INTRODUCTION

Noonan syndrome (NS) is a rasopathy, a genetically heterogeneous condition, which is characterized by characteristic faces, short stature, congenital heart defect, and developmental delay of variable degree. Pathogenic variants for NS have been found in multiple genes encoding the RAS/MAPK pathway. Noonan syndrome with loose anagen hair (NS-LAH) is a subgroup with features of NS but also growth hormone deficiency, distinctive hyperactive behavior that improves with age, hair anomalies, e.g. easily pluckable, sparse, hair (loose anagen hair), darkly pigmented skin with eczema or ichthyosis. Classically it is caused by a single recurrent missense SHOC2 mutation. SHOC2 forms a complex with protein phosphatase 1 (PP1C) which controls activation of signaling proteins such as mitogen activated protein kinases of RAS/MAPK pathway. In 2016, protein phosphatase 1 catalytic subunit beta (PPP1CB) gene has been found to be associated with Noonan syndrome-like disorder with loose anagen hair syndrome (NSLAH2). It is an extremely rare syndromal entity featured by macrocephaly, prominent forehead, low-set and posteriorly rotated ears, and developmental delay and anagen hair. Up till now, less than 20 patients had been reported worldwide. Here we report the first case of NSLAH2 in Hong Kong.

CASE REPORT

The proband presented to clinical genetic service for short stature and dysmorphism at the age of 16 years old. He was born full term in China to a non-consanguineous Chinese couple. Antenatal was uneventful. Physical examination revealed body weight and body height at 3rd centile and relative macrocephaly (head circumference at 97th centile). He had severe hypertelorism, arching eyebrows, bilateral ptosis, hypermetropia, low set ears, pectus excavatum, coarse hair, neck webbing and joint and skin laxity (Figure A). His cardiovascular examination revealed systolic murmur. He had borderline developmental delay. In view of his presentation, Noonan syndrome /rasopathy was suspected. PTPN11 sequencing and further sequence analysis of related twelve genes (BRAF, CBL, RASA1, HRAS, KRAS, MAP2K1, MAP2K2, RAF1, SPRED1, RIT1, SHOC2 and SOS1) were negative at the age of 17 and 18 years old respectively. Due to high suspicion of rasopathy and possibility of new genes discovery with times, at a follow-up visit 5 years later, WES showed a de novo variant c.146C>G (p.Pro49Arg) in PPP1CB, which encodes for an important component of the Ras/MAPK signaling pathway (Figure B). The diagnosis of Noonan syndrome-like disorder with loose anagen hair syndrome (NSLAH2) was substantiated. The mutation was de novo. Prenatal diagnosis and pre-implantation genetic diagnosis can be provided to him for reproductive concern.

Figure A: Facial profile
Figure B: The Ras/mitogen-activated protein kinase (MAPK) signaling pathway. Purple circle highlighted the genes related to noonan syndrome/ noonan like syndrome. PPP1CB was included to illustrate the interaction with the Ras/MAPK pathway.

CONCLUSIONS

This is the first patient in Hong Kong reported to have molecular confirmed NSLAH2. The phenotypic spectrum is wide for Noonan syndrome. Pattern recognition is important. The diagnostic odyssey illustrated the constant review of clinical phenotype and updating latest genetic discovery in different disease entities are essential in arranging appropriate genetic test to confirm the diagnosis.