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Case Report

Multilocus Inherited Neoplasia Alleles Syndrome: Case Report of Two Cases

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Abstract The advancement of genomic testing allows the detection of individuals affected by multilocus inherited neoplasia alleles syndrome (MINAS), a term that refers to those who harbour two or more dominant cancer predisposing germline variants. Although the phenotypic implication for MINAS is yet to be established, it is postulated that it might lead to a more severe or atypical phenotype. Herein we report 2 individuals each harbouring 2 pathogenic germline cancer predisposition gene variants. The first patient is a 18-year-old Chinese boy with likely pathogenic variants in NM_003000.2(SDHB):c.137G>A (p.Arg46Gln) and NM_000264.3(PTCH1):c.2380C>T(p.Gln794*). He has a relatively earlier onset of paraganglioma compared to the mean age of diagnosis in individuals harbouring a pathogenic *SDHB* mutation. The second patient is a 12-year-old Chinese boy with pathogenic variants identified in NM_000729.3(BRCA1):c.4372C>T(p.Gln1458*) and NM_000314.4(PTEN):c.1003C>T(p.Arg335*). He has clinical features of PTEN hamartoma tumour syndrome including developmental delay and macrocephaly, but enjoys good health and has no oncological disease to date.

Key words MINAS; Multilocus inherited neoplasia alleles syndrome

Introduction

The term multilocus inherited neoplasia alleles syndrome (MINAS) was first introduced by Whitworth et al in 2016.[1] It is used to describe patients who harbour dominant germline variants in two or more cancer predisposing genes. Previously believed to be a rare henomenon, more individuals with MINAS are uncovered due to the increasing application of next-generation sequencing that enables simultaneous parallel sequencing of multiple cancer predisposition genes. Although the phenotypic implication for MINAS is yet to be established, it is postulated that it might lead to a more severe or atypical phenotype. In this case report, we presented 2 patients each carrying 2 dominant cancer predisposing genetic variants.

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Case Report

Case 1

The index patient is an 18-year-old Chinese gentleman who is the only child of a non-consanguineous Chinese couple. He first presented to paediatricians for mild developmental delay and macrocephaly at 10 months old. Physical examination revealed hypertelorism and frontal bossing (Figure 1). He was subsequently found to have external hydrocephalus requiring endoscopic ventriculostomy at 2 years of age. He developed maxillary and mandibular odontogenic keratocysts with surgical resection at 13 years of age. He was found to be

hypertensive at 14 years old and subsequent CT scan of the abdomen showed a soft tissue enhancing lesion at the right side of the aortic bifurcation at the aortocaval region. Operative histological evaluation confirmed that he was suffering from para-aortic paraganglioma and complete tumour removal was achieved. He had catch up in development and graduated from a mainstream secondary school. There is no otherwise family history of paraganglioma, pheochromocytoma or hypertension.

He was referred to Clinical Genetic Service at 6 years old for developmental delay and macrocephaly. Genetic testing including karyotyping, NSD1 sequencing and Fragile X testing were unremarkable. Subsequent clinical exome sequencing detected likely pathogenic variants in NM_003000.2(SDHB):c.137G>A (p.Arg46Gln) [PS1, PM2, PP5] and NM_000264.3(PTCH1): c.2380C>T(p.Gln794*) [PVS1, PM2].

Family cascade screening showed that the mother also carries the same pathogenic variants in both the *SDHB* and *PTCH1* genes. On physical examination, she has macrocephaly, frontal bossing and also bilateral palmer pits (Figure 1). She had history of basal cell carcinoma (BCC) over the right cheek and left upper lip and had excision at the age of 54. Both affected individuals were referred to have relevant investigations and regular surveillance.

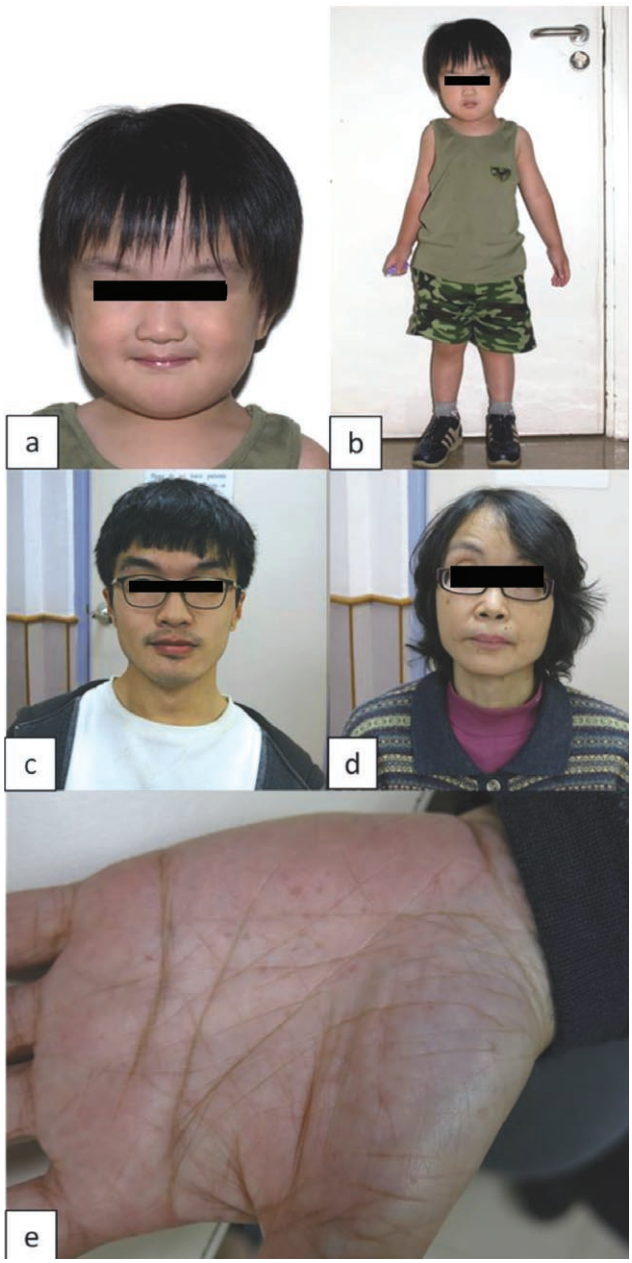

Figure 1 Clinical photos of proband taken at 2 years old. There is macrocephaly, hypertelorism and frontal bossing (a, b). Clinical photo of proband at 18 years old (c). Clinical photo of mother of proband. She has similar facial features including macrocephaly, hypertelorism and frontal bossing (d). She also has bilateral palmer pits (e).

Case 2

The index patient is a 12-year-old Chinese boy who presented with developmental delay and macrocephaly at 2 years old. Physical examination showed frontal bossing and mildly depressed nasal bridge (Figure 2). With PTEN hamartoma tumour syndrome in mind, hereditary cancer predisposition syndrome panel was offered to the proband after detailed discussion with the parents. The possibility of identification of secondary and incidental findings was also conveyed to the parents. The hereditary cancer predisposition syndrome panel revealed two clinically significant pathogenic variants in NM_000729.3(BRCA1): c.4372C>T(p.Gln1458*) [PVS1, PS1, PM2, PP5] and

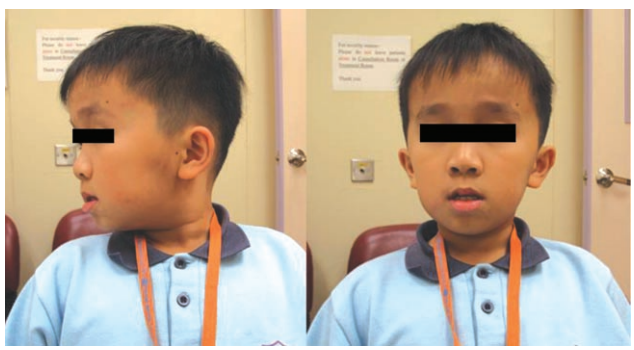

Figure 2 Clinical photos of proband with macrocephaly, frontal bossing and mildly depressed nasal bridge.

NM_000314.4(PTEN):c.1003C>T(p.Arg335*) [PVS1, PM1, PM2, PP5].

The genetic findings and their implications including the risk of developing malignancies and the need of regular surveillances were explained to the parents. The *BRCA1* gene pathogenic variant is paternally inherited while the *PTEN* pathogenic variant is de novo. Currently, both the proband and his father has no known oncological disease. There is no family history of breast or ovarian cancer.

Discussion

SDHB (Succinate dehydrogenase complex iron sulfur subunit B) is an essential component in the mitochondrial respiratory chain and citric acid cycle. *SDHB* gene mutation is associated with paragangliomas 4 [MIM115310], an autosomal dominant disorder that predisposes affected individuals to developing extra-adrenal sympathetic paragangliomas with an increased risk of metastasis; phaeochromocytoma and other malignancies such as renal cell carcinoma. For individuals harbouring the *SDHB* mutations, 34% developed malignancy.[2] The penetrance of paraganglioma/phaeochromocytoma was estimated to be 21.8- 57.6% at the age of 60.[3] Individuals at risk should have annual biochemical and clinical surveillance for features of paraganglioma and full-body MRI or otherwise cross-sectional imaging biennially.

PTCH1 gene is a tumour suppressor gene which encodes the protein patched-1, a receptor for sonic hedgehog, and together they prevent uncontrolled cell proliferation. *PTCH1* gene is associated with basal cell naevus syndrome [MIM109400], also inherited in an autosomal dominant manner. Basal cell naevus syndrome (BCNS), also known as Gorlin-Glotz syndrome (GGS), is characterised by macrocephaly, development of multiple jaw keratocysts, basal cell carcinomas, cardiac and ovarian fibromas. Basal cell carcinomas can occur in early childhood but usually presented at the age of 30s. Surveillance for affected individuals would include head circumference and development monitoring, orthopantogram and skin examination at regular intervals.

In this report, patient 1 has a younger age of diagnosis of paraganglioma when compared to the median age at diagnosis in SDHB carriers (30 years old).[2] Although the *SDHB* and *PTCH1* genes are involved in different cellular pathways and the mother has not developed paraganglioma yet at the age of 56, a synergistic effect from harbouring pathogenic variants in both genes cannot be excluded. In the proband's mother, she had basal cell carcinoma during her 50s, which is slightly later compared to the average age of onset in affected individuals with *PTCH1* variant.

For case 2, PTEN hamartoma tumour syndrome (PHTS) is a tumour suppressor gene that produces phosphatase and tensin homolog, a phosphatase protein product involved in the regulation of cell proliferation via antagonising the P13K/AKT pathway. Affected individuals have an increased risk of developing benign tumours, harmatomas and also malignancies involving different organs (e.g. breast, thyroid, renal cell, endometrial, colon cancer and melanoma) and might have developmental delay. The majority of malignancies occur after the age of 30s, though there is reported case of thyroid cancer occurring as early as 7 years of age.[4] Individuals harbouring PTEN pathogenic variant are recommended to have regular surveillance including annual dermatological examination and thyroid ultrasound. Women are encouraged to have monthly breast self-examination, annual breast screening and transvaginal ultrasound or endometrial biopsy. Regular colonoscopy and renal imaging is also recommended.

BRCA1 is a tumour suppressor gene responsible for DNA break repair or destruction of cells when beyond repair by its interaction with other cyclin protein and cylin-dependent kinase. Mutation of *BRCA1* gene could led to an increased genomic instability and predispose affected individuals to oncological diseases. *BRCA1*-associated hereditary breast and ovarian cancer syndrome (HBOC) is characterised by an increased risk of breast and ovarian cancer development. Monthly breast self-examination, annual/semiannual clinical breast examination, annual mammography and breast MRI is advocated for breast cancer screening in affected female individuals. For affected males, breast self-examination and annual clinical breast examination and annual screening of prostate cancer is also recommended.

Although *PTEN* and *BRCA1* appeared functionally distinct, mutual interaction between these two genes has been proposed as both were involved in the *p53* pathway.[5] However, there is of note no published study regarding affected individuals with both mutations having a more severe/atypical phenotype. A close follow up of our proband is needed to watch out for evolving oncological diseases.

The term multilocus inherited neoplasia alleles syndrome (MINAS) was first introduced in 2016 by Whitworth et al.[1] Previously believed to be a rare phenomenon, more individuals with MINAS are uncovered

due to the increasing application of next-generation sequencing that enables simultaneous parallel sequencing of multiple cancer predisposition genes. Out of the 314 cancer panels performed in our center, only 1 individual was identified to have MINAS. Most of the reported cases involve affected individuals with a hereditary cancer gene mutation that is related to the presenting cancer phenotype; and a second mutation that has no manifestation in the proband and related family members at the time of reporting. Current reported cases of MINAS mainly involve breast and colorectal cancer related genes (e.g. BRCA1 and BRCA2 mutation) or those genes related to constitutional mismatch repair syndrome. Ascertainment bias is difficult to eliminate as certain types of cancer and their related genes are more readily recruited for analysis. Affected individuals with a more severe phenotype and a strong family history are also more likely subjected to genetic testing. It is postulated that MINAS involving a certain combination of mutations might produce a more severe phenotype. However, due to the heterogeneity of mutation combinations and varying mechanisms of oncogenes, whether or not MINAS could lead to a more severe phenotype (e.g. an earlier onset, unusual tumour characteristics) remains inconclusive. Existing data give conflicting information even for the better-known BRCA1 and BRCA2 mutation combination.[6,7] For the other mutation combinations, only limited case reports and animal studies are available.

It is believed with the advancement of medical knowledge and increasing readiness of genetic testing, more individuals with MINAS will be detected. A precise interpretation of mutation combinations will be on demand in order to facilitate personalised management and risk estimation. Based on current limited experiences with MINAS, affected individuals with a more severe phenotype exist but there is not enough evidence to extend to a conclusion. From our data, we can see there is a relatively earlier onset of paraganglioma in the proband harbouring both SDHB and PTCH1 variant, but there is no further evidence to support an atypical or more severe clinical phenotype in individuals with MINAS. Prospective follow up of these two probands and their families would be of value in order to appreciate the age-dependent penetrance of the variants. Further functional studies and tumour profiling might be able to provide further insight into the phenotypic effect of MINAS. Data sharing with continuous update is encouraged as it might hopefully help to improve our understanding of MINAS.

Acknowledgement

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Conflict of Interest

All authors have disclosed no conflicts of interest.

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