Pulmonary Alveolar Microlithiasis

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KEYWORDS

• Pulmonary alveolar microlithiasis • Congenital disease • SLC34A2
• Type II b sodium-phosphate cotransporter (NPT2B) • Phosphate homeostasis

KEY POINTS

- Pulmonary alveolar microlithiasis (PAM) is a genetic lung disorder that is characterized by the accumulation of calcium phosphate deposits in the alveolar spaces of the lung.
- Mutations in the type II sodium phosphate cotransporter, NPT2b, have been reported in patients with PAM.
- Patients typically present without symptoms at a young age, with dense ground glass infiltrates noted on chest radiographs obtained for another purpose.
- PAM progresses gradually, often producing incremental dyspnea on exertion, desaturation in young adulthood, and, ultimately, respiratory insufficiency by late middle age.
- Treatment remains supportive. For patients with end-stage disease, lung transplantation is an option.

INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is a rare hereditary lung disease in which calcium phosphate deposits (calcospherites) accumulate in the distal airspaces. An Italian scientist, Marcello Malpighi, first described PAM in 1868; Harbitz[1] first carefully detailed the histopathology in 1918. The disease was named "Microlithiasis Alveolaris Pulmonum" by the Hungarian pathologist Puhr[2] in 1933. Since the first description of the disease almost 150 years ago, more than 1000 cases have been reported in the world literature.[3] PAM is often discovered on chest radiographs obtained for other purposes during early adulthood. Patients typically remain asymptomatic until middle age, when pulmonary fibrosis, pulmonary hypertension, and chronic respiratory failure ensue. Chest radiographs reveal diffuse, hyperdense, micronodular shadows producing a characteristic snowstorm appearance.[4] The diagnosis can often be established based on radiographic appearance alone, especially in *patients* with a family history. The recent discovery in patients with PAM of genetic mutations in the SLC34A2 gene, which encodes the sodium-phosphate cotransporter NPT2b (*SLC34A2*, NPT2b, NaPi-2b), has opened a window into PAM disease pathogenesis.[5,6] An animal model has been developed that can serve as a preclinical model for testing candidate therapies, and a worldwide network of rare lung disease clinics has identified potential subjects with PAM for trials. Here the authors review the cause, epidemiology, pathology, clinical features, and potential future treatment strategies for PAM.

EPIDEMIOLOGY

PAM has long been considered to be an autosomal recessive disorder because it transmits horizontally

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and is associated with consanguinity. Most patients with PAM have at least one sibling who is also affected by the disease. Mariotta and colleagues[7] reported that 35.8% of patients with PAM were diagnosed before 20 years of age and 88.2% before 50 years of age. PAM has also been reported in newborns and toddlers, including twins who died within 12 hours of birth,[8] and in octagenarians.[9,10] Familial incidence has been reported in 35% to 50% of cases reported from Japan,[11] Turkey,[12] Italy,[13] and other countries.[14] The frequency of PAM mutations in the Japanese population was determined to be less than 0.008.[6] There is no clear sex predilection for PAM.

PATHOLOGY

Molecular Pathogenesis

In 2006 and 2007, *SLC34A2* mutations were identified in patients with PAM by homozygosity mapping.[5,6] The *SLC34A2* gene is located on chromosome 4p15 and comprises 13 exons. It encodes a 2280-nt mRNA and a 690 amino acid sodium-phosphate cotransporter called NPT2b. A total of more than 15 different mutations have been described in 30 patients to date (**Fig. 1**).[3] Mutations have been found on multiple exons in patients from Turkey, but mutations seem to cluster in exon 8 in cases from China and in exons 7 and 8 in Japan.[15] The heterogeneity in mutations found is inconsistent with a founder effect, at least in the Turkish and Japanese populations, which have the largest populations studied. Most DNA aberrations found to date are missense mutations that result in protein truncation, but 3 damaging substitutions (G106R, T192K, Y455H) and a nonsense mutation that introduces a premature stop codon have been described.[5,15,16] In the few family studies that have been completed, the disease has demonstrated 100% penetrance in that all those with homozygous mutations are affected.[5] There does not seem to be any genotype/phenotype correlation based on variation in the age of disease onset in large family cohorts.[5] Genetic heterogeneity (ie, more than one gene involved) is not likely because mutations in *SLC34A2* have been identified in almost all patients studied. Almost all mutations identified to date have been homozygous, suggestive of identity by descent.

NPT2b is abundantly expressed in lung, primarily on the surface of alveolar type II cells, where it is thought to function as an exporter of phosphate generated by the metabolism of surfactant phospholipids.[17,18] In the absence of NPT2b activity, phosphate levels likely increase in the alveolar lining fluid and form complexes with calcium, resulting in the formation of lamellated microliths.[19] Alveolar pH, calcium concentrations, and nucleating proteins, lipids, or other molecules likely play an important role in microlith formation; but little is known about the conditions that favor stone initiation and growth. NPT2b is also expressed in the gut, where it functions as the major transporter for the uptake of dietary phosphorus, as well as in the breast, liver, testes, prostate, kidney, pancreas, and ovaries.[20,21]

Other sodium phosphate cotransporters include SLC34 family members NPT2a and NPT2c, which are predominantly expressed in the kidney, and SLC20 family members PIT1 and PIT2, which are ubiquitously expressed. The pulmonary expression of SLC20, NPT2a, and NPT2c transporters has not been well characterized in humans. Recently Saito and colleagues[19] reported expression of Pit1 and Pit2 but not NPT2a or NPT2c in mouse lung. The 3 SLC34 isoforms (NaPi-IIa, b, c) transport a divalent Pi (hydrogen phosphate [HPO_4^{2-}]) on binding of 2 or 3 sodium ions and use the inwardly directed Na+ electrochemical gradient to drive intracellular movement of inorganic phosphate (Pi).[22] The crystal structure has not been solved for any of the sodium-dependent phosphate cotransporters, and the bacterial dicarboxylate transporter has been used as a model for sodium-dependent anion transport.[23] The 3-dimensional (3D) structures of the wild-type NPT2b and 2 naturally occurring mutants were predicted by protein folding recognition with 3-dimensional position specific scoring matrix (Phyre Version 0.2) and molecular dynamics simulations.[15]

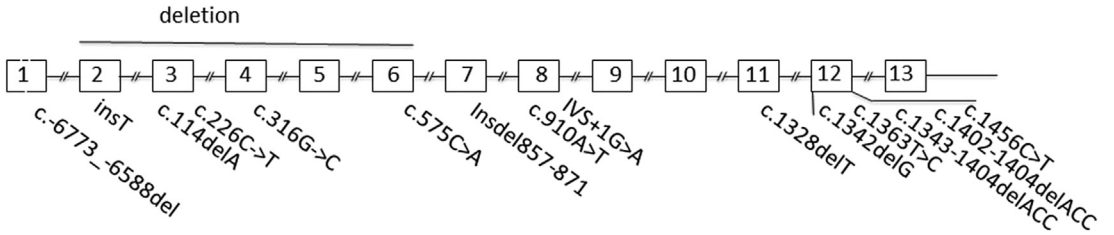

Fig. 1. Map of known SLC34A2 mutations. The SLC34A2 gene comprises 13 exons on chr. 4p15. (*Data from* Castellana G, Carone D, Castellana M. Microlithiasis of seminal vesicles and severe oligoasthenospermia in pulmonary alveolar microlithiasis (PAM): report of an unusual sporadic case. Int J Fertil Steril 2015;9(1):137–40.)