**Author’s response to reviews**

**Title:** A 9-year-old Korean girl with Fontaine progeroid syndrome: a case report with further phenotypical delineation and description of clinical course during long-term follow-up

**Authors:**

Jaehui Ryu (jhryu25@snu.ac.kr)

Jung Min Ko (jmko@snu.ac.kr)

Choong-Ho Shin (chshinpd@snu.ac.kr)

**Version:** 1  **Date:** 09 Oct 2019

**Author’s response to reviews:**

Dear editors and reviewers,

Thank you for your kind comments on our manuscript. We tried our best to revise manuscript according to the reviewers’ recommendation.

Reviewer reports:

Tadashi Kaname, M.D., Ph.D. (Reviewer 1):
It is not clear what is novel in this manuscript, because she has a recurrent variant in SLC25A24. The authors should emphasize what novel point(s) are in the text.
Thank you for your comment. We serially monitored growth profile of our patient and revealed that the short stature of the patient is not due to growth hormone deficiency. We also chronologically organized demographic information of related syndromes including GCMS, FFS, and PLWS. Those points are clarified on the final part of discussion.

Platform and data (not pathogenic CNVs) of chromosomal microarray should be described as supplemental information.

We added the platform and data of chromosomal microarray used in this study as supplemental information.

[Chromosomal microarray testing was conducted using Agilent Human Genome oligonucleotide comparative genomic hybridization (CGH) microarray 4 x 180K (Agilent Technologies, Santa Clara, CA, USA) with 13 kb overall median probe spacing. Genomic DNA was labeled and hybridized to the array, according to the manufacturer’s protocol for Oligonucleotide Array-Based CGH for Genomic DNA Analysis (version 6.2; Agilent Technologies). A DNA reference sample (male or female human genomic DNA; Promega, Madison, WI, USA) was used. The slide was scanned on a microarray scanner (G2565CA; Agilent Technologies). Data were extracted from a *.tif image using Agilent Feature Extraction software (version 10.7.3.1) and]
analyzed with Genomic Workbench software (version 7.0.4.0, Agilent Technologies). The local background was subtracted from the median intensities of the Cy3 and Cy5 channels. The log2 patient-to-reference ratio was calculated for each spot and normalized to the median of the ratio of all chromosomes. All CNVs were called and based on human assembly GRCh37 (hg19).

It might be better to add clinical diagnosis (sub-classified diagnosis) in table 1.

Thank you for your comment; sub-classified diagnosis was added in the table.

Lionel Van Maldergem (Reviewer 2):
Language should be checked by a native English-speaker

Thank you for your comment. We asked a native English-speaker to check the language throughout the paper. (OnlineEnglish OLE35977)

Genetics is poorly described. Nomenclature, NM number p.[.... ....], precise description of methods used rather than vague terms

We changed the phrase about the mutation detail as NM_013386:c.650G>A, p.[Arg217His]

Clinical photographs require absence of eyes blurring for a condition affecting the eyes. More importantly, an added value would be given by serial photographs at different ages. Should the authors be able to obtain a full consent to publish these photographs, it will undoubtedly improve the general quality of the paper.

We strongly agree that serial photographs will improve the quality of the paper. However, unfortunately, we couldn’t get a full consent to obtain serial photographs of the patients.

More attention should be paid to the clinical description. Results of paraclinic investigations, SD, ..

Thank you for your comment. We revised to describe clinical features more organized in order of general appearance, facial appearance, limb & organ abnormalities, and developmental consequences. Serial investigations of height, weight and head circumference are described in terms of standard deviation.

The discussion would benefit from being more structured by describing resemblances and differences between gcms and pp, then explaining why ps might belong to the same spectrum, avoiding a mix-up of speculations and established data, then explaining why their case supports a lumping of ffs and gcms.

Thank you for your comments. We added more structured description of resemblances and differences between GCMF and FFS; there were major differences that GCMS patients were mostly female and most FFS patients dead before 1 year of age. To date, a total of 11 patients including 3 males and 8 females have been genetically confirmed with FPS. Two out of three male patients dead before 12 months and there is only one case of surviving male. Whereas there are only one patient who was dead before 12 months of age and two more patients who dead at 18 and 20 months respectively, among eight female patients.

We also added explanation about specific clinical features of PLWS which might be helpful to explain why PLWS might belong to the same spectrum. We omitted highly speculative part about HGPS and statistics including PLWS.
The discussion on catch-up growth and development and therapeutic issues with comparison to Hutchinspn-Gilford syndrome is highly speculative and does not seem relevant.

Thank you for your comment. We agree that applying the case of HGPS for our patient is highly speculative and not logical since those two syndromes have different genetic background and patho-mechanisms. Relevant discussions are omitted.

Minor comments

P2L28. Outcome should be described in a distinct sentence. Progeroid features deserves specification. Skin wrinkling would benefit from being detailed: face, body, limbs?

Thank you for your comment. Unfortunately, we couldn’t have an opportunity to perform a developmental screening test. However, we could get information that she reached the level of her peers, and is now doing well in school. We revised the description of progeroid features to ‘generalized loose skin with decreased subcutaneous fat, skin wrinkling on forehead and limbs’.

P2L33 Below 1st centile does not tell the reader the number of deviations to the mean. Please express growth parameters in SD

We changed growth parameters from percentile to standard deviation.

P3L11 A reference concerning lumping of GCMS and FFS is required. It seems paradoxical to give a new name referring to the first author of a secondary paper and to neglect the first author of the seminal paper.

Thank you for your comment. Since GCMS and FFS share similar clinical presentations and genetic etiology, Writzl et al (2017) first suggested integrating two syndromes under name of Fontaine progeroid syndrome (FPS), owing to their subjects who were originally diagnosed as FFS. After the suggestion, the syndromes are now considered as the same disorder on OMIM as FPS, with a wide spectrum of clinical manifestations and severity.

P3L33 'recent advances in genetic technology' does not reflect adequately the current state of the art of recent genetic advances

We changed this sentence to “the clinical introduction of next generation sequencing technology including trio exome sequencing and whole genome sequencing” for clarifying the meaning.

P3L50 please use proper nomenclature

We changed this phrase as “a de novo mutation of NM_013386:c.650G&gt;A, p.[Arg217His] in SLC25A24”

P4L8 should read 31w+6days. Oligohydramnios from 26 w

Thank you for your comment. Correction was made as suggested.

P4L15 specify SD

Thank you for your comment. Correction was made as suggested.
P4L20 separate sentence with facial dysmorphism description and other clinical features. Provide a clinical photograph if available.

Thank you for your comment. We separate sentence with facial dysmorphism description and other clinical features. We revised to describe clinical features more organized in order of general appearance, facial appearance, limb & organ abnormalities, and developmental consequences. We added a photo of the patient’s face as 1a (with a problem of de-identification, editors recommend to re-submit a cropped photo including ant. hairline and forehead except eyes after 1st revision submission).

P4L37 specify SD / dilatation?

Thank you for your comment. Correction was made as suggested.

P6L40 needs reference

Relevant information is newly added on background part, and the references are also added.

P7L25 please define the syndrome by its clinical manifestations.

We omitted the discussion regarding to HGPS.

P7L29 Since molecular characterization of Petty's syndrome does not exist until now, it is premature to consider GCMS, FFS and PLWS together.

Thank you for your comment. We agree that it is premature to define PLWS as a same disease entity with FPS. However, according to previous case reports of PLWS, PLWS also presents with typical characteristics of FPS including prenatal growth restriction and further short stature, decreased subcutaneous fat, coronal synostosis, umbilical hernia at birth, short digital phalanges, and normal development. Therefore there is a strong possibility that PLWS will share same genetic background with FPS and we suggest that it would be worthy to figure out whether they harbor the same mutation of SLC25A24.

P7L33 should read differences between genders/ 'specific genetic etiology' Does the author means molecular basis?

In the original sentence, ‘specific genetic etiology’ meant molecular basis. However, we revised that part into more specific explanation; It had been known separately as GCMS and FFS because there were major differences that GCMS patients were mostly female and most FFS patients dead before 1 year of age. To date, a total of 11 patients including 3 males and 8 females have been genetically confirmed with FPS. Two out of three male patients dead before 12 months and there is only one case of surviving male. Whereas there are only one patient who was dead before 12 months of age and two more patients who dead at 18 and 20 months respectively, among eight female patients.

P7L40 statistics are inappropriate for including Petty's syndrome. Similarly, translating therapeutic considerations valuable for HPGS to GCMS and FFS does not make much sense due to different pathomechanisms and courses.

Thank you for your comments. We agree that the statistics are inappropriate for including Petty's syndrome since genetic confirmation has not been performed with any of reported PLWS patients. Thus we omitted the statistics including Petty's syndrome. We also agree that applying
the case of HGPS for our patient is highly speculative and not logical since those two syndromes have different genetic background and patho-mechanisms. Relevant discussions are omitted.

Best regards,

Jung Min Ko