Reviewer 1

1. In the case summary, authors should mention the other possibility apart from the truncated protein.

Dear reviewers, thanks for your valuable suggestion. In terms of the functional changes due to *ALMS1* mutation, the compound heterozygous mutations in this case were nonsense and frameshift mutations. Based on previous publications, the majority (96%) of the variations are nonsense or frameshift variations (insertions or deletions) leading to premature stop codons producing **a truncated protein, or no protein at all** (Marshall et al. Hum Mutat. 2015 Jul; 36(7):660-8; Astuti et al. Hum Mutat. 2017 Jul; 38(7):764-777; Chen et al. Mol Genet Genomic Med. 2017 Jul; 5(4):390-404). Thus, we speculated that the ALMS1 mutation-induced protein dysfunction is likely to be a truncation of ALMS1.

2. Please clearly specify the term "abnormal liver function".

Dear reviewers, based on your suggestion, we provided detailed abnormal liver function in the section of "***Laboratory examinations***" on P7: abnormal liver function (elevated alanine aminotransferase level [ALT], 61 IU/L; aspartate aminotransferase level [AST], 62 IU/L).

3. How was diabetic nephropathy identified in the laboratory? this is not possible. At the end of the laboratory section, the authors describe normal kidney function which contradicts their previous sentence of diabetic nephropathy.

Dear reviewers, thanks for your valuable suggestion. Based on Classification of Diabetic Nephropathy 2014, diabetic nephropathy was classified as follow: (Masakazu et al. J Diabetes Invest 2015; 6: 242–246) :

Table 1 | Classification of Diabetic Nephropathy 2014jdit

Stage	Urinary albumin (mg/g Cr) or urinary protein (g/g Cr)	GFR (eGFR) (mL/min/1.73 m^2)
Stage 1 (prenephropathy)	Normoalbuminuria (<30)	≥30‡
Stage 2 (incipient nephropathy)	Microalbuminuria (30–299)§	≥30
Stage 3 (overt nephropathy)	Macroalbuminuria (≥300) or persistent proteinuria (≥0.5)	≥30¶
Stage 4 (kidney failure)	Any albuminuria/proteinuria status††	<30
Stage 5 (dialysis therapy)	Any status on continued dialysis therapy	

Thus, we provided detailed information on diabetic nephropathy in the section of "***Laboratory examinations***" on P7: diabetic nephropathy (urine microalbumin [MA] level, 12.1 mg/dl; urine MA/creatinine ratio, 164 mg/g Cr;24-hour urine protein level, 378 mg/24 h; glomerular filtration rate [GFR], 90 ml/min/1.73m^2), belong to stage 2 (incipient nephropathy). Although the biochemical examination after 2 years during follow-up indicated an elevation of BUN, the

diabetic nephropathy was classified into stage 2 (incipient nephropathy): urine microalbumin [MA] level, 8.38 mg/dl; urine MA/creatinine ratio, 108 mg/g Cr; GFR, 119.8ml/min/1.73m^2. Thus, we deleted "normal kidney function " and "rapid progression of kidney function" (P3 **CASE SUMMARY**; P7 ***Laboratory examinations***; P11 **OUTCOME AND FOLLOW-UP**; P16-19 **DISCUSSION**).

4. In the imaging section the authors describe pulmonary function with obstructive ventilation disorder, this cannot be done by imaging, please correct it.

Dear reviewers, thanks for your valuable suggestion. Restrictive pulmonary ventilation disorder is completed through a lung function test and should be a special test. Due to the submission template only included "Laboratory examinations and Imaging examinations", we thus provided "Imaging examinations". In the revised manuscript, we have revised the "P8 ***Laboratory examinations***" according to the suggestion.

5. How did the authors conclude that their mutations were gain?

Dear reviewers, thanks for your valuable suggestion. Based on Fig 4, the two mutations in the proband resulted in the formation of stop codons, leading to early termination of ALMS1 protein. Therefore, it is a stop-gain mutation.

6. In the follow-up section, the authors mention the absence of an ovary after cystectomy never mentioned previously.

Dear reviewers, thanks for your valuable suggestion. In "P8 ***Imaging examinations***", it is mentioned that: at the initial visit, the gynecological ultrasound findings revealed a right pelvic cyst (7.8×8.2×7.5 cm), thus the patient underwent surgical removal of the ovarian cyst after the first diagnosis and discharge in the local hospital, but the ovaries were preserved (P11 **OUTCOME AND FOLLOW-UP**: 'The imaging examination revealed disappearance of the right ovarian **cyst** (after cystectomy) '.

7. In follow-up section, the authors refer that development was normal like the other children, this is very difficult due to the evolution of AS.

Dear reviewers, thanks for your valuable suggestion. The proband in this case was 10 years old at the second hospitalization, described in "P10 **OUTCOME AND FOLLOW-UP**": 'when she was 10 years old, with a height of 148 cm (+1.34 SD), weight of 44.8 kg (+1.96 SD), BMI of

20.45 kg/m2 (+1.74 SD), and pubertal stage of Tanner II'. We provided the information of bone age: BA 13.5 years old with a predicted adult height (PAH) of 152cm（-1.59SD）. The linear growth of this proband may be affected, as described in "P15 **DISCUSSION**": 'Most patients with AS whose height is normal in early childhood, but growth retardation occurs in adolescence， but the proband in this case was taller (+1.34 SD). It may be due to the patient's early puberty (BA 13.5 years old), and the PAH was still impaired.' We will continue to follow up to observe if the proband will abnormally grow and develop in the middle and late stages of puberty.

8. In the sentence "In the present case, the patient carried pathogens ..... the exon 16 mutation may play a dominant role ..." the authors must be very cautious since AS is autosomal recessive.

Dear reviewers, thanks for your valuable suggestion. The original meaning of this sentence was "suggesting that the pathogenic mutations in exon 16 may play a major role". The previous version of such description was misleading and has been corrected in P17 **DISCUSSION**.

9. The article does not present the "in silico" analysis of the reported mutations.

Dear reviewers, thanks for your valuable suggestion. As requested, we have provided the procedure of bioinformatic analysis on the section of "P8-9 ***Further diagnostic work-up***": Data were filtered to generate "clean reads" by removing adapters and low quality reads (＜Q20). Sequences were aligned to the hg19 reference genome by NextGENe software (SoftGenetics, State College, PA) using the recommended standard settings for single-nucleotide variant and insertion/deletion discovery. DNA sequence variations were annotated using the population and literature databases (including 1000 Genomes, dbSNP, GnomAD, Clinvar, HGMD, and OMIM databases). Computational analysis of variants was performed using PolyPhen-2, CADD and MutationTaster. The frequency filter adopted the minor allele frequency (MAF) > 1% in Asian population. Variants interpretation was manipulated according to the American College of Medical Genetics (ACMG) guidelines."

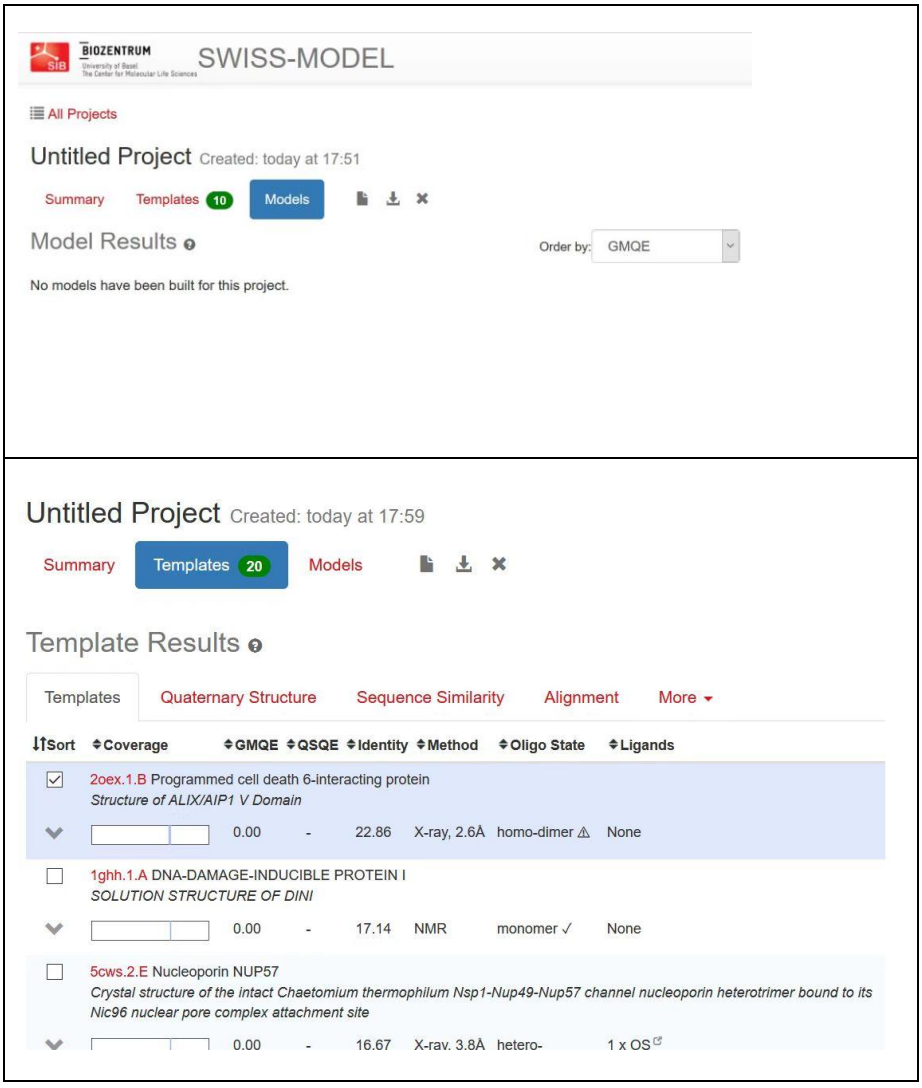
10. In the conclusion the authors state "Our case suggests that the manifestation of hyperthyroidism may indicate a rapid progression of AS", but they had previously mentioned that the development of the proband was comparable to children of their age, this is contradictory.

Dear reviewers, thanks for your valuable suggestion. The proband in this case presented with Graves' hyperthyroidism during the second hospitalization, and she also developed a progressive increase in liver enzymes. Although being classified as diabetic nephropathy（stage 2，incipient

nephropathy），she had a progressive increase of blood BUN. In “P16 **DISCUSSION**”, it was mentioned that 2 cases of hyperthyroidism reported in Turkey: ‘They were both negative for thyroid autoantibodies and **simultaneously** developed renal failure’， which was related to disease progression. Thus, we speculated that ‘the manifestation of hyperthyroidism may indicate a rapid progression of AS’, i.e., liver injury.

11. Figure 4 does not show the truncated protein rather the evolutionary conservation of the amino acid and the stop codon. This has to be corrected. A protein modeling would be very useful and interesting.

Dear reviewers, thanks for your valuable suggestion. We tried to use the software to make the protein model but failed because no homologous sequence could be used for modeling:



Reviewer 2

1. The correlation between the two disease is unclear. Please explain your conclusion：Manifestation of hyperthyroidism may suggest rapid progression of AS.

Dear reviewers, thanks for your valuable suggestion. The proband in this case presented with Graves' hyperthyroidism during the second hospitalization, and she also developed a progressive increase in liver enzymes. Although being classified as diabetic nephropathy（stage 2，incipient nephropathy），she had a progressive increase of blood BUN. In "P16 **DISCUSSION**", it was mentioned that 2 cases of hyperthyroidism reported in Turkey: 'They were both negative for thyroid autoantibodies and **simultaneously** developed renal failure', which was related to disease progression. Thus, we speculated that 'the manifestation of hyperthyroidism may indicate a rapid progression of AS'.

Reviewer 3

1. The association between AS and Graves is not convincing. One can argue that in that case it was just a coincidence. Do the authors have enough evidence that this is indeed an association and not a coexistence? If yes, they should propose a causality mechanism. If not, I recommend to rewrite the statement of purpose and part of the manuscript, to focus only on the new mutations (as innovation). In this case the literature review should focus on all thyroid diseases found in AS patients (eg. cancer).

Dear reviewers, thanks for your valuable suggestion. In "P16 **DISCUSSION**", it was mentioned that: 'Regarding the correlation between AS and the thyroid, most patients have hypothyroidism (11-36%) and several patients have subclinical hypothyroidism. It is currently believed that hypothyroidism (central or primary) may be primary or secondary to AS, and **20% of cases are autoimmune-related**.' **It can be seen that the incidence of autoimmune thyroiditis is not low. AS patients may have autoimmune reactions**, but so far there is no relevant report on the mechanism of autoimmune reactions in AS patients. Considering that the clinical phenotype of AS is very complex, it is mentioned in "P14 **DISCUSSION**": 'it differs greatly even among individuals with the same mutation site'，thus it cannot be completely excluded the relevance of Graves' disease to AS. We will further follow up the thyroid function and disease progression to clarify the correlation, and further conduct the functional test and mechanism study to achieve more findings.

As requested, we searched the publications on AS and thyroid disease, and described in "P16 **DISCUSSION**". Except the case regarding 'follicular variant of papillary thyroid carcinoma', other references were added in "P16 **DISCUSSION**": 'until now, only one study reported a 35 years old female AS patient developed a follicular variant of papillary thyroid carcinoma…while it is not clear that the malignancies represent a true association or a simple coincidence (Fam Cancer. 2015 Dec;14(4):599-602. doi: 10.1007/s10689-015-9816-x).'