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A novel *CHD7* mutation in an adolescent presenting with pubertal and growth delay

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Background

Mutations in the gene encoding the Chromodomain Helicase DNA-binding protein 7 (***CHD7***) are found in ~60%[1] of patients with **CHARGE** syndrome (**C**oloboma, **H**eart Defects, Choanal **A**tresia, **R**etarded growth and development, **G**enital hypoplasia, **E**ar abnormalities and/or hearing problems) and in 6% of patients with Kallmann syndrome[2].

Clinical diagnostic criteria (Verloes 2005)[2]:

Major criteria (3 C's):
- Coloboma
- Choanal atresia
- Hypoplastic semi-circular canals

Minor criteria
- Rhombencephalic dysfunction
- Hypothalamo-hypophyseal dysfunction
- Abnormal middle or external ear
- Malformation of mediastinal organs
- Mental retardation

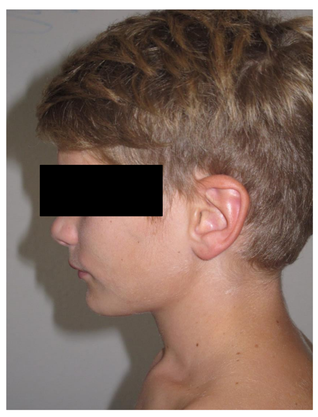
Diagnostic CHARGE criteria interpretation:
- **Typical :** 3 major or 2 major & 2 minor criteria
- **Partial/incomplete :** 2 major & 1 minor criteria
- **Atypical :** 2 major or 1 major & 3 minor criteria

Objective

To describe the diagnostic challenges of CHARGE syndrome using the example of a patient harboring a novel *CHD7* mutation

Case Presentation

A 14 year-old male presented for evaluation of delayed growth and puberty.



Family history:
- Delayed puberty in both parents

Past medical history:
- Born full term; eutrophic after an uneventful pregnancy
- Surgical repair of bilateral choanal atresia (5th day of life)
- Normal development, began walking at 18-months, history of imbalance during childhood - not formally investigated

Clinical examination:
- Anthropometry: Height -2.04 SDS; Weight -1.74 SDS
- Tanner: A1P2G1; Micropenis (4x1cm) [4]
- Ogival palate, left helix anteversion , low set ears

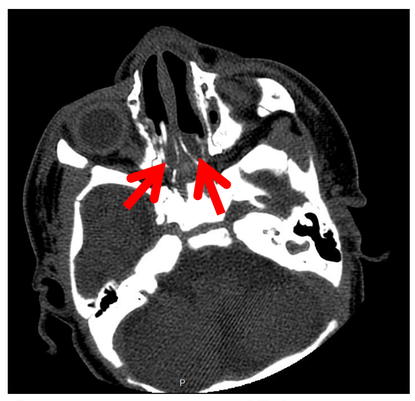
Investigations:
- Cardiac US and ECG: normal
- Ophthalmologic exam: normal
- ORL: conductive hypoacousia, abnormal lateral and posterior semicircular canal function
- Olfactory testing ("Sniffin'-Sticks"): anosmia
- MRI (see right)
  - ✓ semi-circular canal hypoplasia
  - ✓ olfactory bulb hypoplasia
  - ✓ decreased anterior pituitary volume (160mm^3)
  - ✓ vestibular malformation, cochlear & R 7th cranial nerve malformation

Laboratory testing:
- Partial gonadotropin deficiency, otherwise normal pituitary function

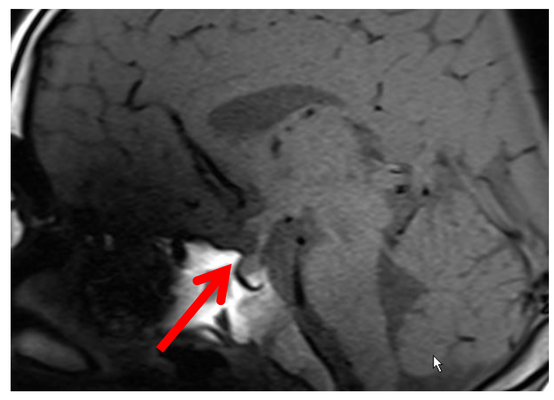
		Patient	Reference value
Testosterone	*nmol/l*	0.3	0.1-17.6
Prolactin	*µg/l*	9.2	<20
TSH	*mU/l*	2.19	0.5 - 4.5
freeT4	*pmol/l*	16	9 - 25
IGF-1	*µg/l*	254	212 - 1043
IGFBP3	*mg/l*	5.4	3.2 - 10.4
ACTH	*pg/ml*	12	10 - 60
Cortisol	*nmol/l*	315	170 - 630
AMH	*pmol/l*	438	5-800
Inhibin-B	*pg/ml*	86.4	60-300

LHRH Stimulation Test

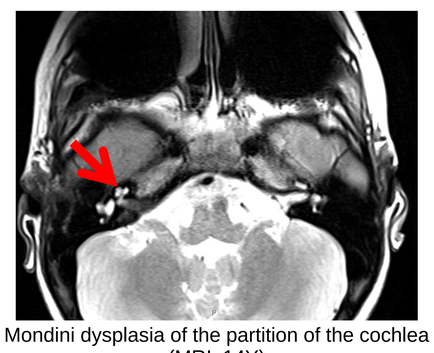
	LH	FSH
	mU/l	*mU/l*
0'	0.5	1.3
15'	3.7	1.9
30'	6.3	2.6
60'	8.3	3.9
90'	7.3	4.2
120'	6.7	4.4



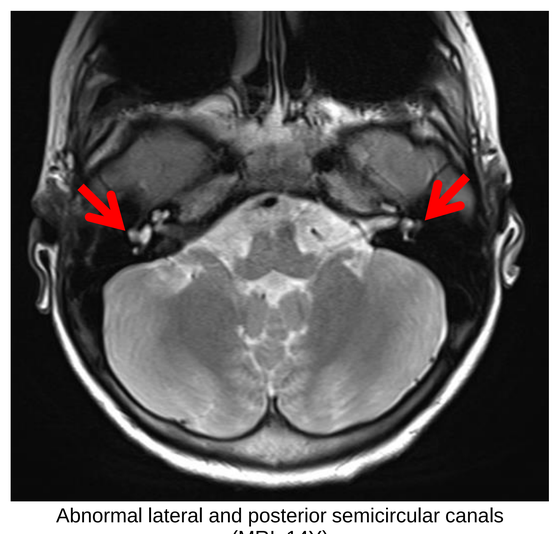
Bilateral choanal atresia (CT, 3rd day of life)



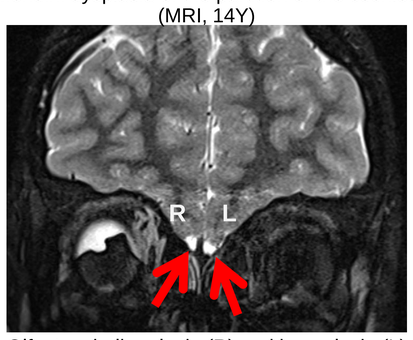
Decreased anterior pituitary volume(MRI, 14Y)



Mondini dysplasia of the partition of the cochlea (MRI, 14Y)



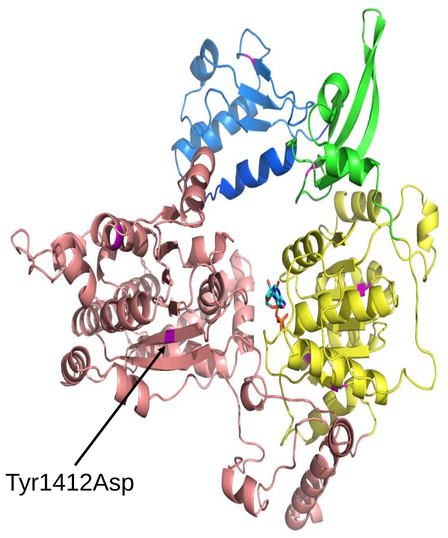
Abnormal lateral and posterior semicircular canals (MRI, 14Y)



Olfactory bulb aplasia (R) and hypoplasia (L) (MRI, 14Y)

Genetic testing (Sanger sequencing)

- *De novo* heterozygous *CHD7* mutation (c.4234T>G, p.Tyr1412Asp) located in the Helicase C domain
- A private variant not found in either the 1'000 Genomes or ExAC databases
- Predicted to be deleterious by 10/10 *in silico* prediction algorithms.



The patient fulfilled criteria for typical CHARGE syndrome.

Discussion & conclusions

We describe a novel *CHD7* mutation (c.4234T>G, p. Tyr1412Asp) located in the Helicase C domain in a patient with CHARGE syndrome who remained undiagnosed until adolescence, despite the presence of suggestive features.
Genetic testing promotes the broadening of phenotypic and genotypic spectrum of CHARGE syndrome and may give insight to the mild end of phenotypic spectrum, ensuring optimal follow up and appropriate genetic counselling.

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