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Case Report

A novel SGMS2 mutation associated with high bone mass; description of an affected family with recurrent fragility fractures

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ABSTRACT

SGMS2 mutation can present with childhood-onset low bone mass and recurrent fragility fractures. We report a 25-year-old man with a three-generation family history of recurrent fragility fractures and diffuse high bone mass. He was found to have a heterozygous frameshift variant c.1052_1074dup in the SGMS2 gene.

Our case highlights a novel genetic mutation in the *SGMS2* gene and reports the first family of *SGMS2* mutation with high bone mass.

1. Introduction

Sphingomyelin synthase 2 *(SGMS2)* enzyme catalyzes sphingomyelin production, a sphingolipid-forming component of the cellular membrane and Golgi complex. *SGMS2* gene is located on chromosome 4, and its mutations has been associated with a rare autosomal dominant inherited bone disease named calvarial doughnut lesions with bone fragility (CDL) with or without spondylometaphyseal dysplasia (OMIM: #126550) (Nowak et al., 2008). *SGMS2* related diseases are included with osteogenesis imperfecta (OI) in the group of bone fragility disorders. It is characterized by low bone mass, increased incidence of spinal and peripheral fractures, and dysplastic bones. In murine models, *sgms2* transcript levels are demonstrated to be maximally expressed in cortical bone and vertebrae (Pekkinen et al., 2019). Neurological manifestations and glaucoma have also been reported in a few cases (Pekkinen et al., 2019). We report an interesting case of a novel *SGMS2* mutation in a young male with a family history of recurrent fractures with paradoxically high bone mineral density.

2. Case presentation

2.1. Clinical history

A 25-year-old man was referred to Endocrinology outpatient department from Orthopedics department with complaints of non-specific bodyache, fatigue and possible high bone mass on skeletal X-rays. There was no history of joint pain or swelling, weight loss or gain, fever, bony deformities, or hearing and visual complaints. On taking a detailed family history, he gave histories of recurrent fragility fractures in family members, including first, second, and third-degree relatives (Fig. 1 **pedigree chart showing affected family members**). His grandfather, father, paternal uncle, paternal aunt, and two cousins had a history of recurrent fragility fractures of both vertebra and long bones. His father and grandfather succumbed to heart failure and sudden cardiac death in 5th decade. He has denied any fragility fracture until now. General and systemic examinations (patient's height 169 cm, weight 65 kgs, body mass index 22.8), including musculoskeletal and neurological examinations and cranial nerve examinations, revealed no significant abnormality.

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2.2. Investigations

Table 1 represents the relevant biochemical investigations for the patient, which revealed no abnormality except mild hypercalcemia.

In view of a family history of recurrent fractures, a complete skeletal survey and DXA (Dual X-ray Absorptiometry) scan were advised. The skeletal survey showed a generalized increase in bone mineral density {noticed in X-rays of the skull (Fig. 2), hand (Fig. 3), vertebra and hip joints (Fig. 4), and both knees (Fig. 5)}. The skull radiograph did not show any calvarial doughnut lesions. DXA (QDR 4500; Hologic, Inc., Bedford, MA) confirmed high bone mass in lumbar spine, femoral neck and distal 1/3rd of the radius. Generalized increased bone mineral density was found in both trabecular and cortical bones. DXA for the affected family members was also done, revealing similar findings (Table 2).

Subsequently, he underwent whole exome sequencing, which revealed the following mutation (Fig. 6). In our case, a heterozygous frameshift mutation at exon seven was found in the SGMS2 gene. The nucleotides from positions 1052 to 1074 were duplicated. The whole genome sequence was examined 105 times, and the mutation was detected 44 times (variant depth/total depth) (Table 3). This variant is predicted to cause a loss of normal protein function through protein truncation. Familial segregation was done to ascertain the significance of the mutation, and it was found in affected family members (paternal uncle and cousin 1) and absent in unaffected family member (mother). No known genetic mutations for osteopetrosis were found.

2.3. Differential diagnosis

With the history of recurrent fragility fractures in the family and possible cardiac death, the possibility of Paget's disease (juvenile onset), osteogenesis imperfecta and related inherited diseases of low bone mass were considered. However, with the high bone mass findings, osteopetrosis and related sclerosing bone diseases, pyknodysostosis, diffuse idiopathic skeletal hyperostosis, skeletal fluorosis, and juvenile-onset Paget's diseases were the usual differentials. Clinically, these conditions were ruled out by the absence of multiple cranial nerve palsies due to narrowing of cranial foramina, bony deformity, or extramedullary hematopoiesis due to poor bony remodeling.

Table 1
Biochemical investigations of the patient.

Biochemical parameters	Patient's value	Normal range
Serum corrected calcium (mmol/L)	2.59	2.04–2.54
Serum phosphorus (mmol/L)	1.35	0.8–1.45
Serum Vitamin D3 (nmol/L)	65.42	<50 Insufficiency <30 deficiency
Serum intact parathyroid hormone (pmol/L)	3.61	1.59–6.89
Serum nonspecific alkaline phosphatase (nsALP) (IU/L)	125	44–147
Hemoglobin (g/L)	163	120–160
Total leucocyte count (cells/L)	6.6×10^9	$4.3–10.8 \times 10^9$
Serum creatinine (mmol/L)	0.07	0.04–0.10

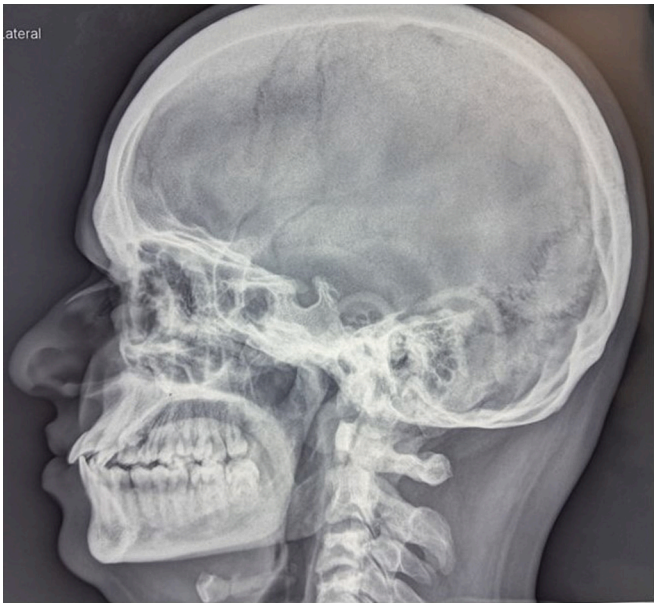

Fig. 2. Lateral skull X-ray depicts diffuse increased bone density involving the calvaria without any focal lesions.

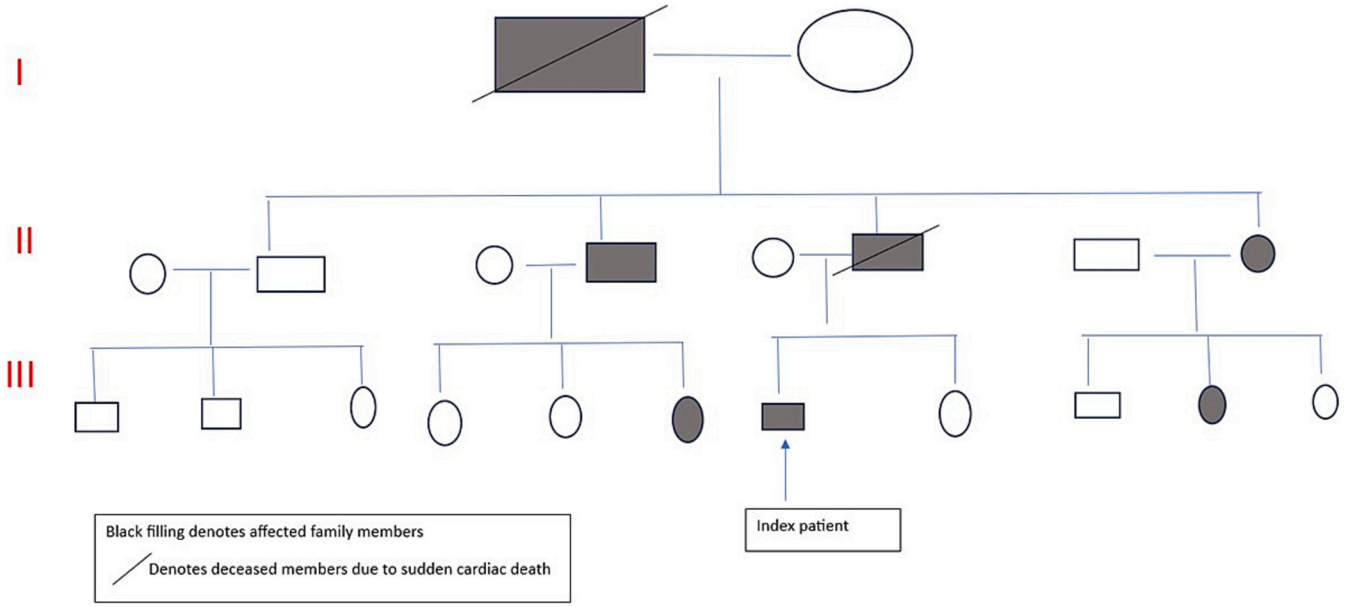

Fig. 1. The pedigree chart of the family with affected members in last three generations (denoted as I, II and III).

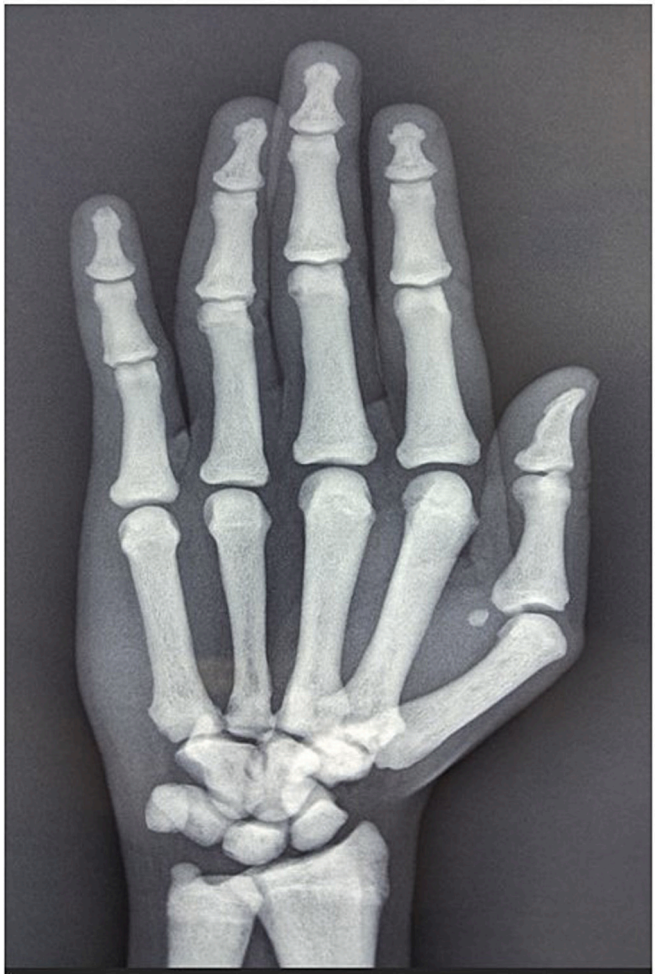

Fig. 3. Anteroposterior view of X-ray of a hand with wrist shows diffuse generalized increased bone density uniformly involving the phalanges, carpal bones, and visualized part of the distal radius and ulna, maintaining the joint space, cortical margins, and shape.

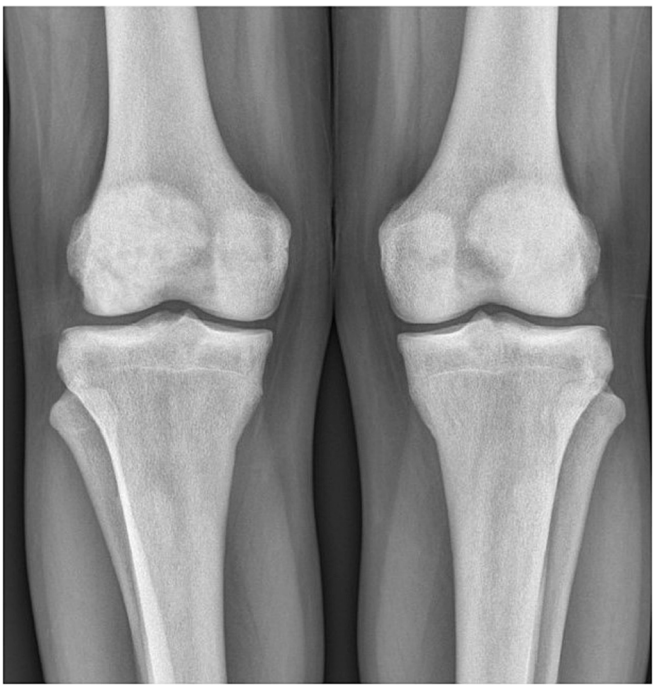

Fig. 5. X-ray anteroposterior view of bilateral knee joints depicts diffuse increased bone density without any obvious metaphyseal dysplasia.

Table 2
DXA parameters of the index patient and his affected family members:

	Z Score Lumbar spine	Z score femoral neck	Z score distal 1/3rd of radius
Index patient	+4.1	+6.1	+4.8
Paternal uncle	+5.5	+7.8	+5.9
Paternal aunt	+6.9	+3.1	+2.5
Cousin 1	+3.5	+2.8	+2.9
Cousin 2	+1.8	+1.9	+2

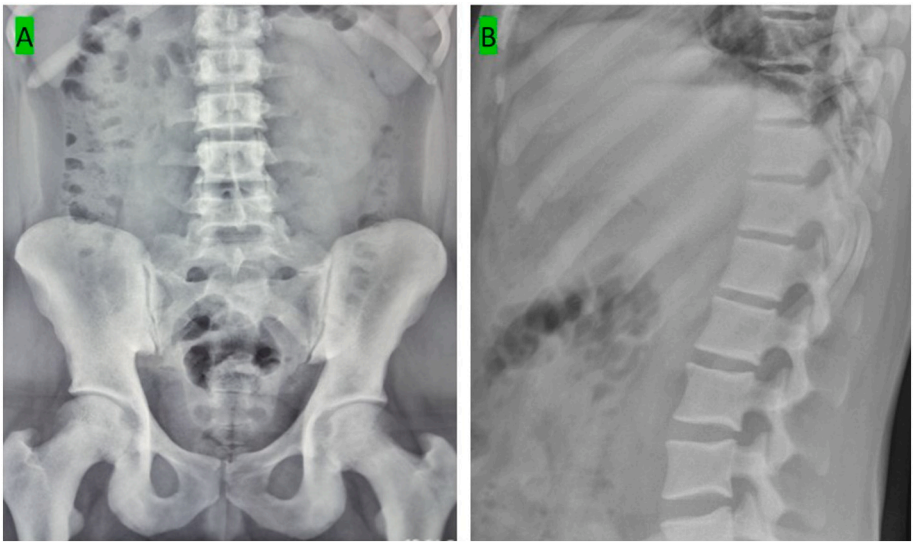

Fig. 4. X-ray anteroposterior view of pelvis with both hips and lateral view of dorso-lumbar spine reveals generalized increased bone density uniformly involving all the visualized bones.

Fig. 6. Integrative Genomic Viewer shows heterozygous frameshift variant c. 1052_1074dup in SGMS2 (NM_001375905.1) gene.

Table 3
Whole exome sequencing of the Index patient.

Gene and transcript	Exon/intron number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Inheritance
SGMS2 (NM_001375905.1)	Exon 7	c.1052_1074dup [44×/105×]	Heterozygous	Autosomal dominant

2.4. Treatment and follow-up

Considering the novelty of this mutation and no accepted guidelines for managing high bone mass with a fragility fracture, a conservative management approach was adapted for the patient with analgesics for bodyache and a maintenance dose of vitamin D supplementation. The index case was explained about fragility fracture risk. He is currently on conservative therapy and hasn't sustained any fragility fractures till now.

3. Discussion

There is no standard definition of high bone mass (HBM) diseases. Michael Whyte suggested that bone mineral density Z scores of more than +2.5 can be regarded as high bone mass (Whyte, 2005). However, various case series have defined variable cut-offs for high bone mass from Z scores of +3.2 to +4. One of the largest series published from UK took 3,35,115 DXA scans performed in 15 centers and defined HBM as Z scores of more than +4. Degenerative disease, vascular calcifications, hyperostosis, and syndesmophytes were the commonest diseases found to have HMB. However, the same study highlighted that all these degenerative diseases had localized high bone mass i.e. lumbar spine bone density Z score of >4 (Gregson et al., 2012). The HBM definition requires the presence of Z score > 2.5 at least at the lumbar spine and femoral neck, like our index case (Paccou et al., 2018). Genetic or inherited sclerotic bone diseases are associated with reduced bone remodeling, narrowing the neural foramina. Multiple cranial nerve palsies can result from this. Failure of adequate remodeling leads to extramedullary hematopoiesis, which can result in hypersplenism.

Calvarial doughnut lesions with bone fragility (CDL) with or without spondylometaphyseal dysplasia, a rare autosomal dominant inherited bone disease (OMIM #126550) described decades ago, has been identified to be associated with *SGMS2* mutation in 2019 (Keats and Holt, 1969). The skeletal manifestations of CDL range from isolated low bone mass to severe skeletal dysplasia. Neurological manifestations include transient nerve palsies, most commonly involving the cranial nerve VII and presenting as Bell's palsy. Recurrent facial nerve palsy has also been reported in patients with CDL. Progressive ataxia due to sensory neuropathy has also been described in literature (Bartlett and Kishore, 1976). Suggested explanations of these symptoms are cranial compression due to bony sclerosis and basilar invagination (Yoshikawa et al., 2019). Altered sphingomyelin metabolism is speculated to cause neurotoxicity, similar to sphingomyelinase deficiency (McGovern et al., 2017). Other systemic features include congenital glaucoma (ophthalmological), peptic ulcers and duodenal inflammations (gastrointestinal), and mixed hearing loss (otological) in those reported cases of *SGMS2* mutations (Pekkinen et al., 2019).

SGMS2 is located on chromosome 4 and codes for a 365 amino acid protein called sphingomyelin synthase 2 (SMS2). It is speculated that SMS2 indirectly affects osteoclast differentiation through osteoblasts (Yoshikawa et al., 2019). Based on bone resorption parameters of transiliac bone biopsies from affected subjects, Pekkinen et al. stated that osteoclast numbers might be increased in *SGMS2* mutations. However, the in vitro study on peripheral blood monocytes showed contradictory findings of normal osteoclast formation and function (Pekkinen et al., 2019). Pathogenic SMS2 variants accumulate sphingomyelin in the endoplasmic reticulum and modify the subcellular organization of sphingomyelin and cholesterol. Additionally, Sokoya et al. demonstrated that pathogenic SMS2 variants significantly alter the glycerophospholipid profile of the endoplasmic reticulum (Sokoya et al., 2022). It can adversely affect bone mineralization by disturbing sphingomyelin symmetry in osteogenic cells' plasma membrane. During bone mineralization, the osteoblast plasma membrane forms apical buds with secretory vesicles that release phosphate and calcium-rich contents at the mineralization site (Murshed, 2018). Pathogenic SMS2 variants may cause depletion of lipid-based phosphate stores and interfere with bone mineralization. The transiliac biopsy showed reduced trabecular and cortical thickness, variable osteoid volume, thickness, and surface and haphazard collagen fibril arrangement (like woven bone) (Pihlström et al., 2023). mRNA expression of *SGMS2* was highest in cortical bone, followed by vertebra, kidney, and liver (Pekkinen et al., 2019). In cancellous bone, bone mineralization density distribution (BMDD) showed significantly reduced mineral content and variable matrix mineralization with an increased fraction of poorly mineralized bone. Bone matrix mineralization is maximally affected in the *SGMS2* pathogenic variant (Pekkinen et al., 2019).

Pekkinen et al. reported 6 families with childhood-onset osteoporosis with mutations in *SGMS2*. Four unrelated families had the same

nonsense variant, c.148C > T (p.Arg50*), whereas the other families had a missense variant, c.185 T > G (p.Ile62Ser) and c.191 T > G (p.Met64Arg). Subjects with p.Arg50* presented with childhood-onset low bone mass with or without cranial sclerosis. A more severe presentation, with neonatal fractures, severe short stature, and spondylometaphyseal dysplasia, was observed in subjects with p.Ile62Ser or p.Met64Arg variant (Pekkinen et al., 2019). Merkuryeva et al. diagnosed the disease in 11 more patients from three unrelated families with underlying heterozygous nonsense variant c.148C > T (p.Arg50*) in the *SGMS2* gene (Merkuryeva et al., 2023). The biochemical profile of such patients is generally within normal limits except for occasional reports of raised bone-specific alkaline phosphatase (Pekkinen et al., 2019). Our mutation, c.1052_1074dup, in exon 7 of the *SGMS2* gene, has not been reported previously, and this can be attributed to a novel mutation.

In our index case, we found the paradox of an increased bone mass (also in family members) and a positive family history of recurrent fractures (involving both trabecular and cortical) in the presence of a mutation in the *SGMS2* gene. To the best of our knowledge, such a novel *SGMS2* mutation and a high bone mass phenotype have not been described in the literature. Few reports have mentioned evidence of increased mineralization in *SGMS2* mutation. However, none of the subjects had overall high bone mineral density on DXA. In mouse osteoblasts, siRNA-mediated SMS2 knockdown downregulated RXRα (retinoid X receptor alpha) mRNA and reduced the expression of RANKL (Receptor Activator of Nuclear Factor kappa-B Ligand) after $1,25(OH)_2D$ stimulation (Yoshikawa et al., 2019). Subsequently, number of differentiated osteoclasts was observed to be decreased. Suppression of this osteoclastogenesis may be speculated to cause the increased bone mass (Oshima et al., 2005). Pekkinen M highlighted that osteoclastogenesis is not much altered in *SGMS2* mutations. This disease is postulated to be more about the defect in matrix mineralization and less about the alteration of bone turnover (Ruffoni et al., 2007). The TRAP 5b (Tartrate resistant acid phosphatase) is considered a useful bone turnover marker (BTM) of bone resorption as it is predominantly expressed in osteoclasts (Nowak et al., 2008). However, P1NP (Procollagen type 1 N-terminal propeptide) and CTX (Cross-linked C-telopeptide of type 1 collagen) are the recommended BTM's to be assayed in bone mineral diseases {according to the International Osteoporosis Foundation and International Federation of Clinical Chemistry (IFCC) Bone Marker Standards Working Group}. Unfortunately, we could not perform any of them due to logistic reasons. *SGMS2* mutation patients have been found to have increased cortical mineralization at a site where interfused Sharpey's fibers were identified, indicating ligament or tendon attachment. Further osteoblastic and osteoclastic-based studies are warranted to solve further enigmas of *SGMS2* mutation in bone and mineral diseases. Interestingly, the index patient had no fracture history, even after harboring the possible pathogenic mutation. This indicates variable phenotypic expressions of this novel mutation.

Treatment options are quite limited in all sclerotic bone disorders. Interestingly, the p.Arg50* variant of *SGMS2* mutation was responsive to bisphosphonates therapy, where BMD increased by 2.1 standard deviations with the treatment with pamidronate. This response was quite similar to bisphosphonates response in osteogenesis imperfecta (Trejo and Rauch, 2016). Due to a lack of an effective treatment choice, our patient is currently on conservative therapy.

CRediT authorship contribution statement

Patra Shinjan: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jena Sweekruti:** Writing – review & editing, Writing – original draft. **Kedar Ketki:** Resources, Methodology, Investigation, Formal analysis, Data curation. **Pande Minal:** Resources, Methodology, Investigation, Formal analysis, Data curation. **K. Katam Kishore:** Writing – review & editing, Resources, Methodology, Investigation, Formal analysis, Data curation. **Prajapti Ashka:** Resources, Methodology, Investigation. **Kotecha Udhaya:** Resources, Methodology, Investigation. **Vyas Parin:** Resources, Methodology, Investigation.

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Declaration of competing interest

None.

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Data availability

Data will be made available on request.

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