THE H SYNDROME

Next Generation Sequencing for Molecular Genetic Diagnosis

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BACKGROUND

❑Monogenic auto-inflammatory diseases are a group of hereditary disorders characterized by a clinical and biological inflammatory syndrome without evidence of autoimmunity.

❑The mutated proteins are involved in the altered regulation of inflammation.

❑The 'H' syndrome has been recently described as a monogenic auto-inflammatory autosomal-recessive genodermatosis with several systemic manifestations.

❑It is caused by mutations in the solute carrier family 29 (SLC29A3) gene, which encodes the human equilibrative nucleoside transporter-3 (hENT3).

OBJECTIVES

To study the clinical features and establish the genetic diagnosis of a subject with young onset of diabetes.

SUBJECTS AND METHODS

Utilizing next generation sequencing we carried out mutational analysis of SLC29A3 gene in the chr.10q22.1 and selectively investigated this patient for various other features of this genodermatosis.

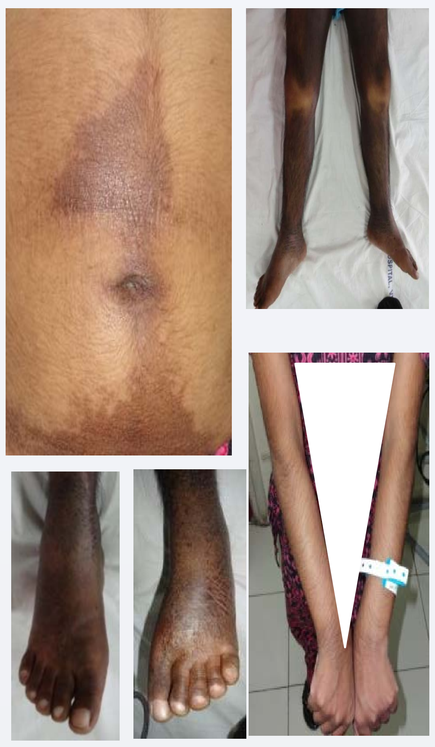
CLINICAL PRESENTATION

- A 20 year girl born to parents of non-consanguineous marriage developed diabetes at the age of 6 years, with ketosis at onset.
- On Insulin from the time of diagnosis.
- Noticed progressively increasing hyperpigmented lesions and generalised hypertrichosis from age 6 years .
- Hypothyroidism and hearing loss at 9 years of age.
- She also has delayed puberty with short stature.

ON EXAMINATION

- Hyperpigmented patches over the lower abdominal wall.
- Symmetrical large hyperpigmented, indurated plaques with terminal hair [hypertrichosis] over the lower limbs with characteristic sparing the face, buttocks and knees, face. Ferriman Galleway Score (FGS) 12/36.
- Ichthyosis of the feet with non-pitting pedal edema.
- Short stature, hypertelorism, no acanthosis nigricans
- Arcus juvenilis, clinodactyly, arthrogryposis at the ankles.

CLINICAL IMAGES



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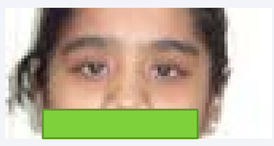

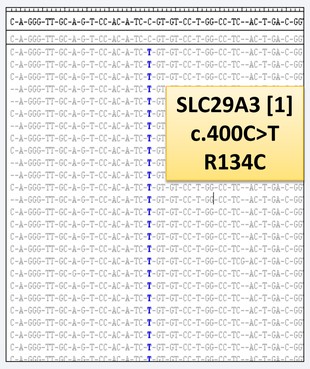

Homozygous mutation of SLC29A3 gene by next generation sequencing

To summarize she had the following features of "H-syndrome"

- **H**yperpigmentation,
- **H**ypertrichosis,
- **H**ypertelorism
- **H**yperglycemia,
- **H**ypothyroidism,
- **H**eight low (short stature)
- **H**ypogonadotropic hypogonadism
- **H**earing loss (sensori-neural)
- **H**eart anomaly (bicuspid aortic valve)

BIOCHEMICAL INVESTIGATIONS

PARAMETERS	PATIENT	NORMAL
HbA1c (%)	8.5 & 6.3	< 6.5
C-PEPTIDE (ng/ml)	< 0.10	> 0.6
GAD (U/ml)	< 5	< 5
TSH (uIU/ml)	13.6	0.3 – 4.5
IGF-1 (ng/ml)	48.5	127-424
FSH (mIU/ml)	6	0.5-7
CRP (ng/ml)	56.1	< 6
ESR (mm 1st hr)	109 & 120	< 20
TG (mg/dl)	139	< 150

HbA1c – Glycosylated haemoglobin
GAD – Glutamic Acid Decarboxylase antibodies
TSH – Thyroid Stimulating Hormone
IGF – Insulin like Growth Factor
FSH – Follicular Stimulating Hormone
CRP - C-Reactive Peptide
ESR – Erythrocyte sedimentation rate
TG – Triglycerides

RESULTS OF GENETIC TESTS

The next generation sequencing of SLC29A3 gene was performed on the Ion torrent personal genome machine (PGM) using 314 chips and Ion PGM™ 200 Sequencing Kit (Ion Torrent, Life Technologies).

Sequencing revealed a previously reported homozygous mutation c.400C>T, p.R134C, which was further confirmed by Sanger sequencing.

DISCUSSION

- The subject was evaluated for young onset diabetes mellitus with a peculiar feature involving the skin namely hyperpigmentation with hypertrichosis involving trunk and lower limb. This led to the suspicion of a genodermatosis, 'H' syndrome, that refers to the major clinical and laboratory findings starting with the letter "H". The presence of hypothyroidism, hearing loss, hypogonadism, low height and hyperglycemia led us to suspicion of this entity.

- The elevated inflammatory markers (CRP,ESR) added to the clue and targeted genetic sequencing of the implicated gene SLC29A3 confirmed the diagnosis.

- The peculiar features in our subject were icthyosis, arcus juvenilis, clinodactyly and arthrogryposis of the ankle.

CONCLUSIONS

- H-syndrome must be considered in any subject with young onset of diabetes and the dermatological phenotype of pigmentary hypertrichosis.

- Next generation sequencing (NGS) forms a useful platform in genetic testing of monogenic disorders and would aid in the diagnosis and further counseling.

REFERENCES

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