Author’s response to reviews

Title: A novel compound heterozygous mutation of the SMARCAL1 gene leading to mild Schimke immune-osseous dysplasia: A case report

Authors:
Shuaimei Liu (719305071@qq.com)
Mingchao Zhang (zmchj99@163.com)
Mengxia Ni (nimengxia@126.com)
Peiran Zhu (980346785@qq.com)
Xinyi Xia (xiaxynju@163.com)

Version: 2 Date: 08 Mar 2017

Author’s response to reviews:

Dear editor:

We would like to resubmit the revised manuscript entitled “A novel compound heterozygous mutation of the SMARCAL1 gene leading to mild Schimke immune-osseous dysplasia: A case report” for consideration by BMC Pediatr. We would like to thank the reviewers for thoroughly reviewing our manuscript and making many thoughtful comments. We have added significant new data, described in detail below, and revised the manuscript to address reviewers’ comments. Here are our point-by-point responses:

To Reviewer 1:

Comment 1: The English is not acceptable.

Answer: Thank you for your comments, which are very helpful to our research. The manuscript has been revised by a reputable English language editing service. The typography mistakes, language mistakes and repetitive references have been corrected.
To Reviewer 2:

Comment 1: The manuscript has considerable English grammar and spelling errors- this needs detailed review and probably best re-written.

Answer: Thank you for your comments, which are very helpful to our research. The manuscript has been revised by a reputable English language editing service. The typography mistakes, language mistakes and repetitive references have been corrected.

Comment 2: Clinical detail are scatty- there are no clinical photographs and X-ray pictures to demonstrate extent of skeletal dysplasia in the case.

Answer: Indeed, as you said, we lack clinical photographs and X-ray pictures to demonstrate extent of skeletal dysplasia in the article. Here please allow me to do some simple descriptions, firstly, After receipt of your comments, we called up the proband, unfortunately, we could not contact the proband and he has not been to hospital for review at present yet. So we do not get his clinical photographs. However, according to his previous report, we got his X-ray pictures (Figure 1). Secondly, urinary routine examinations found that protein 3+, after given prednisone 10 mg tid immunosuppression, urine protein dropped to 2+. However, after methylprednisolone sodium succinate and cyclophosphamide (three cycles) therapy, proteinuria is continuous positive result. And the litter patient had puffy eyelids and in the diagnosis of edema of lower extremity. The hospital diagnosed with IgM nephropathy. Thirdly, lymphocytes percentage has declined by 10.52%, The proportion of B cell has increased and lymphocyte T has declined. Blood IgG decreased, showing a congenital immune deficiency. However, it's worth mentioning that spine of the litter patient has scoliosis. Ludman (Am J Hum Genet. 1993 PMID: 8267014) reported the presence of the immune deficiency, spondyloepiphyseal dysplasia, and renal abnormality is specific to immuno-osseous dysplasia. The diagnosis of SIOD is doubtful. Gene sequencing was applied for further diagnosis. So the next generation sequencing was used for genetic testing. Then we identified two missense mutations of SMARCAL1. Finally, the disease was diagnosed for SIOD.
Comment 3: There is no comparative analysis with other publishes cases

Answer: Thank you for your constructive comments, which are very helpful to our research. In order to further enrich the contents of the article. Here are some of the additions in second paragraph of discussion: Boerkoel (Nature Genetics. 2002 PMID:11799392) reported the genotypes present in three families with the milder form of SIOD. One family had compound heterozygous mutations (I548N, R645C), while the R586W, and K647T mutations were respectively identified in homozygotic states in the remaining two families. The mild clinical phenotype found in this patient corresponds exactly with that described by Boerkoel (Nature Genetics. 2002 PMID:11799392). All of the affected individuals were short in stature, and had renal disease and lymphocytopenia, while lacking recurrent infections. It is noteworthy that affected individuals described in previous studies were all more than 15 years of age after undergoing renal transplantation. The patient presented in this study had a mild clinical phenotype but had not yet undergone renal transplantation. This milder phenotype caused by missense mutations may be due to residual SMARCAL1 function (Nature Genetics. 2002 PMID:11799392). However, Yue (Nephrology Dialysis Transplantation. 2010 PMID:20179009) and Jimena (European Journal of Medical Genetics. 2016 PMID:27282802) have reported compound heterozygous affected individuals presenting with a severe phenotype due to missense mutations. These differences may be attributed to environmental or genetic influences. The presence of missense mutations is therefore unlikely to accurately predict disease phenotype.

Comment 4: Discussion needs to provide clarification on molecular links with skeletal dysplasia and immune deficiency.

Answer: Thank you for your genuine comment, which are very helpful to my article. So I made some changes, and add some contents in fourth paragraph of discussion. To date, the common missense mutations R586W, R645C and R820H have all been detected in the conserved arginine residues of the SMARCAL1 protein. Mutations R586W and R820H belong to a region associated with DNA binding and ATPase activity. Since the novel R817H mutation detected in this study is located adjacent to the R820H mutation found within the DNA/RNA helicase domain, the R817H variant may similarly affect ATPase function through altering the SMARCAL1 structure or protein interaction capacity. The known missense mutation R645C is located in the SNF2 domain and is associated with putative nuclear localization. It is predicted to interfere with the mobility of the hinge region and prevent competent clamping of SMARCAL1 on the DNA (Cell. 2005 PMID:15882619). This is similar to the effects observed with the R644W, K647Q and K647T mutations. SMARCAL1 mutations result in cell proliferation defects and a promotion of apoptosis. SMARCAL1-deficient zebrafish were associated with
growth retardation and defects in hematopoiesis (Developmental Biology. 2010 PMID:20036229). Growth failure caused by skeletal dysplasia in SIOD patients is not as a result of renal disease. The functional loss of SMARCAL1 in SIOD patients contribute to multiple phenotypes resulting from the instability of DNA replication throughout the genome (Nucleus. 2010 PMID:21327070). In an vitro study, Marie (Nucleus. 2016 PMID:27813696) reported that a deficiency of SMARCAL1 altered the chromatin structure, thereby affecting gene expression. Recently, SIOD patients with a deficiency in SMARCAL1 had increased hypermethylation of the IL7R promoter, but reduced expression in T cells (Clinical Immunology. 2015 PMID:26499378). This is consistent with the results obtained by Marie.

Thank you for your consideration of our manuscript. If you have any question about this paper, please don’t hesitate to let me know.

Yours sincerely,

Xinyi Xia, M.D., Prof.