

# A Tuberos Sclerosis Family with *TSC1* (c.1030-1G>A) Mutation Found through a Female Presenting as Multiple Ground Glass Nodules in Chest Computed Tomography Incidentally

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Chest computed tomography (CT) screening is becoming more popular in China. Therefore, more and more rare diseases and early stages of lung diseases were found. Here, we reported a case who presented as multiple ground glass nodules incidentally found in chest CT scan who had been suspected as synchronous multiple primary lung cancer (SMPLC) and/or metastatic cancer. She was finally diagnosed as tuberous sclerosis complex (TSC), an autosomal-dominant disorder characterized by the formation of hamartomatous lesions in the skin, eyes, kidney, and central nervous system.<sup>[1,2]</sup> Tuberos sclerosis complex 1 (*TSC1*) gene mutation (c.1030-1G>A) was found in her and her family members. This is a very rare report in China.

A 37-year-old woman was referred to our institution for multiple bilateral ground glass nodules from 1 mm to 5 mm in diameter found in an incidental chest CT scan on April 12, 2016 [Figure 1a]. She had no complaint and suspected as SMPLC and/or metastasis cancer in the local hospital. The positron emission tomography/CT (PET/CT) was proceeded, showing multiple ground glass nodules on the bilateral lungs and sclerotic bone changes including vertebral bodies, ribs, sternum, and pelvis which revealed normal 18F-deoxyglucose intake [Figure 1b]. We proceeded the transbronchial lung biopsy (TBLB) in different sites of the left lung, including the superior lobe and the outer and posterior basal segments of the inferior lobe, obtaining >20 lung tissue specimens. The pathologic findings revealed that the lesions were multifocal and pneumocyte hyperplasia with atypical

epithelial cells [Figure 1c]. She was discharged and followed up since there was no evidence of malignance.

Six months later, re-examined PET/CT showed similar lesions on the lung and bones.

She reported one episode of “epilepsy” 8 years before for unknown reasons. Some physical signs were found, including hypopigmented macules on her back, right forearm, and right calf, unguis fibromas on her left hand, and shagreen patch on dorsolumbar area of the back [Figure 1d]. Brain magnetic resonance imaging was performed and abnormal signals were found in the left parietal lobe and right frontal lobe [Figure 1e]. Her mother and son showed similar physical signs. The same chest CT manifestations were found in her mother and uncle (her mother’s brother). According to these information, *TSC* family was suspected. *TSC1* and *TSC2* mutations were further tested.

Genomic DNA was extracted from whole blood and formalin-fixed and paraffin-embedded (FFPE) samples of TBLB of the patient, respectively, using the QIAamp DNA

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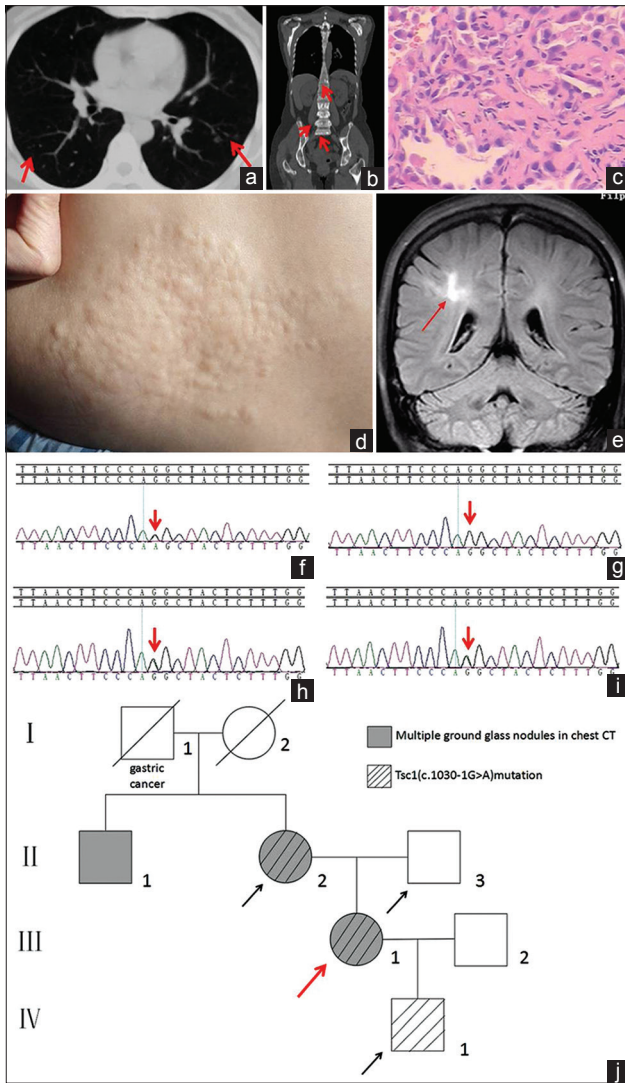


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**Figure 1:** Representative images of the patient. (a) First chest computed tomography on April 5, 2016: Multiple bilateral ground glass nodules in chest computed tomography scan (red arrows); (b) sclerotic bone changes in vertebral bodies and pelvis on April 12, 2016 in positron emission tomography/computed tomography (red arrows); (c) histopathological findings of the transbronchial lung biopsy specimen. Multifocal and pneumocyte hyperplasia with atypical epithelial cells (H and E, original magnification,  $\times 200$ ); (d) shagreen patch on dorsolumbar area of back; (e) abnormal signals were found in the right frontal lobe in brain magnetic resonance imaging (red arrow); (f-i) sequencing of tuberous sclerosis complex 1: f (the patient), h (her mother), and i (her son): One splice site mutation (c.1030-1G>A) in intron 10 of tuberous sclerosis complex 1 was detected (red arrow); g (her father) no mutation in tuberous sclerosis complex 1 was detected (red arrow); (j) the family pedigree: the roman numerals at the left side represent generations. III-1 was the case to be reported (red arrow). Tuberous sclerosis complex 1 genetic testing was performed in the index cases (II-2, 3, III-1, IV-1, black and red arrows).

Mini Kit (Qiagen Inc., Venlo, The Netherlands) according to the manufacturer's instructions. Customized NimbleGen array (NimbleGen, Roche, USA) was used to capture and enrich 27,000b target region (all exons and flanking 100 bp) of *TSC1* and *TSC2*. Sequencing was performed with IlluminaNextSeq CN500 (Illumina, San Diego, USA).

After removing low-quality or adapter contamination reads in the sequencing data, the filtered reads were mapped to the human genome build GRCh37 using BWA (a Burrows-Wheeler aligner). Single nucleotide variant and indel calls were generated using MuTect and GATK, respectively. To verify the mutation detected by target region capture sequencing, we designed primers flanking mutation regions according to gene sequence (NG\_005895.1 and NG\_012386.1) provided by the NCBI, and then used genome DNA as templates to amplify target region. Sanger sequencing was performed with ABI 3730 DNA Analyzer (Thermo Fisher Scientific, Massachusetts, USA).

One splice site mutation (c.1030-1G>A) in intron 10 of *TSC1* was detected [Figure 1f] in both blood and FFPE samples. The whole blood samples of her familial members including her mother, father, and son were also examined. The same mutation was detected in her mother and son [Figure 1g-1i]. The family pedigree is shown in Figure 1j. The familial TSC was determined. Since multifocal micronodular pneumocyte hyperplasia (MMPH) does not appear to be fatal and remained stable,<sup>[2]</sup> close follow-up was chosen for the patient, her mother, her uncle, and her son.

TSC was initially described approximately 150 years ago by von Recklinghausen in 1862. The incidence is approximately 1 in 5000–10,000 births.<sup>[2]</sup> The presence of common manifestations include cortical or subependymal tubers, white matter abnormalities, cardiac rhabdomyoma, renal angiomyolipoma, and skin lesions. The lungs, digestive system, retroperitoneum, and bone can be less frequently involved.<sup>[1]</sup> The pulmonary manifestations of TSC include MMPH and lymphangiomyomatosis (LAM).<sup>[2]</sup> MMPH in TSC was first described by Popper *et al.*<sup>[3]</sup> in 1991. On high-resolution CT, the MMPH was characterized by multiple nodules ranging in size from 1 mm to 10 mm, scattered throughout the lungs in a random distribution.<sup>[1]</sup> For the cases presented as MMPH in chest CT as this case, SMPLC or miliary metastatic malignancy must be carefully differentiated. Hence, pathological examination of the nodules in the lung was essential.

*TSC1* or *TSC2* mutation has been regarded as an independent criterion for the diagnosis or prediction of TSC, regardless of the clinical findings.<sup>[2]</sup> They are indicated as tumor suppressor genes due to their function in the regulation of cell growth and differentiation by inhibiting the mammalian target of rapamycin (mTOR) in the Akt-mTOR-S6kinase cell growth pathway.<sup>[4]</sup> A "pathogenic" mutation was defined as a mutation that clearly prevents protein synthesis and/or inactivates the function of the *TSC1* or *TSC2* proteins.<sup>[2]</sup> The mutation in intron 10 (c.1030-1G>A) we reported in this case is a splice mutation in *TSC1* gene. It does not directly change the encoded amino acid sequence of the *TSC1* protein. However, this variant affected splice acceptor site directly, thus it might interrupt the recognition of spliceosomes and result in incorrect splicing. This mutation was first reported in a familial TSC by Niida *et al.*<sup>[5]</sup> in 1999. However, this report did not provide the family pedigree.

To our knowledge, this is a very rare report regarding the c.1030-1G>A mutation in a family TSC pedigree in China.

The clinical diagnostic criteria of TSC include 11 major features and six minor features according to the 2012 International Tuberous Sclerosis Complex Diagnostic Criteria.<sup>[2]</sup> Some features appeared only at birth or infancy. Lesions such as hypomelanotic macules are the major features observed in about 90% of individuals with TSC which could be ignored by clinicians due to limited knowledge about TSC. Hypopigmented macules, unguil fibromas, and shagreen patch found in this case had been neglected for a long time, causing the delay of diagnosis.

TSC presented as MMPH was reported having better prognosis and specified treatment was usually unnecessary since the patients were usually asymptomatic and remained stable for a long time. Long-term follow-up is reasonable for this case and her family.

In conclusion, TSC presented as MMPH is a rare disease, and further examinations should be performed when multiple ground glass nodules were found in chest CT scan. The mutation in intron 10 (c.1030-1G>A) of *TSC1* might indicate a pathogenetic mechanism which could be beneficial for differential diagnosis and future therapy exploring.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s)/patient's guardians has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patient(s)/patient's guardians understand that their names and initials will not be published

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

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