Rishi Vansh

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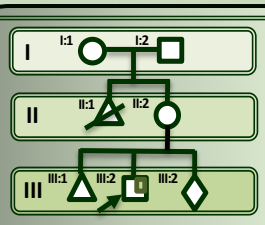
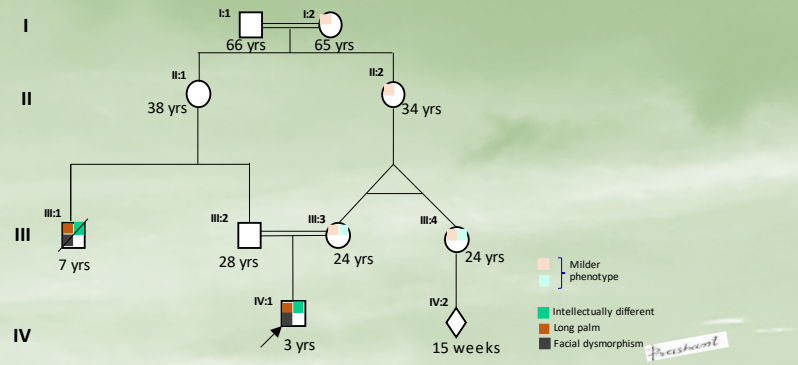
Neurogenetics -XXI / Intellectual deficiency / X-Linked /Intellectual developmental disorder, X-linked syndromic, Claes-Jensen type

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.

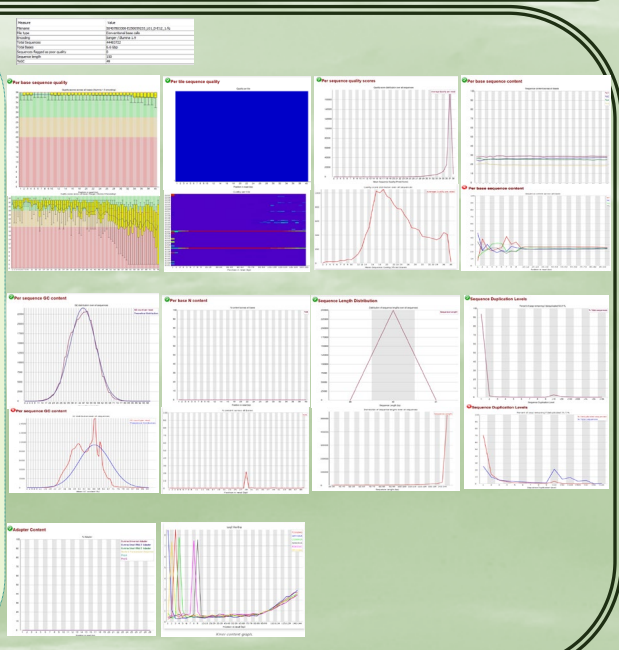




Component of FastQC

FASTQC, a software program, is used for checking the quality of high-throughput sequencing data like NGS. (https://www.bioinformatics.babraham.ac.uk/projects/fastqc/)
The Prerequisite software to run FASTQC is the Java Runtime Environment (JRE), which provides a platform to run JAVA applications.
Input: **.fq** file [a processed raw file(binary basecall *bcl files) after BCL2FASTQ]
Output: summarized HTML data with ten to twelve modules. On the basis of predefined thresholds, there are three categories in each module: "pass," "warn," or "fail."
Modules:

1. **Basic Statistics: summary of data:** inform about that the data is bad/good, and other details such as total sequence number, sequence length, %GC, and % sequence flagged as poor quality.
2. **Per Base Sequence Quality:** The Y axis shows the Phred quality score; a central line of each Box Whisker-type plot should be in the green part of the plot (PQS >30).
3. **Per-tile Sequence Quality:** Only Illumina data retains original sequence identifiers (tile), so it represents each tile quality score individually. Normal plots have blue all over.
4. **Per Sequence Quality Scores:** Plot distribution of Phred score for all reads; most of the reads must have a higher Phred score.
5. **Per Base Sequence Content:** proportion of each base position in a file; all bases should not have significant differences from each other.
6. **Per base N content:** it indicates no base call with sufficient confidence; it must be zero.
7. **Per Sequence GC Content:** having a modeled GC curve that compares the data GC content of the whole length of each sequence.
8. **Sequence Length Distribution:** represents the shortest and longest sequence distribution over all sequences.
9. **Sequence Duplication Levels:** show the duplication level for every sequence; ideally, it must be around zero.
10. **Overrepresented sequences**: enlist the sequences that are more present by counting, percentage, and possible source; *limitation* - represents only the sequences that constitute > 0.1% of the total and appear in the initial 200k sequences.
11. **Adapter Content:** shows the presence of overrepresentation of sequences; it should be below 5% for all reads.
12. **Overrepresented Kmers:** counts the augmentation of every 5-mer; adapter sequences could be overrepresented k-mers, but not always. K-mer enrichment must be less than 3-fold overall or less than 5-fold at any individual position.



Insight:

1. How would you counsel for the antenatal fetal molecular report of **Case IV: 2**?
2. What is the FastQC and its component?
3. What are the differences between Type 1 and Type 2 restrictive dermopathy?
4. What is the normal facial morphology determinant?
5. What is the RE-1-silencing transcription factor (REST) complex?

RE-1-silencing transcription factor (REST) complex or NRSF (Neuron-Restrictive Silencer Factor)

- **NRSF, located on 4q12.**
- It represses transcription through binding the targeted genomic sequences that have **21-bp RE1 (Repressor Element-1).**
  5'-TATCAGGTCACGTGTCCTCT-3'
- After attachment, it forms a co-repressor complex with other proteins **[CoREST, HDAC1, and HDAC2 as deacetylases (HDACs)].**
- HDACs silence the genes by epigenetic mechanism in selected tissues **(non-neuronal cells).**
- Mutation leads to deafness, autosomal dominant 27 **(specific variants);** and fibromatosis, gingival, 5 **(dominant-negative or gain-of-function effect).**
- **It also increases susceptibility to Wilms tumor 6.**

X linked Mental retardation:

- Overall prevalence of ID: **1-3%.**
- **Around 30%** of all ID is due to XL.
- Carrier frequency approx. **2-3/1000**
- Yielding of molecular test **variable.**
- Key factors for achieving a high-yielding molecular report: **specific dysmorphology, familial case, consanguinity, moderate to severe ID, neuro-regression, other neurological findings, & abnormal lab parameters.**
- **Essential details in evaluation: In the case of a carrier, the mother might have subtle feature(s) that must be evaluated thoroughly.**
- **In OMIM, divided into two groups: syndromic (PS309510 - 54 Entries) and non-syndromic (PS309530 - 55 Entries).**
- **KDM5C leads to 2.5 to 3.5% XLMR**

Plausible tenets:

Gene: KDM5C (Lysine Demethylase 5C), Xp11.22, genomic coordinates (GRCh38): X:53,176,277-53,225,207

- Also called JARID1C (Jumonji, AT-RICH Interactive Domain 1C) initially.
- A transcriptional repressor works by RE-1-silencing transcription factor (**REST**) complex.
- it does not monomethylate but demethylates trimethylated and **dimethylated 'Lys-4'** of histone H3 as a specific H3K4me3 and H3K4me2 demethylase.
- **ARX gene** enhances its expression by bidnig at a specific site on the 5-prime region, and ARX might work as a disease modifier.
- **KDM5D, a paralog gene** located on Yq11.223, has quite similar overlapping function; additionally, its an alternative splicing product acts as **a sex-specific minor histocompatibility antigen.**
- Gene: 49,146 bases, 10 paralogues, 126 orthologues, and 23 splice variants.
- Transcript: 26 exons & 26 coding exons; 59 domains and features; transcript length 5,810 bps.
- Protein: 1560 AA with 175720 Da molecular mass.
- **Gene tree** (**a pedigree of gene**) ENSGT00940000161236, ***Number of-*** genes - 115, speciation nodes - 107, duplication -4, ambiguous - 2, gene split events - 1
  https://asia.ensembl.org/Homo_sapiens/Gene/Compara_Tree?db=core;g=ENSG00000126012;r=X:53176277-53225422;t=ENST00000375401

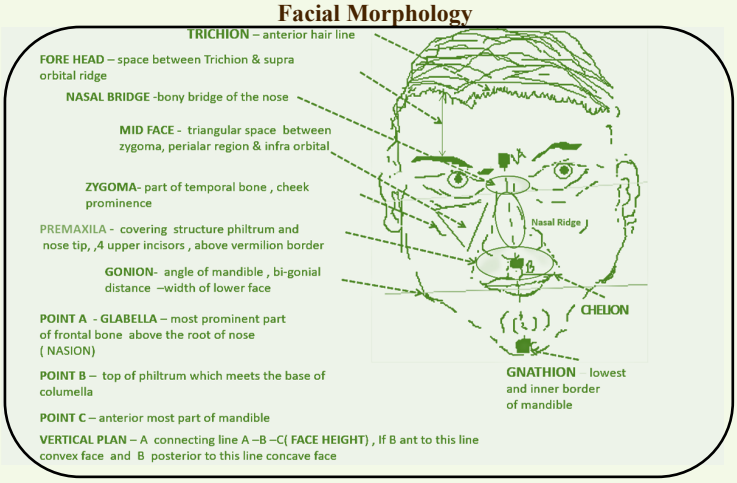
- **In 2000, S Claes** had described this phenotype as a **X-linked complicated spastic paraplegia**, while in 2005, Lars Riff Jensen discovered the variant in the JARID1C gene for this syndrome.

Phenotype: Intellectual developmental disorder, **X-linked** syndromic, Claes-Jensen type (**MRXSCJ**)

- Dysmorphic features: short stature, micro- or macrocephaly, hypotonia, **maxillary hypoplasia**, hypertrichosis, **small deep-set eyes**, hypotelorism, **flat philtrum**, **large ears**, **brachydactyly**, prominence of the right antitragus, an open mouth, pectus excavatum, partial shawl scrotum, **scrotal tongue**, diastema, low columella, short philtrum, **thin upper lips**.
- Neurological findings: slowly progressive spastic paraplegia, hyperreflexia, mild to severe mental retardation, stereotyped mannerisms, aggressive behaviour, epilepsy, and strabismus.
- Females might have a mild variable phenotype with more endocrine abnormalities.

Management: An Individualized Education Program (IEP), routine evaluation, & symptomatic.

Facial Morphology



Spastic paraplegia (SPG)

- Prevalence 0.1 to 9.6/lakh
- Symmetric progressive bilateral spasticity (stiffness) with weakness of the legs; onset from infancy to adulthood.
- Usually associated with the corticospinal tracts and dorsal columns' degenerative features (decreased vibration sense & urinary bladder dysfunction)
- Uncomplicated or **P**ure (90%) & **C**omplicated (10%) type (with other neurological problems)
- OMIM Phenotypic Series: Spastic paraplegia - PS303350 - 86 Entries - 54 AR, 27 AD, 4 XL, & AD/AR for type 7 SPG

X- linked Spastic paraplegia (SPG)

Disease/OMIM	Gene/locus	Phenotype (**C**/ **P**)
Spastic paraplegia 16, X-linked, complicated/ 300266	SPG16/Xq11.2	**C**- optic atrophy, nystagmus, ID, cerebellar ataxia, & sensory loss
Spastic paraplegia 2/ 312920	PLP1/ Xq22.2	**C**, & variable, Pelizaeus-Merzbacher disease (an allelic disorder)
Spastic paraplegia/300750	SPG34/ Xq24-q25	**P**, onset from 1st to 3rd decades, slowly progressive, between ages 30-40 yrs wheelchair-bound
MASA syndrome (**SPG1**) /303350	L1CAM/ Xq28	**C**, MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs)

Counsel the family for Case III: 4 – Molecular reporting of X-linked disease depends upon the state legal laws related to the declaration of fetal sex. In the Indian scenario, a declaration in any form about the sex is prohibited and illegal with a few exceptions. In case of XLR disease, labs usually mention affected or not affected without opening the carrier status, but in the XL condition, the reporting is quite complicated, and the family must be counselled about the legal limitation of the reporting before testing the fetus.

Thought Riveting:

- ***What are the different molecular mechanisms for X-linked neurodevelopmental genes for the balanced gene dosage expression in both sexes in early embryonic life?***
- ***Can the KDM5C induced overexpression be used as a non-specific future therapy for advanced cancer treatment?***
- ***Does a different pattern of androgenization happen in subsequent male fetuses after maternal sensitization with Y chromosome genetic material?***
- ***Why has the KDM5C-related spastic paraplegia not been included in the OMIM Phenotypic Series of Spastic Paraplegia?***