P1-808

Identification of 11p14.1-p15.3 Deletion Probably Associated with Short Stature, Relative Macrocephaly and Delayed Closure of the Fontanelles

Sumito Dateki,[1*] Satoshi Watanabe ,[1,2] Fumiko Kinoshita,[1] Koh-ichiro Yoshiura,[2] and Hiroyuki Moriuchi[1]

[1] Department of Pediatrics, Nagasaki University Hospital, Nagasaki, Japan

[2] Department of Human Genetics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Disclosure statement
The authors declare no conflict of interest.

Introduction

■ **Interstitial deletions of the short arm of chr 11 are rare chromosomal anomalies, and are considered to be associated with several clinical conditions including WAGR syndrome**

■ **A few other interstitial deletions of other regions on 11p have been associated with distinct phenotypes [Shinawi et al., 2011].**

■ **We herein report the clinical and molecular findings in *the first case of a hemizygous 11p14.1-p15.3 deletion*. We additionally discuss the candidate gene in the deleted region for the phenotype.**

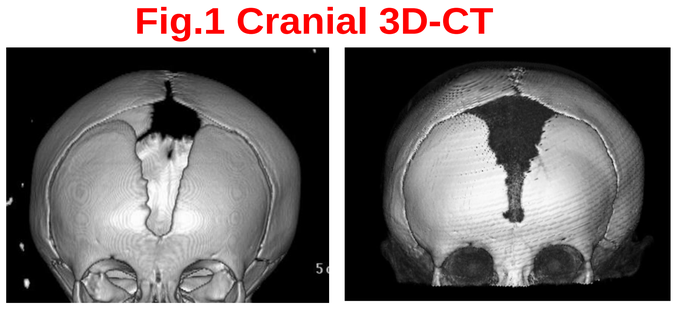
Case report

A Japanese female patient was born at 39 weeks of gestation after an uncomplicated pregnancy and delivery. At birth, her length was 42.0 cm (–3.3 SD), weight 3.15 kg (+0.9 SD), and OFC 36 cm (+2.2 SD). She was found to have large cranial fontanelles and sutures. The closure of the cranial fontanelles was delayed (Fig.1).

At 3 years and 7 months of age, the patient was referred to us because of short stature. Her height was 83.8 cm (–3.5 SD), weight 11.2 kg (–1.8 SD), and OFC 51 cm (+1.8 SD). She had relative macrocephaly and frontal bossing (Fig.2). She did not show either any motor or mental development delay. Endocrinological studies indicated normal growth hormone secretion and thyroid functions.

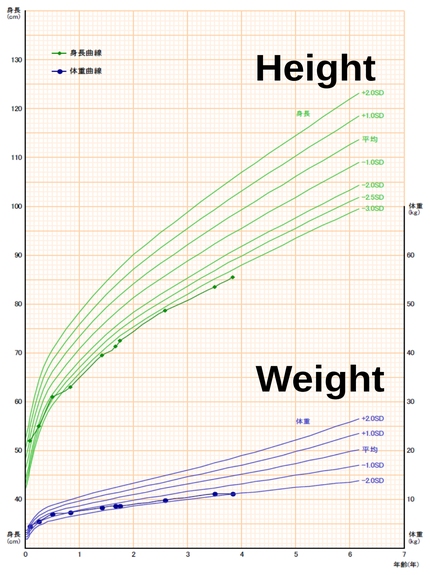
The non-consanguineous parents had well-proportioned figures without any dysmorphic features.

Fig.1 Cranial 3D-CT



At 3 months of age | At 6-months of age

Growth chart



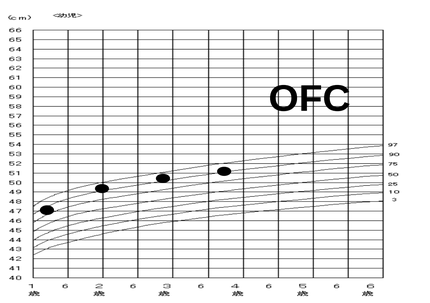
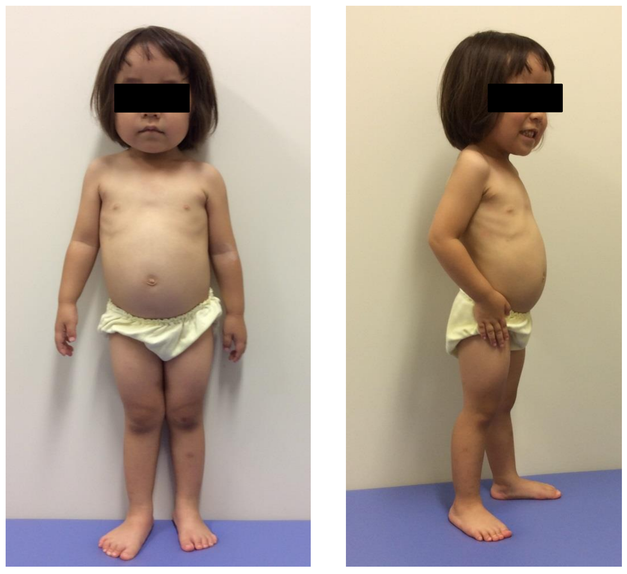


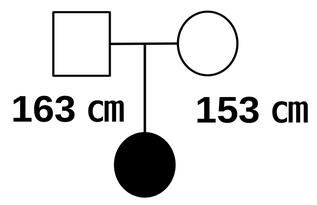
Fig.2



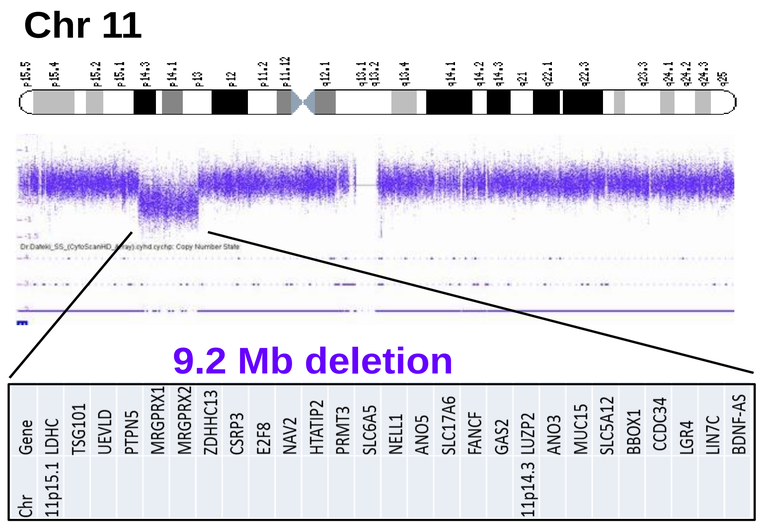
Genetic Analyses

G-banding

Pedigree

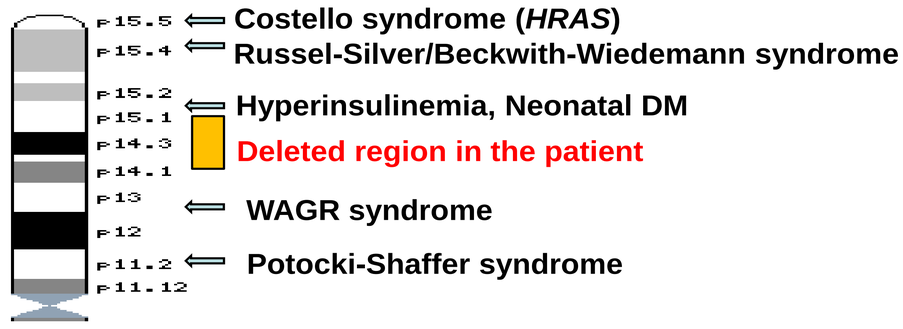


SNP array



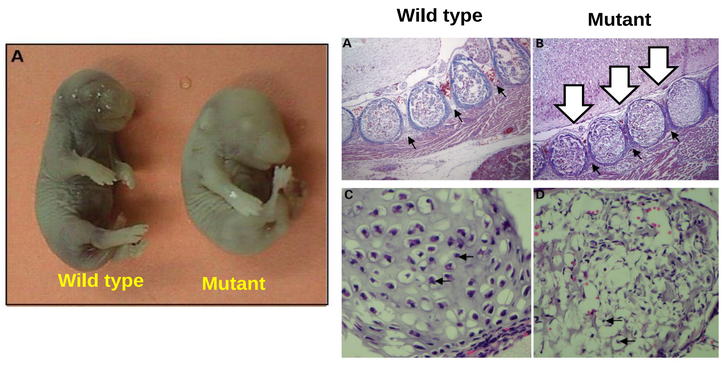
Discussion

Disease specific regions in the short arm of chromosome 11



The phenotype is likely associated with haploinsufficiency of *NELL1*.

1. The loss of the Nell1 function leads to skeletal defects in the cranial vault and vertebral column in mice

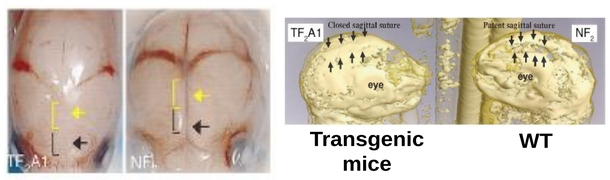


The homozygous mutant fetus demonstrated An enlarged skull with thinning at the calvarial bone edges, reduced intervertebral disc spaces (white arrows), and abnormal shape and size of the ribcage at 18.5 days of gestation.

[Desai et al., 2006]

2. Overexpression of *Nell1* causes craniosynostosis in mice and human

Transgenic mice overexpressing *Nell1* display a phenotype similar to human craniosynostosis at birth and premature suture closure.

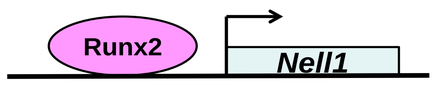


Transgenic mice | WT | Transgenic mice | WT

[Zhang et al., 2002]

The phenotypes in the *Nell1* overexpressing mice appeared to be inverse that of *Nell1* defective mice.

3. Runx2 directly activates human *NELL1* transcription



***NELL1* is a downstream target gene of Runx2 and may play a critical role in membranous ossification following cranial formation and the closure of the fontanelles**

[Truong et al., 2002]

Conclusion

■ **The results broaden the clinical spectrum of 11p interstitial deletion syndrome and provide further evidence for *NELL1* being involved in osteogenesis and chondrogenesis in human.**

■ **Further studies and accumulation of additional cases of *NELL1* mutations are needed to clarify the phenotype in patients with 11p14.1-15.3 deletion and pathogenesis of *NELL1* haploinsufficiency.**

sdateki1@nagasaki-u.ac.jp

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Syndromes : Mechanisms and Management

Sumito Dateki

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