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Case Report

XXXYY variant of Klinefelter syndrome: A case report

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ABSTRACT

This case report is about a 19-month-old boy, product of an *in vitro* fertilization twin pregnancy and born to young non-consanguineous parents, who presented with speech and motor developmental delay. On genetic evaluation, he was found to have the exceedingly rare variant 49, XXXYY of Klinefelter syndrome. Given the rarity of this condition and the limited literature available, this case report will surely add value to the literature.

Keywords: Rare, chromosome aneuploidy, genetic disease

Introduction

Klinefelter Syndrome (KS) has a prevalence of approximately in 660 live born males and is known to have the karyotype of 47, XXY.[1] Other variants described in the literature include mosaic KS (46,XY/47,XXY), 48,XXYY, and 49,XXXYY. These additional sex chromosomes may possibly lead to the deleterious mental and physical outcomes found in patients.[2,3]

The variant 49,XXXYY was first reported at 1963 in a young male with intellectual disability and features similar to KS.[4] This variant is extremely rare, with a prevalence being estimated to be < 1 in one million. Patients typically have intellectual disability, autism, distinctive facial features, cryptorchidism, hypogonadism, skeletal malformations, and others.[5] The proposed mechanism is a nondisjunction that takes place during the formation of gametes or at conception.[6]

A few cases of the variant 49, XXXYY have been reported in the literature.[6] The literature was limited to case reports that were mostly published in the previous century.[3,4,7-10] Hence, the case presented in this report is considered to be a significant addition to the literature, as it is the most recent case report highlighting this rare variant.

Case Presentation

The 19-month-old patient presented with developmental delay, including decreased sucking reflex, inability to stand or walk without support, and speech delay, in comparison to his twin. Antenatal history was uneventful and prenatal DNA study showed a normal karyotype, which is done routinely in those who conceive through *in vitro* fertilization. As a product of *in vitro* fertilization twin pregnancy, he was delivered at 36 weeks with a birthweight of 1.5 kg by elective lower segment cesarean section. The patient was admitted to the neonatal intensive care unit for 10 days due to his low birth weight and decreased sucking reflex, completed uneventfully. Bilateral cryptorchidism was noted and operated twice (one for each testis) at 3 and 18 months of age. The birth weight of the twin was 2.5 kg with an uneventful postnatal history. His weight is 12 kg (at 50.798 percentile) with a height of 77 cm (at 2.442 percentile) and his milestones are appropriate for his age. *In vitro* fertilization was done due to the paternal oligozoospermia, with the mother being free from any medical illnesses. The parents lacked dysmorphic features and were young upon conception; the father was 28 years old and the mother was 25 years old. In addition, no family history of any congenital anomalies was present in either parent.

On physical examination, the patient was 73 cm (at 0.1 percentile) tall and weighed 11.3 kg (at 29.46 percentile). He had prominent forehead and mild hypertelorism with wide nasal bridge [Figure 1], micrognathia with macrodontia [Figure 2], and bilateral ear creases [Figure 3]. Genital exam revealed small testis with micropenis. Other features were notably musculoskeletal, which were postural lumbar kyphosis (There was difficulty obtaining picture of Kyphosis), bilateral forearms fixed in mid-prone position with limitations in supination and pronation but with a full flexion and extension of the elbow, left fifth digit clinodactyly [Figure 4], right varus knee deformity, bilateral pes planus [Figure 5], and an out toeing gait. Wrist and hip examination were normal, as well as other systems.

Laboratory investigations

Laboratory investigations done to rule out other causes of delayed milestones were all normal, including hemoglobin, iron profile, Vitamin D, renal, and liver function tests.

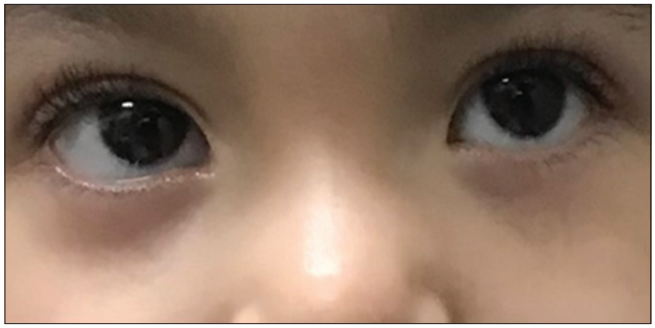

Figure 1: Hypertelorism with wide nasal bridge

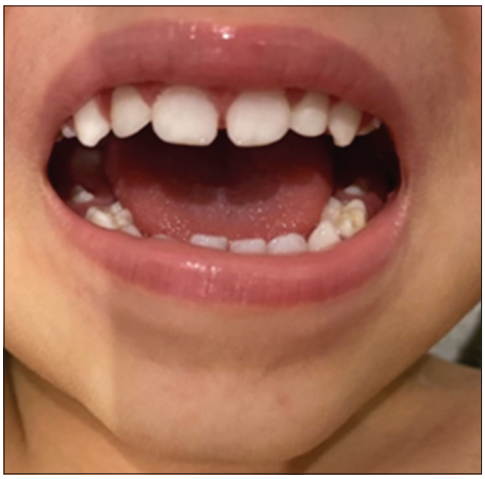

Figure 2: Micrognathia with macrodontia. The image was taken recently, at the age of approximately 2 years and 10 months

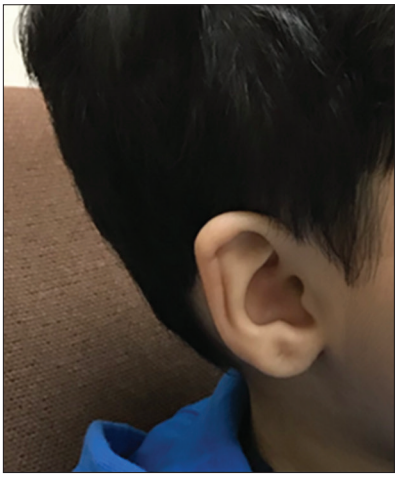

Figure 3: Ear crease

Cytogenetics studies

A standard karyotype was performed, revealed an abnormal male karyotype of two additional copies of X and one additional copy of Y chromosome in all analyzed metaphases [Figure 6]. Thus, 49, XXXYY variant of KS was diagnosed. Furthermore, parental standard karyotype was found to be normal, which ruled out numerical and/or structural chromosomal anomalies in the parents such as paternal KS [Figures 7 and 8].

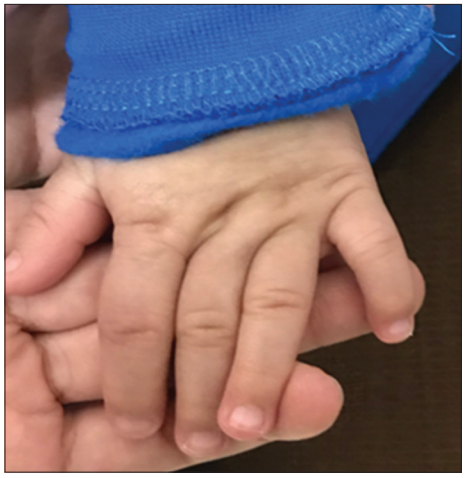

Figure 4: Left 5th digital clinodactyly

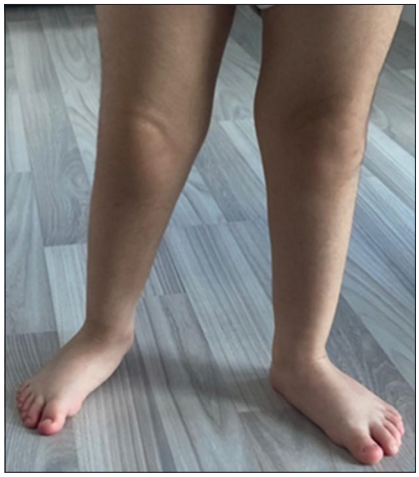

Figure 5: Right varus knee deformity and bilateral pes planus

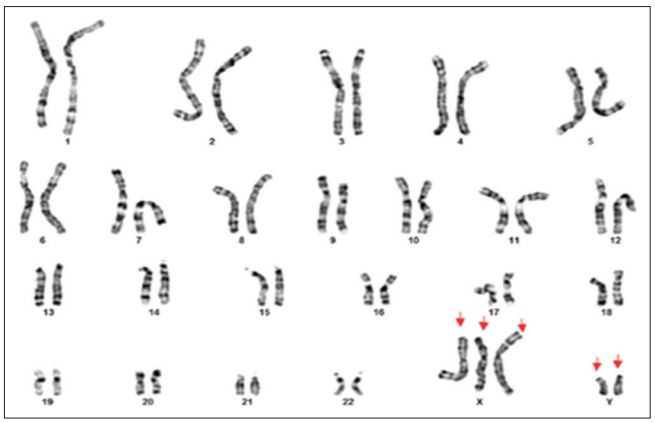

Figure 6: Patient's Karyotype, XXXYY pattern

Radiological studies

Forearm X-ray revealed bilateral proximal cartilaginous radioulnar synostosis [Figure 9], which then progressed to a bony type on the newer X-Ray [Figure 10]. X-ray of the spine and hips showed spina bifida in addition to bilateral mild hip acetabular dysplasia with acetabular index of 24.2° at the left and 23° at the right [Figure 11].

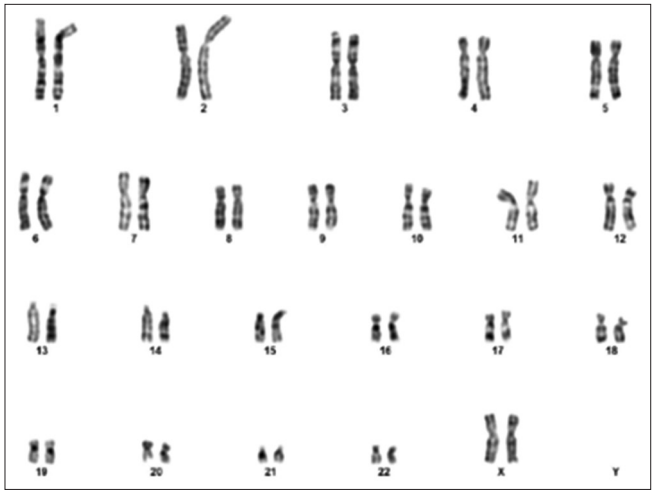

Figure 7: Maternal karyotype showing normal 46, XX

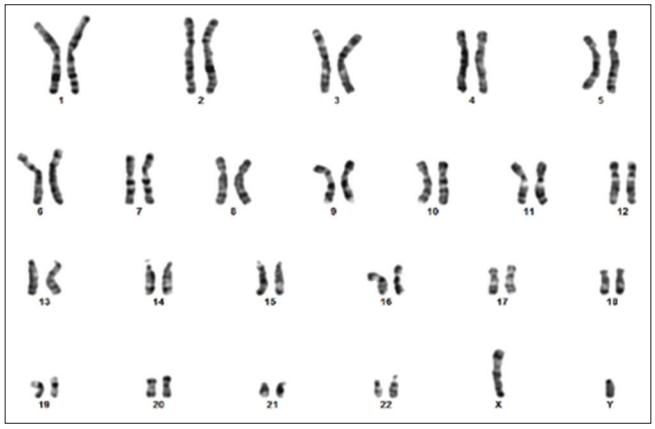

Figure 8: Paternal karyotype showing normal 46, XY

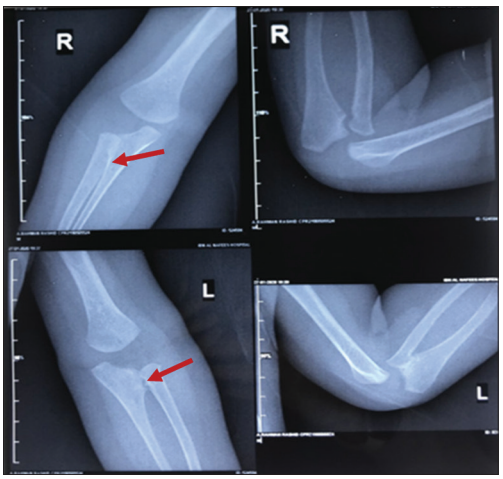

Figure 9: Previous X-ray of both forearms shows bilateral proximal radioulnar cartilaginous synostosis, as highlighted by the red arrows. This X-ray was done when the patient was approximately 7 months of age

Discussion

The manifestations of our patient with the other confirmed XXXYY patients are summarized in Table 1. Three case

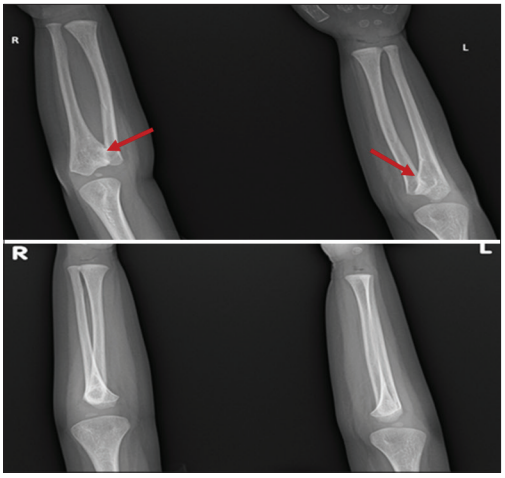

Figure 10: Newer X-rays of both forearms shows bilateral proximal radioulnar synostosis of bony type, as highlighted by the red arrows. This X-ray was done when the patient was approximately 2 years and 10 months old

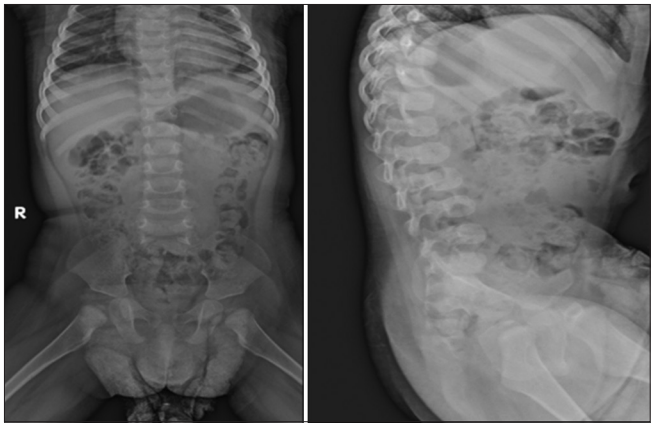

Figure 11: Hip and spine X-rays. Hip X-Ray shows bilateral mild hip acetabular dysplasia with acetabular index of 24.2° at the left and 23° at the right. Spine X-ray shows spina bifida. This X-ray was taken when the patient was approximately 20 months old

reports presented patients who are relatively close to our patient's age.[3,4,8] Facial features, genital abnormalities, delayed milestones, and intellectual disability were similar with minor variations between the cases. Our patient was noticed to have certain facial and musculoskeletal features such as micrognathia, wide nasal bridge, bilateral hip dysplasia, and an out toeing gait which may have gone unnoticed or were absent in other patients reported by the case reports.[1-11] Clinodactyly was reported by us and by Benn *et al*. only.[8] Our patient had radioulnar synostosis which was only seen in a mosaic 48,XXYY/49,XXXYY patient reported by Salamanca *et al*.[9] It is crucial to note that case reports of adult patients do show some features that are age related, such as scantiness or absence of facial hair, which may be seen in our patient when he advances in age.[7,9,10]

The extra sex chromosomes attribute to the mental and physical development of such cases. The proposed mechanisms by which this aneuploidy occurs are either: Fertilization of a

Table 1: A comprehensive comparison between the current case report and the other case reports found in the literature

Case reports	Age (Years)	Parental Factors	Body measurements	Body, Hair and Facial Features	Gynecomastia	Musculoskeletal Features	Genitalia	Hormonal Studies	Delayed Milestones	Intellectual Disability	Other Features
Our Case	1 years and 7 months	- Maternal Age: 25 - Paternal Age: 28 - Karyotype: Normal, Twin brother has a normal karyotype as well - Consanguinity: no	- Height: 73 cm - Weight: 11.3 Kg	Mild Hypertelorism Low set ears Prominent Forehead Micrognathia Wide nasal Bridge Bilateral ear creases Macrodontia	-	- Postural Lumbar kyphosis - Right Varus Deformity - Bilateral pes planus - out toeing gait - Bilateral Proximal Radioulnar synostosis of bony type - Mild acetabular dysplasia of both hips Left 5th digit clinodactyly	Small Testicles with micropenis Had bilateral cryptorchidism with bilateral orchidoplexy done.	-	Yes: - Cannot stand or walk without support. - speech delay	Yes	- Mental and developmental age with regards to the cognitive, linguistic and motor domains are less than his peers compared to the chronological age. - Does not fall into the autism spectrum disorder category
Gupta et al., 2013	3.5	- Paternal Age: < 30 - Karyotype: - Consanguinity: no	- Height: - - Weight: -	-	-	-	- Cryptorchidism with empty scrotal sac. - Testes in inguinal region	-	Yes	Yes	-
Cowie et al., 1986	42	- Maternal Age: 41 - Paternal Age:- - Karyotype:- Consanguinity:-	-Height: 170 cm -Weight: Moderately obese - Pubis-sole: 86.5 cm - Upper-to-lower segment ratio: 0.97	- Very scanty facial hair - No body hair except diminutive patches of axillary hair and a small female pubic escutcheon. - Slight external strabismus of left eye. - Large prognathic lower jaw -Deeply set eyes - Overhanging frontal bone.	Moderate. - Female distribution of body fat	- Small hands and feet with marked pes planus. - Some degree of genu valgum. - Eunuchoid habitus with wide hips and relatively narrow shoulders. - Apparently short neck	Normal penis - Cryptorchidism	-	No, But at 10 months, contracted illness resembling measles and he did not walk or talk again until 7 years of age.	Yes - Solitary, shy, outbursts of aggressive behavior without apparent reason.	- High pitched voice - Course tremor of both hands.

(Contd...)

Table 1: (*Continued*)

Case reports	Age (Years)	Parental Factors	Body measurements	Body, Hair and Facial Features	Gynecomastia	Musculoskeletal Features	Genitalia	Hormonal Studies	Delayed Milestones	Intellectual Disability	Other Features
Benn et al., 1982	Prenatally diagnosed, terminated pregnancy at 23.5 weeks. The findings mentioned were noted during postmortem exam.	Maternal Age: 44 - Paternal Age:35 - Karyotype:- normal Consanguinity:-	- Height: - - Weight: 0.46kg - crown-heels: 29 cm - Crown rump: 19 cm - Arm span: 27 cm - Head circumference 20.5 cm	- Hypertelorism (with the inner canthal distance of 1.7 cm) - Slightly low set ears - mild prominent forehead	-	- Bilateral clinodactyly. - Decreased carrying angles (0^0)	- cryptorchidism	-	-	-	- Grossly Macerated male fetus - Microscopic exam: fresh interstitial hemorrhage of the lungs. - High set left coronary ostium - Dermatoglyphic findings: left simian line and small ulnar loops on five fingers, arch on one thumb, whorl on two fingers and unclear pattern on the remaining two fingers, total finger ridge count appeared to be reduced
Salamanca-Gòmez et al., 1981	29	Maternal Age: 38 - Paternal Age:44 - Karyotype:- Consanguinity: no	Height: 16 cm - Weight: - - UBS: 84 cm - LBS:92 cm - Upper-to-lower segment ratio: 0.91 - Head circumference: 54.3 cm - Chest circumference: 89.3 cm	Absence of facial, axillary, and pubic hair. - Prognathism - Prominent cheek bones and supraorbital ridges. - Short upper lip. - Malaligned opalescent teeth - High palate - Eyes: Convergent strabismus, myopia, amblyopia, and bilateral myopic macular degeneration	Yes - Gynecoid distribution of fat	- Eunuchoid - Apparently short neck - Thoracic scoliosis - Genu Vara - Limitation of extension, pronation, and supination at elbows with apparent dorsal dislocation of head of radii. --Radiological examination: bone age 16 years (retarded bone age), generalized osteoporosis, hyperostosis of the skull, thoracic scoliosis, radioulnar synostosis, and gynecoid pelvis	- Small penis (at most 3.2 cm long, unstretched). - Cryptorchidism - Hypoplastic and hypopigmented scrotum	FSH: 246.2-370.4 ng/ml LH: 513.3-714.1 ng/ml Testosterone: 12.5-135 pg/ml DHT: 6.25 pg/ml	-	Yes, mental age on psychological testing was found to be between 3-4 years	- Possibly mosaic 48, XXYY/49, XXXYY - Acute DM and associated pancreatitis. - High-pitched voice - Dermatoglyphic findings: Total ridge count was 102. On right hand the ridge count was 55, the a-b ridge count 36 and atd angle 39". On the left hand the ridge count was 47, the a-b ridge count 33, and atd angle 30". The mainline formula was Right 5, 7, 9, 7, 13"; Left 3, 4, 7, 9, 13".

(Contd...)

Table 1: (*Continued*)

Case reports	Age (Years)	Parental Factors	Body measurements	Body, Hair and Facial Features	Gynecomastia	Musculoskeletal Features	Genitalia	Hormonal Studies	Delayed Milestones	Intellectual Disability	Other Features
Lecluse-van der Bilt et al., 1974	New born – 3.5 years	Maternal Age: 30 - Paternal Age: 35 - Karyotype: normal. His two brothers have normal karyotypes as well. - Consanguinity: -	Height : Age of 5 months: 63 cm Age of 21 months 80 cm Age of 3.5 years: Between 3rd and 10th percentile for dutch standard - Weight: Birth weight: 2.99 Age of 5 months: 6.54 kg Age of 21 months: 11.8 kg Age of 3.5 years: normal for height Head circumference at age of 3 years: 50.2 cm (50th percentile)	-Prognathism -Hypertelorism -Prominent forehead	-	Retarded bone age at the age of 5 months (less than 3 months) -At the age of 2 10/12 years bone age was 1 6/12 years. -Club feet	At birth: - Ambiguous genitalia - Small penis - two indeterminate labioscrotal folds with small palpable nodules (?testes). At age of 21 months: Normal sized testes and were located in the scrotum.	Urinary 17 ketosteroids is 0.2 and 0.4 mg. d-1 17-hydroxysteroid 0.8 and 1.0 mg. d-1	Yes	Yes	Dermatoglyphic analysis: a palmar triradius in normal position. Four ulnar loops, one radial loop and five whorls were found on the fingertips. Epidermal ridge counts have not been performed. On the hallux of both feet a peculiar, very small whorl was placed between a normal arched pattern.
Bray & Josephine, 1963	26	- Maternal age: 20 - Paternal Age:- - Karyotypes:- - Consanguinty:-	-Height: 199.04cm - Weight: 119.748 kg -Pubis to Floor:101.6 cm	- Absenceof facial, Axillary, or body hair, except for a fine feminine escutcheon - Large head - Proganthism - Narrow palpebral fissures - Prominent cheek bones	Yes	Apparently short neck Retarded bone age Eunuchoid habitus	Hypogentalism Small penis Small, soft tests	24 -hr gonadotropin excretion: 144 units: 17-ketosteroid excretion: 3.5 mg/24 hours	yes	Yes	High pitched voice Heart: right ventricular hypertrophy, right axis deviation, cardiac enlargement, query mild congestive heart failure

normal ovum with one X by an XXYY sperm which arose from two paternal meiotic non-disjunctions at both meiotic divisions, fertilization of an XX ovum by an XYY sperm, or fertilization of an XXX ovum by a YY sperm.[8] For each possibility for the origin of the polysomy, a minimum of two independent non-disjunctions must be postulated; at least one of which is paternal in origin. In our case, parents and sibling had normal karyotypes, similar to what Lecluse-van der Bilt *et al*. reported.[4] Gupta *et al*. reported a patient who had a young, non-consanguineous parents, similar to our patient.[3] This may suggest that other unknown factors exist.

49,XXXYY variant is extremely rare with only two cases reported in the 21st century, with our patient being the third. Our case report presents a unique finding of XXXYY syndrome in a patient who was an IVF product and a twin of a normal sibling who had a normal prenatal DNA karyotype. The future studies may shed light upon additional features as well as the possible outcomes and complications of this variant.

Author's Declaration Statement

Ethical approval

Not applicable.

Declaration of patient consent

Written informed consent has been obtained from the father of the studied patient and not the patient himself.

Data availability statement

All data are available in the manuscript.

Competing interest

The author reports no conflicts of interest.

Funding Statement

None.

Authors' contributions

1. Dr. Ali Alekri Case recognition
2. Dr. Maryam Busehail Supervisor and editor
3. Dr. Noorhan Moussa Rhayel Data collection, data interpretation, discussion and conclusion
4. Dr. Sayed Mohamed Almosawi Data collection, data interpretation, discussion and

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