The autoimmune and immunodeficiency manifestations of ACP5 mutations

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Abstract

Spondyloenchondrodysplasia is a rare immuno-osseous dysplasia caused by biallelic mutations in the gene ACP5, which encodes tartrate resistant acid phosphatase (TRAP). I will present data pertaining to the recognized skeletal, neurological and immune phenotypes, most particularly the immune manifestations. In a recent analysis of 26 patients, 22 manifested clinical autoimmune disease, most frequently autoimmune thrombocytopenia and systemic lupus erythematosus and further two demonstrated positive autoantibodies. In the majority of patients tested we detected up-regulated expression of interferon stimulated genes (ISGs), in keeping with the autoimmune phenotype and the likely immune-regulatory function of the deficient protein TRAP. Two mutation positive patients did not demonstrate an up-regulation of ISGs, including one patient with significant autoimmune disease controlled by immunosuppressive therapy perhaps demonstrating a useful treatment for the autoimmune manifestations. Of further note recurrent bacterial and viral infections were reported in five of 26 patients, raising the suggestion that immunodeficiency is a part of ACP5-associated disease. Interpretation of immunological testing undertaken in the cohort was difficult, in terms of differentiating disease-related immunodeficiency from immune defects resulting from immunosuppressive therapy. Whilst additional data are needed, we would recommend in the interim that patients with biallelic ACP5 mutations should be monitored for an infectious susceptibility and should undergo lymphocyte phenotyping and serum immunoglobulin values prior to immunosuppressive therapy. Spondyloenchondrodysplasia (SPENCD) is a rare skeletal dysplasia, characterized by metaphyseal lesions, neurological impairment and immune dysregulation associated with lupus-like features. SPENCD is caused by biallelic mutations in the ACP5 gene encoding tartrate-resistant phosphatase. We report on a child, who presented with spasticity, multisystem inflammation, autoimmunity and immunodeficiency with minimal metaphyseal changes due to compound heterozygosity for two novel ACP5 mutations. These findings extend the phenotypic spectrum of SPENCD and indicate that ACP5 mutations can cause severe immune dysregulation and neurological impairment even in the absence of metaphyseal dysplasia. Spondyloenchondrodysplasia with immune dysregulation (SPENCDI) is an inherited condition that primarily affects bone growth and immune system function. The signs and symptoms of SPENCDI can become apparent anytime from infancy to adolescence. Bone abnormalities in individuals with SPENCDI include flattened spinal bones (platyspondyly), abnormalities at the ends of long bones in the limbs (metaphyseal dysplasia), and areas of damage (lesions) on the long bones and spinal bones that can be seen on x-rays. Additional skeletal problems occur because of abnormalities of the tough, flexible tissue called cartilage that makes up much of the skeleton during early development. Individuals with SPENCDI often have areas where cartilage did not convert to bone. They may also have noncancerous growths of cartilage (enchondromas). The bone and cartilage problems contribute to short stature in people with SPENCDI. Individuals with SPENCDI have a combination of immune system problems. Many affected individuals have malfunctioning immune systems that attack the body's own tissues and organs, which is known as an autoimmune reaction. The malfunctioning immune system can lead to a variety of disorders, such as a decrease in blood cells called platelets (thrombocytopenia), premature destruction of red blood cells (hemolytic anemia), an underactive thyroid gland (hypothyroidism), or chronic inflammatory disorders such as systemic lupus erythematosus or rheumatoid arthritis. In addition, affected individuals often have abnormal immune cells that cannot grow and divide in response to harmful invaders such as bacteria and viruses. As a result of this immune deficiency, these individuals have frequent fevers and recurrent respiratory infections. Some people with SPENCDI have neurological problems such as abnormal muscle stiffness (spasticity), difficulty with coordinating movements (ataxia), and intellectual disability. They may also have abnormal deposits of calcium (calcification) in the brain. Due to the range of immune system problems, people with SPENCDI typically have a shortened life expectancy, but figures vary widely. Spondyloenchondrodysplasia is a rare immuno-osseous dysplasia caused by biallelic mutations in ACP5. We aimed to provide a survey of the skeletal, neurological and immune manifestations of this disease in a cohort of molecularly confirmed cases. Methods: We compiled clinical, genetic and serological data from a total of 26 patients from 18 pedigrees, all with biallelic ACP5

mutations. Results: We observed a variability in skeletal, neurological and immune phenotypes, which was sometimes marked even between affected siblings. In total, 22 of 26 patients manifested autoimmune disease, most frequently autoimmune thrombocytopenia and systemic lupus erythematosus. Four patients were considered to demonstrate no clinical autoimmune disease, although two were positive for autoantibodies. In the majority of patients tested we detected upregulated expression of interferon-stimulated genes (ISGs), in keeping with the autoimmune phenotype and the likely immune-regulatory function of the deficient protein tartrate resistant acid phosphatase (TRAP). Two mutation positive patients did not demonstrate an upregulation of ISGs, including one patient with significant autoimmune disease controlled by immunosuppressive therapy. Conclusions: Our data expand the known phenotype of SPENCD. We propose that the differentiation between spondyloenchondrodysplasia and spondyloenchondrodysplasia with immune dysregulation is no longer appropriate, since the molecular evidence that we provide suggests that these phenotypes represent a continuum of the same disorder. In addition, the absence of an interferon signature following immunomodulatory treatments in a patient with significant autoimmune disease may indicate a therapeutic response important for the immune manifestations of spondyloenchondrodysplasia

Biography:

Tracy Briggs was qualified from Liverpool Medical School in 2003 and trained in Pediatrics and then Clinical Genetics. She undertook a PhD during her clinical training at The University of Manchester and is currently an NIHR Clinical Lecturer. She spends 50% of the time working in the Genomic Medicine Department at the Central Manchester NHS Foundation Trust and 50% of the time at The University of Manchester. Her research interest is immunogenetics, particularly innate and autoimmune genetic disorders.

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