C in JBTS5 and SLSN6. 2 Publications Corresponds to variant dbSNP:rs62635288	Ensembl, ClinVar.		1
Natural variant[1] (VAR_068168)	534	E → K in JBTS5. 1 Publication Corresponds to variant dbSNP:rs895126773	Ensembl.		1
Natural variant[1] (VAR_075696)	2134	I → T in JBTS5; benign variant. 1 Publication Corresponds to variant dbSNP:rs117852025	Ensembl, ClinVar.		1

©UNIPROT ***Figure 9: - Natural variants that take place in CEP290***

The table shows the mutations occur in the natural variants. The change in the residue is due to the Tryptophan (W) to Cytosine (C) at position 7 (W7C, p.Trp7Cys). The place of the variation is 7 which is probable pathogenic. The protein sequence length is 2479 and the location on the sequence is as follow [MPPNIN W KEIMKVDPDDLPRQEELADN]

(D). Diagnosis and relevance to Roger's phenotypes

Answer(D). Changes in CEP290 might cause a wide range of clinically and hereditarily heterogeneous issues, each portrayed by an alternate mix of basically neurological, renal and visual elements. Changes in CEP290 might cause a wide range of clinically and hereditarily heterogeneous issues, each portrayed by an alternate blend of essentially neurological, renal and visual elements. Beneath, a concise presentation is given for every one of these autosomal latent problems, along with the commitment of CEP290.

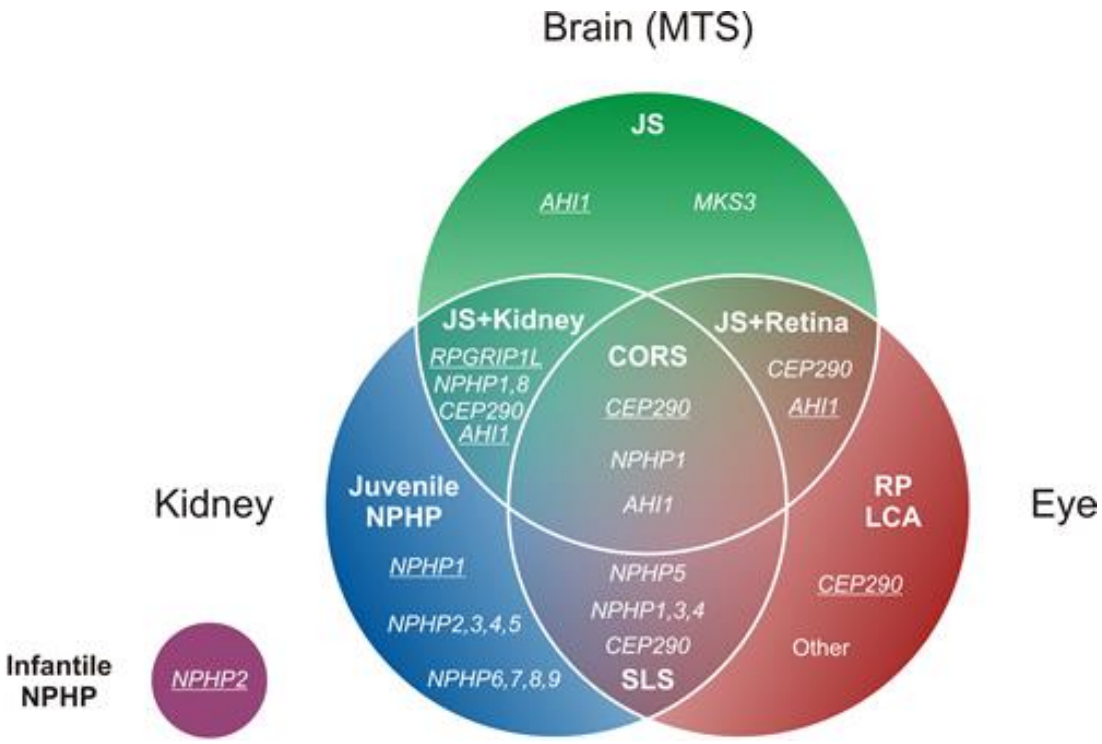


Figure 10: - Mutations caused by CEP290.

Overall, the mutations in CEP290, because phenotypes are neurological, renal and visual elements. The coloured circle represents the Joubert Syndrome, Nephronophthisis and Leber congenital amaurosis. The circle where they intersect shows the multiorgan phenotypes of JS plus kidney, retina, cerebello-oculo-renal syndrome(CORS) and Senior-Loken syndrome(SLS).

These aggregates except for Leber inherent amaurosis, are predominantly brought about by changes in qualities communicated in the cilia. The broad presence of cilia all through the entire body may clarify the wide scope of aggregates related with transformations in qualities encoding ciliary proteins. To be particular, the majority of these ciliopathies show a clinical cross-over which is apparently because of the correlative components of the ciliary proteins that expect a section in the disease cycle.

(E). Ethical implications for family members.

Answer(E). Hereditary science has progressed to the stage that its ability to improve or lessen the personal satisfaction is huge. Issues encompassing testing will persistently develop as science and innovation progresses work on the capacity to identify and treat hereditary diseases. A suitable dread of the abuse of hereditary data serves to give alert as society strongly accepts new advances. As science keeps on expanding our capacity to distinguish and treat hereditary sicknesses, family members should remain ever watchful in securing individual privileges and opportunities. The discussion encompassing hereditary danger exposure will be discussed into the prospects as society endeavours to set up moral rules for the execution of hereditary and innovative advances.

(F). Further testing or treatment implications for Roger and

other members of the family.

Answer(F). There some implications family members should keep in mind is as follows,

Data and informed assent

The option to be tried or not

The freedoms of others

Classification and security

Hazard of segregation

Outcomes of pre-birth determination.

• Variant 2 Location (GRCh37): chr5:37167148C>T

Location (GRCh38): chr5:37167046C>T

Gene: C5ORF42

Variant: homozygous splice donor variant

A. Molecular biological consequence of the variants

Answer(A). The protein C5ORF42, a splice donor variant which can also be called Ciliogenesis and planar polarity effector 1, which comes under the gene name CPLANE1.

Gene and Transcript consequences

Show/hide columns

Gene	Transcript (strand)	Allele (Tr. allele)	Consequence Type	Position in transcript	Position in CDS	Position in protein	AA	Codons	Detail
ENSG00000197603 HGNC: CPLANE1	ENST00000425232.7 (-) biotype: nonsense_mediated_decay	T (A)	downstream gene variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000508244.5 (-) biotype: protein_coding	T (A)	splice donor variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000509849.5 (-) biotype: nonsense_mediated_decay	T (A)	splice donor variant NMD transcript variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000510830.2 (-) biotype: retained_intron	T (A)	upstream gene variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000511210.5 (-) biotype: processed_transcript	T (A)	upstream gene variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000511781.1 (-) biotype: retained_intron	T (A)	downstream gene variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000514429.5 (-) biotype: protein_coding	T (A)	splice donor variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000651892.2 (-) biotype: protein_coding	T (A)	splice donor variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000675149.1 (-) biotype: retained_intron	T (A)	splice donor variant non coding transcript variant	-	-	-	-	-	Show
ENSG00000197603 HGNC: CPLANE1	ENST00000676304.1 (-) biotype: retained_intron	T (A)	downstream gene variant	-	-	-	-	-	Show

©ENSEMBLE

Figure 11: - Gene and transcript consequences.

The figure 11 depicts the consequences of genes and transcripts in the genes. the consequence types of the each are provided throughout. The gene under the name ENSG00000197603 has the reverse transcript strand with the genotype: - nonsense mediated decay. Even if it reduces nonsense codons, roger is likely to be affected by it due to various deleterious or dominant mutations which can lead to other diseases. The mutation in the gene is due to the downstream gene variant. However, this gene ENSG00000197603 which has the reverse transcript strand too but the genotype is different here which is retrained intron. Intron retention instead of exon skipping can result when a mutation of a splice donor site is located in a small intron such that the combination of the intron and the flanking upstream and downstream exon is regarded as an acceptable exon (Stover et al., 1993). Furthermore, the consequence type is the splice donor variant and the non- coding variant.

Overall, Splice donor variant and the downstream variant is the most common variants among the genes here.

B. Allele Frequency.

Answer(B).

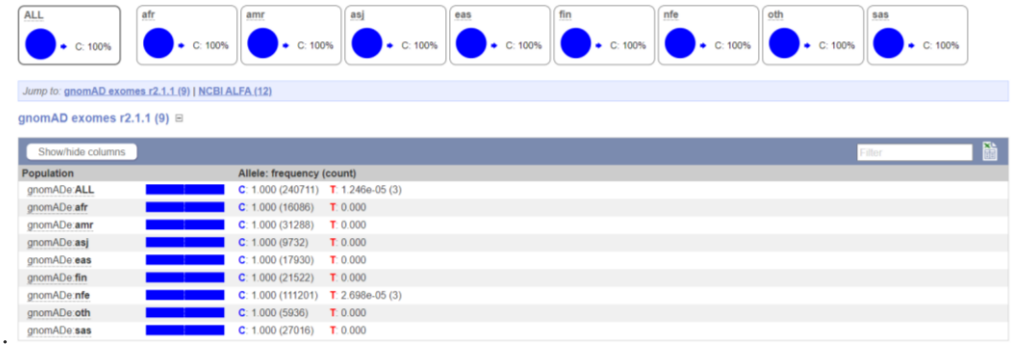


Figure 12: - Allele frequency.

Figure depicts the allele frequencies of the gene. The Genome Aggregation Database shows that the percentage of Cytosine is higher than the Thymine. Meanwhile Thymine is only found in Non-finnish Europeans. This shows that the Africans, Europeans, ..., etc Possesses the same genetic locus but Nigeria is different as it differentiates.

(C). Likely pathogenicity.

Answer(C). C5ORF42 can lead to many diseases such as Joubert syndrome (JBTS17). Moreover, this disorder also represents oculomotor apraxia. This variant is found on position 1336 while the protein length is 3197 and is a likely pathogenic type of variant. Moreover, the location on the sequence is [CMIEHCLSAVEWAYRMLPFS R FFNMEELIQDIILSLIGELP]. Orofacidigital syndrome 6 (OFD6), affects the oral cavity, face and is also associated with the phenotypic abnormalities. The diseases occur due to the residue change from Serine(S) to Leucine(L) at position 1127, which is pathogenic variant. In addition, the location of the sequence is [LFGSVQEVLKASVMADADIL S ETFQLLIDSAKDFSKRLWGL].

D. Diagnosis and relevance to Roger's phenotypes

Answer(D).

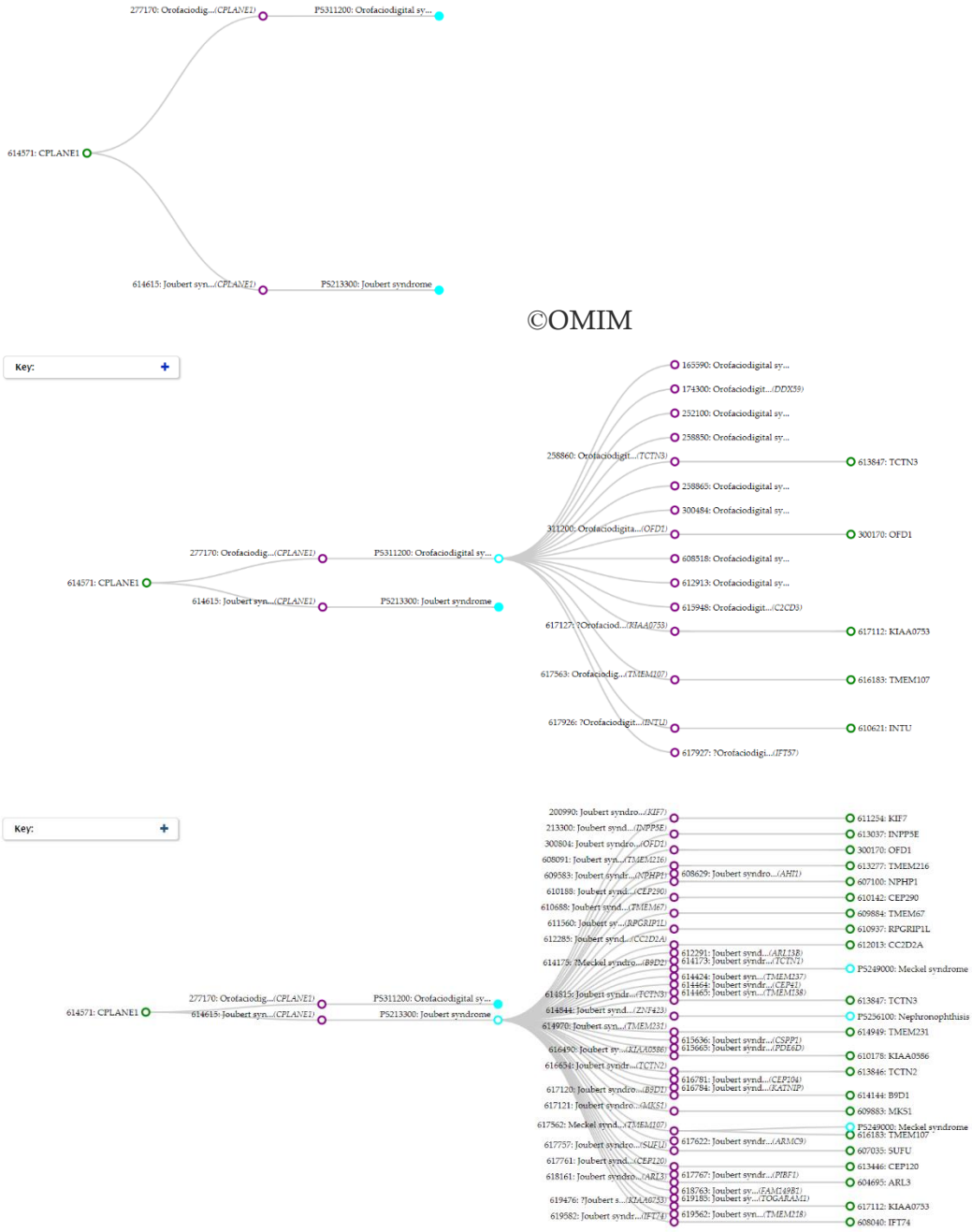


Figure 13: - The graphical representation associated with the C5ORF42.

The figure Shows the phenotypic relationships with the protein C5ORF42.

Furthermore, JBTS17 is a significant quality changed in ciliopathies, for example, Joubert disorder and oral–facial–advanced condition type VI. Most patients with loss of capacity transformations in JBTS17 display cerebellar vermis hypoplasia and brainstem mutation. A couple of patients with JBTS17 changes show microcephaly and uncommon gyration. Likewise, the OFD6 is an incredibly exceptional subtype of Joubert condition and related issues (JSRD, see

this term) described by the neurological elements of JS related with orofacial peculiarities and frequently polydactyly.

(E). Ethical implications for family members.

Answer(E). Issues looked by guardians of persistently sick kids incorporate protection inclusion and reprieve help. The physical, enthusiastic, and mental weights of really focusing on people with exceptional requirements frequently block parental business. Government-supported protection programs, like Medicaid, are regularly the main decision for persistently sick and unique necessities kids and grown-ups. Strangely, numerous strength medical services suppliers don't take an interest in Medicaid programs, further restricting access. PCPs can be exceptionally viable in perceiving psychosocial issues influencing a family, making fitting references, and giving data on accessible assets.

(F) Further testing or treatment implications for Roger and other members of the family.

Answer(F). Pre-birth assessment of pregnancies that are of expanded danger for JS and JSRD can be assessed for AHI1-, CEP290-, TMEM67-, NPHP1-, and CC2DA-related JSRD by means of amniocentesis or chorionic villus testing. Notwithstanding, all together for this testing to be of worth, the infection causing alleles of the impacted relative must be distinguished. Sequential ultrasounds might be helpful in distinguishing abnormalities beginning at 11-12 weeks development. Fetal X-ray has been utilized to analyse some back fossa irregularities and the exemplary indicative MTS.

• Variant 3 Location (GRCh37):

chr13:32945142_32945143delAG Location

(GRCh38): chr13:32371005_32371006delAG

Gene: BRCA2

Variant: heterozygous 2 base pair deletion

A. Molecular biological consequence of the variants

Answer(A). BRCA2 is a Breast cancer type 2 susceptibility protein, involving in the process of break, repair or homologous recombination of double-stranded DNA.

Gene	Transcript (strand)	Allele (Tr. allele)	Consequence Type	Position in transcript	Position in CDS	Position in protein	AA	Codons	Detail
LRG_293 HGNC: BRCA2	LRG_293t1.1 (+) biotype: LRG_gene	AG (AG)	frameshift variant	8760-8765 (out of 11386)	8533-8538 (out of 10257)	2845-2846 (out of 3418)	RE/X	AGAGAG/AG	Show
LRG_293 HGNC: BRCA2	LRG_293t1.1 (+) biotype: LRG_gene	AGAG (AGAG)	frameshift variant	8760-8765 (out of 11386)	8533-8538 (out of 10257)	2845-2846 (out of 3418)	RE/RX	AGAGAG/AGAG	Show
ENSG00000139618 HGNC: BRCA2	ENST00000380152.8 (+) biotype: protein_coding	AG (AG)	frameshift variant	8732-8737 (out of 11954)	8533-8538 (out of 10257)	2845-2846 (out of 3418)	RE/X	AGAGAG/AG	Show
ENSG00000139618 HGNC: BRCA2	ENST00000380152.8 (+) biotype: protein_coding	AGAG (AGAG)	frameshift variant	8732-8737 (out of 11954)	8533-8538 (out of 10257)	2845-2846 (out of 3418)	RE/RX	AGAGAG/AGAG	Show
ENSG00000139618 HGNC: BRCA2	ENST00000528762.1 (+) biotype: nonsense_mediated_decay	AG (AG)	frameshift variant, NMD transcript variant	31-36 (out of 495)	31-36 (out of 195)	11-12 (out of 64)	RE/X	AGAGAG/AG	Show
ENSG00000139618 HGNC: BRCA2	ENST00000528762.1 (+) biotype: nonsense_mediated_decay	AGAG (AGAG)	frameshift variant, NMD transcript variant	31-36 (out of 495)	31-36 (out of 195)	11-12 (out of 64)	RE/RX	AGAGAG/AGAG	Show
ENSG00000139618 HGNC: BRCA2	ENST00000544455.6 (+) biotype: protein_coding	AG (AG)	frameshift variant	8632-8637 (out of 11854)	8533-8538 (out of 10257)	2845-2846 (out of 3418)	RE/X	AGAGAG/AG	Show
ENSG00000139618 HGNC: BRCA2	ENST00000544455.6 (+) biotype: protein_coding	AGAG (AGAG)	frameshift variant	8632-8637 (out of 11854)	8533-8538 (out of 10257)	2845-2846 (out of 3418)	RE/RX	AGAGAG/AGAG	Show
ENSG00000139618 HGNC: BRCA2	ENST00000614259.2 (+) biotype: nonsense_mediated_decay	AG (AG)	3 prime UTR variant, NMD transcript variant	8541-8546 (out of 11763)	-	-	-	-	Show
ENSG00000139618 HGNC: BRCA2	ENST00000614259.2 (+) biotype: nonsense_mediated_decay	AGAG (AGAG)	3 prime UTR variant, NMD transcript variant	8541-8546 (out of 11763)	-	-	-	-	Show

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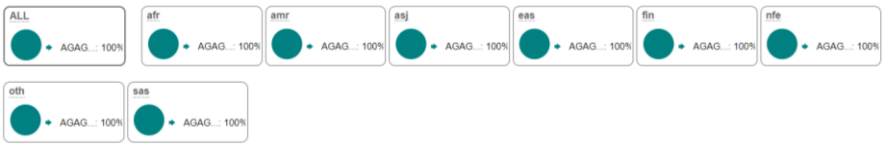
Figure 14: - Gene and Transcript consequences.

The gene LRG_293 which is located on Chromosome 13: 32,310,480-32,401,672 . This gene are a forward transcript strand, the genotype of the gene is LRG_gene. The consequence type is due to the frameshift variant between the positions 8760 to 8765 in the transcript. The length of the transcript is 11386. Due to the frameshift of the variant. The position in the protein is between 2845-2846 meanwhile the position in the CDS is between 8533-8538. Moreover, the location of variations within a codon is **AGAGAG/AG.**

C. Allele frequency.

Answer(C).



(1)

Population	Allele: frequency (count)	
gnomADe ALL	AGAGAG: 1.000 (251139)	AGAG: 1.195e-05 (3)
gnomADe afr	AGAGAG: 1.000 (16254)	AGAG: 0.000
gnomADe amr	AGAGAG: 1.000 (34586)	AGAG: 0.000
gnomADe asj	AGAGAG: 1.000 (10066)	AGAG: 0.000
gnomADe eas	AGAGAG: 1.000 (18382)	AGAG: 0.000
gnomADe fin	AGAGAG: 1.000 (21646)	AGAG: 0.000
gnomADe nfe	AGAGAG: 1.000 (113467)	AGAG: 2.644e-05 (3)
gnomADe oth	AGAGAG: 1.000 (6122)	AGAG: 0.000
gnomADe sas	AGAGAG: 1.000 (30616)	AGAG: 0.000

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(2)

Figure 15: - Allele frequency.

Figure shows the allele counts of the variant. The allele counts according to the Genome Aggregation Database of AGAGAG is the most common. In picture (2) the allele count of AGAG in Non-Finnish Europeans is different than. The allele count of Non-Finnish European is 2.644e-05. Moreover, Non-Finnish Europeans are only the one who possesses this type of allele.

(C). Likely pathogenicity

Answer(C). Roger can possess disorder like Fanconi anemia complementation group D1 (FANCD1) which can affect his bone marrow which may result into anemia, leukopenia and thrombopenia. However, this disease is in corelation with the cardiac, renal and limb malformations and can also affect the DNA and can result into damaging its agents.

In humans this variant affects the protein slicing and expression, which decreases homologous recombination-mediated DNA repair. The location of this sequence is [KDRRLFMHHVSLEPITCVPF R TTKERQEIQNPNFTAPGQEF].

If roger's father ha familial pancreatic cancer, therefore roger has high percentage of suffering from Pancreatic cancer 2(PNCA2) due to this variant. Moreover, this variant can also affect the gene with Glioma 3 (GLM3) which affects the central nervous system neoplasms derived from glial cells

(D). Diagnosis and relevance to Roger's phenotypes.

Answer(D). Roger has a high rate of suffering from the pancreatic cancer has his father also died from the same diseases too. Moreover, susceptibility to pancreatic cancer is conferred via heterozygous mutation within the BRCA2 gene on chromosome 13q13. In addition, Fanconi anemia is a disorder that causes genomic instability. It is excessive to DNA crosslinking and high recurrence of chromosomal abnormalities highlighting an imperfection in DNA fix. Gliomas are central nervous system neoplasms derived from glial cells and comprise astrocytoma's, glioblastoma multiforme, oligodendrogliomas, ependymomas, and sub ependymomas. Glial cells can show various degrees of differentiation even within the same tumour (summary by Kyritsis et al., 2010)

(E). Ethical implications for family members.

Answer(E). Breast cancer is a typical disease whose rate is expanding and at prior ages. While a large portion of this peculiarity is clarified by screening mammography and the expanding identification of DCIS, bosom disease is presently seen by general society. Breast cancer is a principal and emblematic issue in ladies medical care and numerous political fights base on counteraction, early conclusion and therapy, admittance to explore and to screening programs all ladies. At long last, the affliction and demise from metastatic bosom disease are crushing and their apparition is occupant on any BRCA positive lady.

(F). Further testing or treatment implications for Roger and other members of the family.

Answer(F). Roger's family members should know the risk of cancer. They should plan out the future family planning because the kids would have 50% of chance of inheriting the mutation or else, they can decide not to have children at all. To reduce the risk of developing Ovarian cancer, females can choose to remove both the ovaries and fallopian tubes but there are chances of cancer if the cancer has started to grow in the stomach.

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