Monostotic fibrous dysplasia is a single disorder caused by somatic mosaic activating mutations in *GNAS*

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Take Home Message

Monostotic fibrous dysplasia is a single disorder caused by somatic mosaic activating mutations in *GNAS*

Introduction

- Monostatic fibrous dysplasia (MFD) is thought to be caused by somatic mosaic activating mutations in *GNAS*
- In previous *GNAS* mutation analyses of MFD patients, direct sequencing using paraffin embedded bone sample detected activating *GNAS* mutations only in 21 of 40 cases (52.5%)[1)]
- We reported that next generation sequencing (NGS) detected somatic activating *GNAS* mutations sensitively from peripheral blood leucocytes (PBL) samples in McCune-Albright syndrome[2)]

Objective

To determine if we could detect somatic activating GNAS mutations in MFD patients using direct sequencing of bone samples and NGS of peripheral blood samples

Methods

Participants

< Inclusion criteria>

- Diagnosed as having MFD by pathological study
- Underwent operation at our institution between April 2012 and July 2015

< Exclusion criteria >

We excluded patients with any of the following

- Café-au-lait skin spots
- Endocrine disorder
- More than one lesion of FD on X-ray examination

Detection of somatic activating *GNAS* mutations

< Direct sequencing of bone samples>

- Material: frozen bone or formalin fixed paraffin embedded sample (FFPE) decalcified by formic acid
- *GNAS* analyses: Direct sequencing

< NGS of blood samples >

- Material : PBL
- *GNAS* analyses: NGS and combinatory method of peptide nucleic acids (PNA) probe with NGS

Nothing to disclose

Results

Table1. Characteristics of 8 patients with MFD

			PCR amplification using bone sample			Detection of *GNAS* mutations	
Case	Age (years)	Sex	Material	*GNAS*	*GAPDH*	DS-Bone	NGS-PBL
1	10	M	FFPE	-	-	ND	R201H
2	14	F	FFPE	-	-	ND	R201C
3	19	M	Frozen sample	+	ND	R201C	Negative
4	23	F	Frozen sample	+	ND	R201H	R201H
5	34	M	FFPE	-	-	ND	R201H
6	41	M	Frozen sample	+	ND	R201H	Negative
7	42	F	Frozen sample	+	ND	R201H	Negative
8	67	F	Frozen sample*	-	-	ND	R201H

DS: direct sequencing, ND: not done

* Previous repeated operations caused severe bone calcification

Discussion

- Somatic activating *GNAS* mutations were detected in all cases by direct sequencing of bone samples and/or by NGS of PBL samples
  - This result indicates that MFD is a single disorder caused by somatic mosaic activating mutations in *GNAS*
- In cases1, 2, 5, and 8, neither *GNAS* nor *GAPDH* were amplified by PCR using bone samples
  - In cases 1, 2 and 5, formic acid used for decalcification might cause DNA degradation
  - In case 8, severely calcified bone due to repeated surgery might not contain enough DNA to be amplified
- There was a discrepancy in detection probabilities of somatic activating *GNAS* mutations between previous study and present study
  - Materials (e.g., formic acid, hydrochloric acid) used for decalcification of paraffin embedded bone sample in previous study might cause this discrepancy

< Reference >

1. Lee SE, et al. Hum Pathol 2012; 43: 1234
2. Narumi S, et al. PLoS One 2013; 8: e60525

DOI: 10.3252/pso.eu.55ESPE.2016