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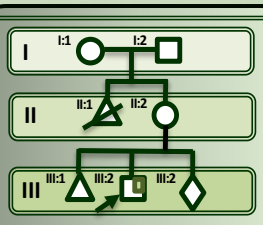
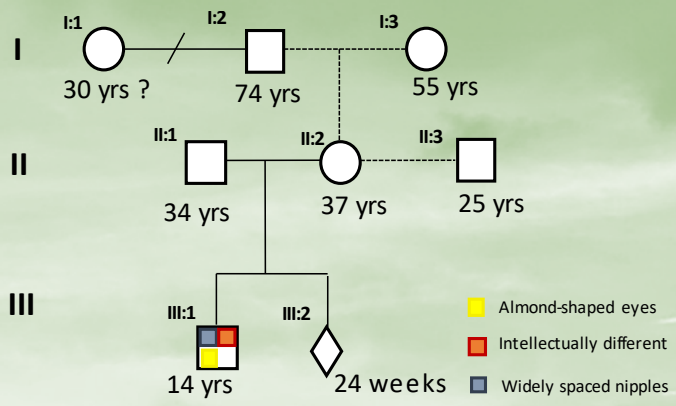
Neurogenetics -XXI / Intellectual deficiency / X-Linked / Intellectual developmental disorder, **X-linked syndromic, Nascimento type**

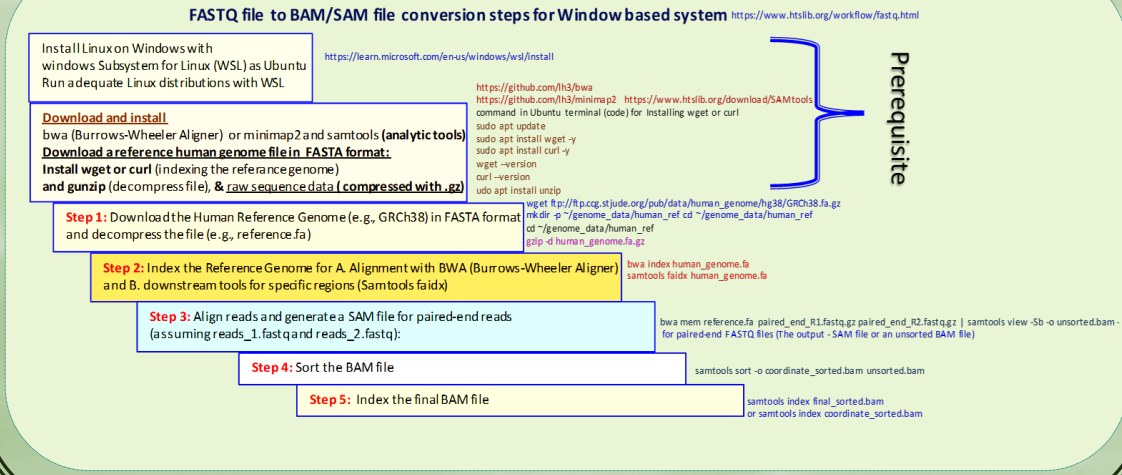
From the desk of Editor

The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.





How to convert BAM/ SAM file from FASTQ file



Insight:

1. How will you conduct the antenatal counseling for **Case III: 2**?
2. What are the basic steps for converting a FASTQ file to BAM/ SAM file?
3. What is the Mitophagyopathy?
4. How would you approach a syndromic child with almond-shaped eye?
5. What are the common online clinical resources for genetic disorders?

Plausible tenets:

Gene: UBE2A (Ubiquitin Conjugating Enzyme E2 A) Xq24, genomic coordinates (GRCh38): X:119,574,563-119,584,423

- An enzyme that conjugates UBB (second step of ubiquitination), **belongs to UBE2 family, and is involved in protein degradation.**
- Indirectly helps in epigenetic regulation through histone monoubiquitination (H2BK120ub1), which leads to transcriptional activation. It is involved in **mitophagy**, and inhibits the mitochondrial stress response.
- Gene: 116,282 bases, 212 orthologues, 24 paralogues, and 16 splice variants. Ensembl (ENSG00000077721)
- Transcript: 6 exons & coding exons; 9 domains and features; transcript length 718 bps. https://www.genecards.org/cgi-bin/carddisp.pl?gene=UBE2A#genomic_location
- Protein: 149 AA with a molecular mass of 17315 Da. https://www.uniprot.org/uniprotkb/P49459/entry#sequences
- **Gene tree (a pedigree of gene)** ENSGT00940000155075, ***number of*** genes - 308, speciation nodes - 255, duplications -31, ambiguous - 21, gene split events – 0. https://asia.ensembl.org/Homo_sapiens/Gene/Compara_Tree?db=core;g=ENSG00000077721;r=X:119574536-119583347;t=ENST00000346330
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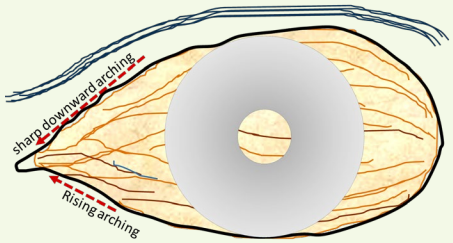
Phenotype: Intellectual developmental disorder, X-linked syndromic, **Nascimento** type (**Latin word nascimentum,means 'to be born'**)

Almond-shaped eye



Outline of palpebral fissure look like almond

Mitophagyopathy

- Disorders related to the failure of elimination of defective mitochondria from cytoplasm.
- Progressive accumulation of defective mitochondria affects cytoplasmic function, and is reported in various diseases.
- **Cardiovascular Disease:** myocardial ischemia-reperfusion injury, cardiomyopathy and heart failure
- **Age-related neurodegenerative diseases**: Parkinson's Disease (PD), Huntington's Disease, Amyotrophic Lateral Sclerosis, Alzheimer's Disease.
- **Metabolic disease or syndrome**: non-alcoholic fatty liver disease (NAFLD), diabetes, vasculopathy.
- **Others:** cancer cell survival in hypoxia, hereditary disorders that involve the genes implicated in mitophagy, and various aging related physiological changes

OMIM "almond-shaped eyes": 39 Entries with: Clinical synopsis

S No.	Entries / OMIM number /Gene/ MOI	Features besides "Almond-shaped eyes"
1.	**Neurodevelopmental Disorder** with Motor Abnormalities, **Seizures**, and **Facial Dysmorphism**; NEDMSF, #620719, **PUM1, AD**	**Severe intellectual different (SID), Sloping forehead, bitemporal narrowing, Sparse and abnormal eyebrows, low set ears, hypotonia, stereotypic hand movements, progressive disorders, atrophic changes in brain MRI**
2.	Prader-willi syndrome; PWS, #176270, **paternal 15q deletion (P, 70 %), AD and variable with others**	**Post infantile obesity, stubbornness, ID, behaviour problems (BPs), endocrine issues,**
3.	Congenital Disorder of Glycosylation, Type IIt; CDG2T, #618885, **GALNT2, AR**	**Infantile onset seizures, long face, seizures, SID, BPs, decreased fasting triglycerides and HDL cholesterol**
4.	Intellectual developmental disorder, X-linked, syndromic, Bain type; MRXSB, #300986, **HNRNPH2, XLD**	**SID, BPs, micrognathia, short philtrum, course facial features, sternum deformity, joint laicity**
5.	Chromosome 6pter-p24 deletion syndrome, #612582, **Contiguous gene syndrome, Isolated cases**	**ID, various eye anomalies, dental dysplasia, heart defects, mid face hypoplasia (overlap with branchiooculofacial syndrome, BOFS)**
6.	Chromosome 6q24-q25 deletion syndrome, #612863, **Contiguous gene syndrome, AD**	**ID, Heart defects, upslanted palpebral fissures, medial flared eyebrow, anteverted nares**
7.	Fanconi anemia, complementation group P; FANCP, #613951, **SLX4, AR**	**Cafe-au-lait spots, radial ray defect, progressive bone marrow failure**
8.	XIA-GIBBS syndrome; XIGIS, #615829, **AHDC1, AD**	**SID, BPs, hypotonia, hypertelorism, flat nasal bridge, laryngomalacia, craniosynostosis**
9.	Cohen syndrome; COH1, #216550, **VPS13B, AR**	**SID, prominent incisors, obesity, downslanting palpebral fissures and hypotonia**
10.	Wieacker-Wolff Syndrome, Female-Restricted; WRWFFR, #301041, **ZC4H2, XLD**	**SID, neuropathy, carp-shaped mouth, arthrogryposis multiplex congenita**
11.	Hypotonia-cystinuria syndrome, #606407, **Contiguous gene syndrome 2p21 (SLC3A1, PREPL, PPM1B, C2ORF34), AR**	**SID, obesity, hypotonia, nephrolithiasis**
12.	CK syndrome; CKS, #300831, **NSDHL, XLR**	**SID, BPs, hypotonia, cortical malformations, asthenic built, upslanting palpebral fissures, joint hyperlaxity**
13.	**Intellectual Developmental Disorder, X-Linked, Syndromic, Nascimento Type; MRXSN, #300860, UBE2A, XLR**	**ID, seizures, BPs, obesity, synophrys, hypertrichosis, widely spaced nipples, micropenis, midface hypoplasia, macrocephaly, upslanting palpebral fissures, deep-set eyes, low nasal bridge, large mouth with thin lips**
14.	Pilarowski-Bjornsson Syndrome; PILBOS, #617682, **CHD1, AD**	**ID, BPs, hypotonia, speech apraxia, seizures, macrocephaly, downslanting palpebral fissures, immunodeficiency**
15.	Baker-Gordon Syndrome; BAGOS, #618218, **SYT1, AD**	**SID, BPs, movements disorders, EEG changes without clinical seizures, thin upper lip, smooth philtrum, short nose**
16.	Neurodevelopmental disorder with dysmorphic facies, sleep disturbance, and brain abnormalities; NEDFASB, #619103, **KAT5, AD**	**SID, BPs, hypotonia, progressive cerebellar atrophy, corpus callosum dysgenesis, horseshoe kidney, thick lower lip**
17.	Luo-Schoch-Yamamoto Syndrome; LUSYAM, #619460, **RNF2, AD**	**SID, BPs, hypotonia, seizure, diffuse white matter loss, deep set eyes, arched eyebrows, microcephaly, diastema**
18.	Chopra-Amiel-Gordon Syndrome; CAGS, #619504, **ANKRD17, AD**	**SID, variable complex neurological features, recurrent bacterial infections, thick nasal alae, joint hyperlaxity,**
19.	Galloway-mowat syndrome 9; GAMOS9, #619603, **GON7, AR**	**Early onset nephrotic syndrome with progressive renal failure, acquired microcephaly, low set ear, pinched nose**
20.	Neurodevelopmental disorder with language delay and behavioral abnormalities, with or without seizures; NEDLBAS, #620292, **AGO1, AD**	**SID, Severe BPs, hypotonia, seizures, nonspecific facial dysmorphism, and brain MRI changes**
21.	Paul-chao neurodevelopmental syndrome; NEDPACH, #621122, **PPFIA3, AD**	**SID, BPs, hypotonia, seizure, broad feet, toes and nose, diastema, depressed nasal bridge, long columella**
22.	Microcephaly, growth retardation, cataract, hearing loss, and unusual appearance, 612947	**Microcephaly, hearing loss, upslanting palpebral fissures, phenotypic overlap with Dubowitz syndrome**
23.	Palant cleft palate syndrome, 260150	**SID, upslanting palpebral fissures, cleft palate, camptodactyly of fingers 4 and 5**
24.	Keratitis-Ichthyosis-Deafness Syndrome, AD; KIDAD, #148210, **GJB2, AD**	**Hyperkeratosis, sensorineural hearing loss, erythrokeratoderma, recurrent infection, scrotal tongue, sparse hairs**
25.	Spondylometaphyseal dysplasia, corner fracture type; SMDCF, #184255, **FN1, AD**	**Short stature, joint restriction, corner fracture-like lesions of the metaphyses, vertebral anomalies, glaucoma**
26.	Schaaf-yang syndrome; SHFYNG, #615547, **MAGEL2, AD**	**SID, BPs, hypotonia, Prader-Willi-Like Syndrome, distal arthrogryposis, hypopituitarism, overlapping digits**
27.	Temple syndrome, #616222, **(maternal UPD14mat) at chromosome 14q32**	**ID, hypotonia, relative macrocephaly, short stature, small hands and feet, joint hyperlaxity, precocious puberty,**
28.	Myasthenic syndrome, congenital, 22; CMS22, #616224, **PREPL, AR**	**Myasthenic syndrome, growth hormone deficiency, symptoms may decrease with age**
29.	Ring chromosome 14 syndrome, #616606	**ID, seizures, flat occiput, microcephaly, retinopathy, low-set ears, anteverted nostrils**
30.	Congenital disorder of glycosylation, type Ia; CDG1A, #212065, **PMM2, AR**	**SID, encephalopathy, retracted nipple, abnormal subcutaneous fat, retinitis pigmentosa, cerebellar hypoplasia**
31.	Intellectual developmental disorder, X-linked, syndromic, turner type; MRXST, #309590, **HUWE1, XL**	**ID, hypotonia, seizures, both sexes can be affected, highly variable phenotype, deep-set eyes, cryptorchidism, hypotelorism, ear anomalies, brachydactyly**
32.	Dental anomalies and short stature; DASS, #601216, **LTBP3, AR**	**Short stature, absent enamel, oligodontia, aortic root dilation, platyspondyly, delayed bone age**
33.	Cohen-Gibson Syndrome; COGIS, #617561, **EED, AD**	**ID, overgrowth syndrome, advanced bone age, skeletal abnormalities**
34.	Chromosome 1p35 deletion syndrome, #617930, **a contiguous gene deletion**	**ID, hypotonia, short stature, ataxia, myopathic facies, hypertelorism**
35.	Rauch-Steindl Syndrome; RAUST, #619695, **NSD2, AD**	**Mild ID, BPs, hypotonia, no seizure, phenotype overlap with a mild form of Wolf-Hirschhorn syndrome**
36.	Tessadori-bicknell-van haaften neurodevelopmental syndrome 2; tebivaned2, #619759, **H4C11, AD**	**ID, short stature, short philtrum, hypertelorism, microcephaly, upslanting palpebral fissures, limb muscle atrophy**
37.	Developmental and epileptic encephalopathy 31b; DEE31B, #620352, **DNM1, AR**	**SID, BPs, hypotonia, epileptic encephalopathy, visual impairment, brain atrophy, acquired microcephaly**
38.	Neurodevelopmental disorder with dysmorphic facies, brain anomalies, and seizures; NEDFBS, #621201, **GTF3C3, AR**	**ID, BPs, microcephaly, hypotonia, abnormal movements, seizures, course facial features, full cheek, broad nasal tip, cerebellar atrophy/hypoplasia**
39.	Hunter-Mcalpine Craniosynostosis Syndrome, 601379	**ID, craniosynostosis, skeletal anomalies, short stature, microcephaly**

Ubiquitin, Ubiquitination, deubiquitination and Ubiquitin-conjugating (E1, E2, E3) enzymes

- Ubiquitin (UBB, 17p11.2): 76-amino acid protein present in all eukaryotic cells, conserved in all species including plant kingdom, removes cytoplasmic defective proteins by making "eat me" signals and activating proteolytic pathway (ubiquitin-proteasome system (UPS) machinery), while in non-degradative functions it works in various cellular processes such as cell cycle and DNA repair. Covalent attachment of ubiquitin to the targeted protein called ubiquitination, while reversed process call deubiquitination. Three enzymes E1, E2, and E3 assist in this process.
- **Activating enzyme (E1, seven types):** ATP based activation of UBB for establishing a thioester bond with E1
- **Conjugating enzyme (E2, types, and subtypes around 35):** UBB-E1 complex transfers UBB to cysteine site on E2
- **Protein ligase (E3, types -A, B, C, D):** transfers UBB from UBB-E2 complex to lysine site on target protein

Counsel the family for Case III: 4 – 75% of offspring will not be affected (all carrier females are unaffected), recurrence risk is 25% in each pregnancy, and antenatal testing could help for irreversible decision. However, multiple factors determine the need for testing, such as gestational age (24th week is the upper limit for legal termination of pregnancy in Indian scenario, but it is not in other countries; late termination could be planned, but it needs induce fetal asystole and parental consent as a prerequisites). Therefore, in the Indian scenario, reports of molecular testing should be available before the 24th week; otherwise, it will not aid in legal termination and will cause significant psychological stress to the family. All these

Thought Riveting:

- ***What are the possible phenotypes for pathological variants of UBE2B, and UBE2C genes?***
- ***Can therapeutic doses of mitochondrial supplementation modulate the premature aging features of Down syndrome or other hereditary progeroid syndromes?***
- ***Can induction of mitophagy by SAH-UBE2A be used as adjuvant to standard chemotherapy for leukemia?***
- ***What could be the diagnostic and therapeutic uses of UBE2A polyclonal antibody (E-AB-18779)?***