

# A Case Report of Dyschromatosis Universalis Hereditaria (DUH) with Primary Ovarian Failure (POF)

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## ABSTRACT

Dyschromatosis Universalis Hereditaria (DUH) belongs to a group of congenital diffuse reticulate pigmentary disorders characterised by both hypo and hyper pigmented macules. It is both hereditary and sporadic. A number of associated cutaneous and systemic diseases have been reported. The recent discovery of the mutation in ATP binding cassette protein, ABCB6 in DUH attempts to explain the reason behind the pigmentary abnormalities and varied associations. We add a new association by reporting a case of DUH with primary ovarian failure (POF) and hypothyroidism.

**Keywords:** ATP-binding cassette transporters, Hypothyroidism, Primary ovarian insufficiency

## CASE REPORT

An 18-year-old female presented with history of mottled pigmentation all over the body since birth. She had not attained menarche and was on medication for hypothyroidism for the past one year. She was the first born of a second degree consanguineous marriage. There was no history of similar disease in any of her family members. On examination she was of normal stature and average build. Dermatological examination revealed multiple hypo and hyper pigmented macules in a reticulate and mottled pattern over chest, back, upper and lower extremities sparing the face [Table/Fig-1]. Palms and soles were involved [Table/Fig-2]. Dermatoglyphic pattern was preserved. Scalp, hair, nails and mucosae were normal. Secondary sexual characters were poorly developed and corresponded to Tanner Stage 2 [Table/Fig-3]. No signs of virilisation were observed. On investigation, karyotyping was 46XX [Table/Fig-4]. Blood estradiol level was pre-pubertal (5pg/ml against a normal of 20 – 200pg/ml) and FSH level was elevated (130.20 mIU/ml against a normal of 3.5- 12.5mIU/ml - Hypergonadotropic hypogonadism). Serum testosterone level was also elevated (17.83pg/ml against a normal of 0.02 – 3.09pg/ml). Sex hormone binding globulin level was sub-normal (23.39nmol/L against a normal of 26.1 – 110nmol/L). Serum LH (39.69mIU/ml; normal value: 14.0 – 95.6mIU/ml) and prolactin levels (12.26ng/ml; normal value: 4.79 – 23.3ng/ml) were normal. Serum T3 (3.22pg/ml; normal value: 2.3 – 4.2pg/ml) and T4 levels (1.14ng/dl; normal value: 0.8 – 2.0ng/dl) were normal with medications and TSH level was slightly elevated (7.560mIU/ml; normal value: 0.35 -5.50mIU/ml). Random blood sugar was normal (96mg/dl) but fasting insulin level was slightly elevated (27.76mIU/

ml against a normal value of 2.6 – 24.9mIU/ml). An ultrasonogram showed prepubertal uterus with tubular configuration and bilateral small ovaries with few follicles. Complete blood count, liver and renal function tests, anti-thyroid antibody levels and anti-nuclear antibody titre were normal. Hearing and vision was normal. Cardiovascular, respiratory, and central nervous system examination revealed no abnormality clinically. Her IQ was normal. Skin biopsy showed normal epidermis with increased pigmentation of basal layer with melanin incontinence in the dermis [Table/Fig-5]. A diagnosis of Dyschromatosis Universalis Hereditaria (DUH) with Primary Ovarian Failure (POF) and hypothyroidism was made.

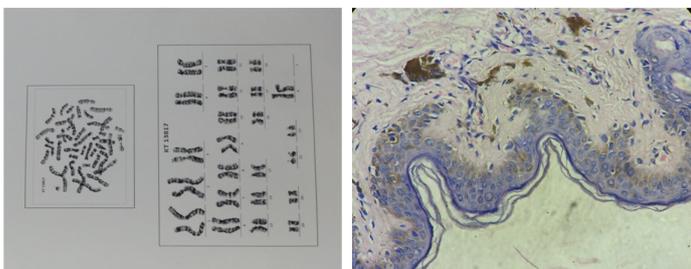
Patient was started on cyclical hormonal supplements for development of secondary sexual characters and prevention of osteoporosis after consultation with an endocrinologist and gynaecologist. Genetic counselling was given.

## DISCUSSION

DUH was first described in Japan by Ichikawa and Hiraga in 1933 [1]. The disease was initially thought to be confined to Japan but several case reports have been made from Europe, China, Saudi Arabia, Tunisia and India [2]. Autosomal dominant, autosomal recessive and sporadic cases have been documented. Another similar disorder, Dyschromatosis Symmetrica Hereditaria (DSH) was initially thought to be a localised form of DUH. But DSH had mutations in ADAR1 gene, localised to chromosome 1q21.3 and this mutation was not present in DUH [3]. Now they are considered as two different entities. DSH involves the face and dorsal extremities whereas DUH involves mainly the trunk with or without sparing of palms, soles and face



**[Table/Fig-1]:** Multiple hypo pigmented macules in a reticulate and mottled pattern over chest. **[Table/Fig-2]:** Involvement of palms. **[Table/Fig-3]:** Poorly developed secondary sexual characters.



**[Table/Fig-4]:** Normal Karyotyping. **[Table/Fig-5]:** High power view of histopathology shows increased pigmentation of basal layer and pigment incontinence in the dermis.

[4]. However, palmar and oral mucosal involvement [5], nail and hair involvement [6] and adermatoglyphia [7] have been documented.

DUH was thought to be a disorder of melanocyte number, melanosome production or distribution of epidermal melanin unit [8]. Recently the molecular basis of DUH was identified by a genome wide linkage analysis in a Chinese pedigree and confirmed using DNA sequencing and animal models [9]. The candidate gene was identified as ABCB6 gene located on chromosome 2q36 and is a member of ATP Binding Cassette (ABC) transporters. ABC transporters, responsible for transport of various molecules across cell membranes, are present ubiquitously including the skin. They play a role in cellular transition and metal homeostasis, especially copper. It is thought that mutations of ABCB6 leads to abnormalities in copper homeostasis thereby causes dysfunction of tyrosinase and further leads to abnormal melanin synthesis. It is also expressed in exosomes and plays a role in melanosome transport to surrounding keratinocytes [10].

ABCB6 protein has different functions at different sites and hence mutations of ABCB6 domains produces disease with diverse phenotypes. Consistently, DUH has been reported to be associated with a wide range of cutaneous and systemic diseases such as tuberous sclerosis, learning difficulties, mental retardation [4], short stature and high tone deafness [11], X- Linked oculo-cutaneous albinism [12], epilepsy [13], erythrocyte, platelet and tryptophan metabolism abnormalities [14] and renal failure [15].

Regarding the cause of POF, no precipitating factors like viral infections, irradiation or chemotherapy in childhood could be identified. Her karyotyping was normal. There was no evidence of adrenal insufficiency. Antithyroid antibody profile was normal. As antiovarian antibodies are neither sensitive nor specific in diagnosing autoimmune oophoritis as a cause of POF, it was not measured. FSH receptor polymorphisms also can cause hypergonadotropic hypogonadism. Interestingly, the FSH receptor is also localised to chromosome 2 where the gene for ABCB6 protein is located. However, in more than 90% of patients with POF, no cause could be identified.

Possible differential diagnoses for skin lesion include xeroderma pigmentosum, dyskeratosis congenita and other reticulate

pigmentary disorders. The absence of photosensitivity, presence of skin lesions in covered areas of the body, asymptomatic nature, absence of nail, mucosal and scalp involvement rules out the above disorders. There is no specific treatment for the skin condition. Removal of the skin lesions with Q-switched alexandrite laser has been tried [16]. DUH with POF has not been reported in literature so far to the best of our knowledge.

## CONCLUSION

We report this case for its rarity and to highlight the recent discovery of the molecular pathogenesis behind DUH and its diverse systemic associations. Advanced genetic analysis may elucidate the association of DUH with POF taking into consideration the co-localization of the FSH receptor gene and ABCB6 gene on chromosome 2.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Oct 26, 2015**  
Date of Peer Review: **Dec 31, 2015**  
Date of Acceptance: **Jan 08, 2016**  
Date of Publishing: **Mar 01, 2016**