Case Report

A *de novo* pure 21q22.3 deletion in a 9-year-old boy with buried penis: a case report and literature review

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Abstract: 21q deletion has been associated with a wide range of clinical signs, from very mild to severe phenotypes, and with the progress of genetic technology, more patients with this deletion are being diagnosed. This study reports on a 9-year-old boy with a terminal deletion of 4.5 Mb on chromosome 21 in the locus of chr21: 43531239-48119895 (GRCh37/hg19). Dark skin, a buried penis, small testes, dental caries, microcephaly, a low auricle, mental and intellectual retardation, balance disorder and pituitary and callosum dysplasia were observed. The results of a literature review and observation of similar abnormalities, including hypoplasia of corpus callosum, in two patients with non-overlapping deletion regions suggest that there are multiple gene loci regulating brain development on 21q. By comparing the overlapped deletion region in 21q22.3 cases of brain anomalies and/or gonadal dysgenesis, we concluded there were two overlapped microdeletion regions (chr21:43531239-43792093 and chr21:46625055-46884297) that may be related to brain and gonadal development. The same 16.49 Mb deletion of chr21:31578129-48119895 (GRCh37/hg19) was shared in 10 cases, and 24 cases shared the same 5.59 Mb deletion of chr21:42478130-48119895 (GRCh37/hg19) in DECIPHER (Database of Chromasomal Imbalance and Phenotype in Humans using Ensembl Resources), suggesting these were two commonly deleted regions of pure partial 21q. Those patients with the same breakpoints had different phenotypes suggesting the heterogeneity of 21q deletion.

Keywords: 21q deletion; buried penis; brain development; case report

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Introduction

Trisomy is the most common abnormality of chromosome 21. Whereas fetuses with complete 21q deletion die before or shortly after birth, cases with partial deletion of chromosome 21 have a better survival expectancy. While a very rare condition (<1/1,000,000), partial deletion of chromosome 21q can affect a variety of human systems due to the gene dosage deficiency (1). The diagnosis and treatment of 21q22.3 deletion is difficult and easy to misdiagnose, which is worthy of clinicians' attention. Typical clinical symptoms include intrauterine growth retardation, microcephaly, a low auricle, heart defects, seizures, intellectual disability, mental and language disorders, and dysplasia of the corpus callosum (2). While most 21q deletions are associated with other chromosomal abnormalities, the patient in the present study has a rare pure 21q22.3 deletion. At present, the most comprehensive studies about 21q deletion are from Roberson *et al.* (3) and Lyle *et al.* (4), who discussed 11 and 10 cases of partial 21q

deletion respectively. The size of the deletions ranged from 1.48 to 21.06 Mb, and all cases were unique, without an identical breakpoint. Roberson *et al.* (3) summarized the chromosome 21q deletion breakpoints for 36 cases and found that 20 involved aneuploidy and/or a translocation on a chromosome other than 21. Lyle *et al.* divided 21q into three regions according to the severity of phenotypes and found region 1 (centromere to 31.2 Mb), region 2 (31.2 Mb to 36 Mb), and region 3 (36 Mb to telomere) were respectively associated with mild, moderate, and severe phenotypes. Deletions in region 1 tended to be large. Errichiello *et al.* (1) later proposed to delimit region 1 to two subregions. The deleted fragment described in this article was in region 3, which is reported as the most frequently altered area.

Partial deletion of chromosome 21 is heterogeneous in terms of phenotypic severity. We report a rare case of a boy aged 9 with concurrent intellectual disability, brain anomalies, and gonadal dysgenesis resulting from 21q22.3 partial deletion. We compared the deletion regions in cases listing brain anomalies and gonadal dysgenesis from the literature and DECIPHER, and summarized two microdeletion regions that may be related to gonadal and brain development.

We present the following case in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/tp-21-377).

Case presentation

The case concerns a 9-year-old Chinese boy of Han ethnicity who was the product of the first pregnancy of unrelated healthy parents and was delivered by caesarean section at full term with a birth weight of 3.1 kg. His mother was 26 years old, 156 cm in height and weighed 57 kg, and her prenatal history revealed no evidence of teratogen or drug exposure. His father was 33 years old at the time of his birth and was 166 cm tall and weighed 51 kg. The developmental milestones of raising the head, turning over, and sitting up were achieved at normal times by the child. He walked at the age of two and started speaking at three and a half years of age. While there was no history of epilepsy, he occasionally fell down and was unable to run due to the instability and poor coordination of his limbs during exercise. His intelligence lagged behind peers, and he was poor at language expression, interpersonal communication, learning, calculating, and writing. He had a low attention span and often laughed involuntarily. His eyes had astigmatism and myopia and his penis was short and could not be exposed (*Figure 1*).

On physical examination, the boy had a regular pulse (86 beats per min), blood pressure (100/78 mmHg), height of 129 cm (which was less than others of the same age and sex by 1 SD), weight of 32 kg, BMI of 19.22 kg/m^2, head circumference of 51 cm, fingertip distance of 130 cm, upper body height of 65 cm, and lower body height of 64 cm.

He had multiple dental caries, a low hairline, a low auricle, dark skin (especially at the elbow and interphalangeal joints) and his hands and toes showed oblique deformity. Cardiopulmonary and abdominal examination showed no abnormality. His pubic hair and genitalia were at Tanner stage I, the penis was not exposed, and the testes could not be touched. The penile length from the tip of the glans penis to the suprapubic bone was 1.5 cm. The patient had a poor sense of balance and could not complete a both-hands alternating movement test, heel-knee-tibia test, or finger-nose test. The muscle strength and tension were normal, and the pathological sign was negative.

An auxiliary examination (Infant-Junior Middle School Student's Ability of Social Life Scale) (5) showed moderate mental retardation. The following tests were all normal: liver and kidney function, blood lipid, myocardial enzyme, ACTH and cortisol levels and rhythm, thyroid function, ECG, chest X-ray, adrenal CT, color Doppler ultrasound of heart, abdomen, and urine. IGF-1 was 68.2 ng/mL (74–388 ng/mL). Growth hormone could not be stimulated by insulin hypoglycemia test or levodopa stimulation test (*Table 1*), indicating a deficiency. Gonadal hormones analysis showed LH 0.05 IU/L (0.57–12.07 IU/L), FSH 0.32 IU/L (0.95–11.95 IU/L), estradiol 37.0 pmol/L (40–161 pmol /L), prolactin 13.9 ng/mL (3.4–19.2 ng/mL), and testosterone 0.44 nmol/L (6.5–33 nmol/L). These levels suggested a deficiency of LH and FSH secreted by the pituitary gland. EEG showed mild abnormality, and testicular color Doppler ultrasound showed that the left testis was approximately 13 mm × 7 mm × 11 mm, the right testis was 15 mm × 8 mm × 12 mm, and the volume of the bilateral testis was small. The bone age was about 8 years old, and pituitary MRI showed the prepontine cistern and annular cistern to be widened and the pituitary gland to be thinned and hypoplastic (*Figure 2*).

After informed consent was obtained, 5ml of peripheral blood was collected from the patient and his parents. The process of whole exome sequencing was performed by WeHealth Biomedical Technology Co., Ltd. (Shanghai, China), and all genomic DNA was extracted using a

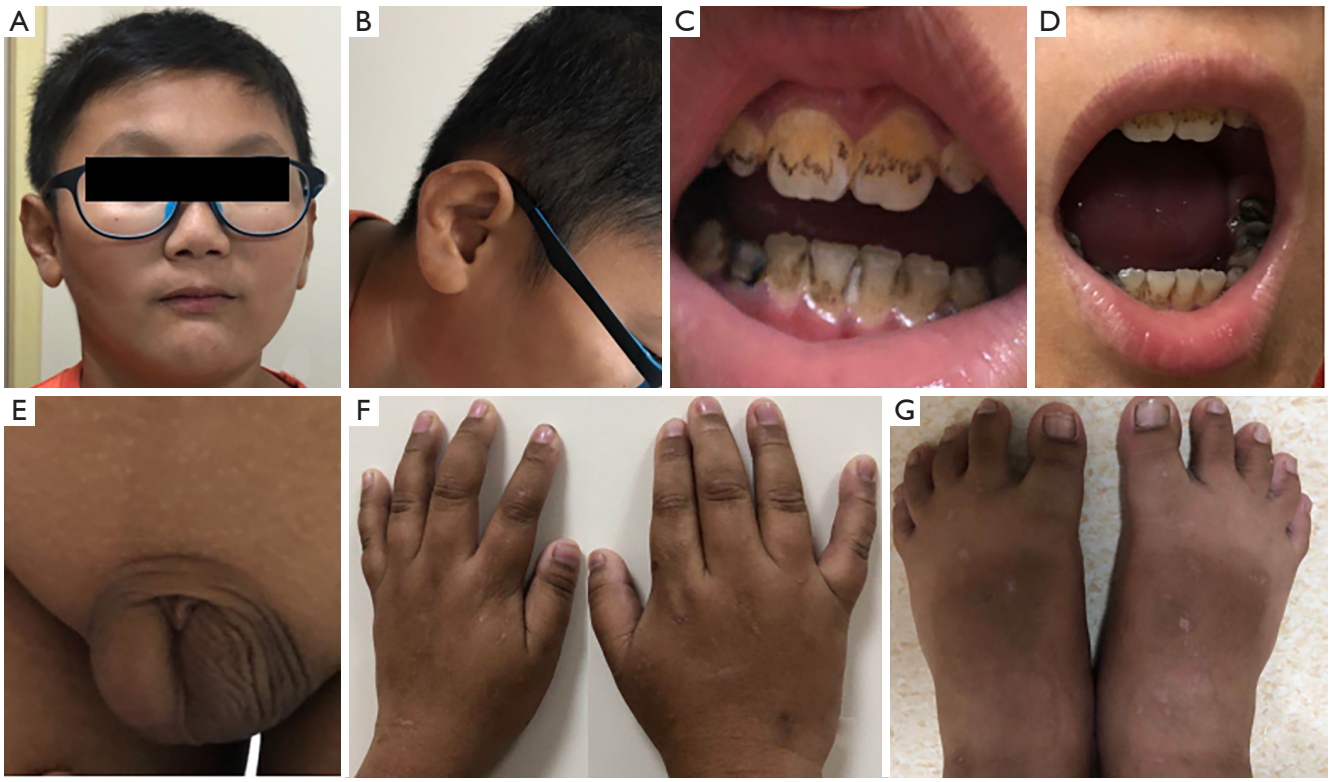

Figure 1 Photos of the patient. (A,B) Small head, large auricle and loss of visual acuity; (C,D) multiple dental caries; (E) concealed penis; (F,G) dark skin, hands, foot fingers oblique deformity. This image is published with the consent from the patient's parents.

Table 1 Insulin hypoglycemia test and levodopa stimulation test

Test	Factor	0 min	15 min	30 min	60 min	90 min	120 min
Insulin hypoglycemia test	GH (ng/mL)	0.03	0.03	0.355	1.08	0.25	0.103
	BG (mmol/L)	4.5	1.7	2.1	3.9	4.6	4.6
Levodopa stimulation test	GH (ng/mL)	0.03		0.03	0.03	0.03	0.45

GH, growth hormone; BG, blood glucose.

commercial kit (TIANGEN, China). The quantity/quality of DNA was assessed using a Onedrop OD1000 spectrophotometer and by agarose gel electrophoresis. Exome capture was performed with xGen Exome Research Panel v1.0 (Integrated DNA Technologies, Inc., USA) and 150 bp paired-end sequencing was executed using the Illumina HiSeq4000 platform (San Diego, CA, USA).

For whole-exome sequencing bioinformatic analysis, the raw reads were aligned by the sequencing company using the Burrows-Wheeler Aligner and SAMtools. After removing duplicates from the sorted alignment using Picard, variants were called using the Genome Analysis Toolkit (GATK v3.70) pipeline.

For low depth whole genome sequencing, low-quality reads were removed by Trimmomatic v0.32. Sequences were aligned to the hg19 reference genome by Bowtie 2 v2.3.4.3 and duplicates reads were removed by Picard. A CNVkit v0.9.6 software toolkit was used to infer and visualize the copy number.

Based on the analysis of genome copy number variation by low depth whole genome sequencing technology, the patient was found to have a deletion of 4.5Mb on chromosome 21 (*Figure 3*) in the location of chr21: 43531239-48119895 (GRCh37/hg19). The karyotype

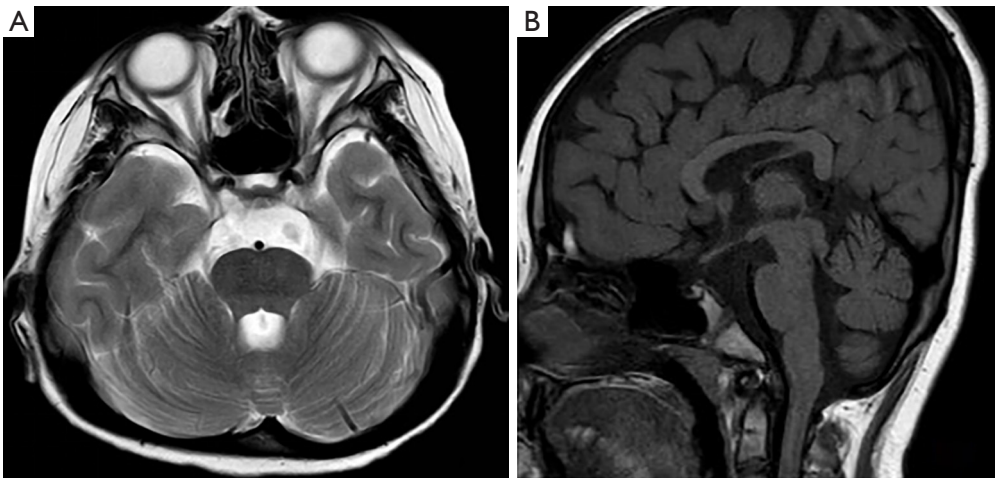

Figure 2 MRI images. (A) Enlarged anterior pontine cistern; (B) hypoplasia of corpus callosum and pituitary gland.

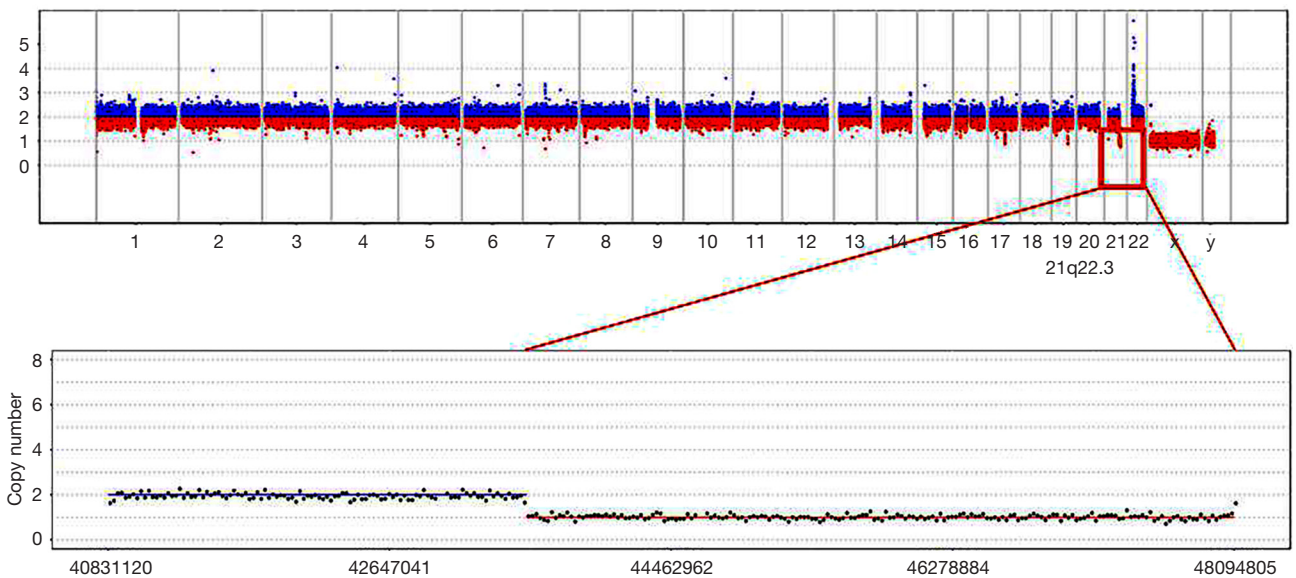

Figure 3 Genomic copy number variation analysis showed a 4.5 Mb deletion in 21q22.3 region.

was 46, XY, del (6) (q22.3), which involves 124 genes, including 18 known pathogenic genes in OMIM (including WDR4, SIK1, and TSPEAR) and 106 non-pathogenic genes (including DIP2A, S100B, and PRMT2). By low depth whole genome sequencing detection, there was no abnormality in his parents' 21q22.3 region, confirming a *de novo* alteration.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient' parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Comparing phenotypes between patients with 21q deletion is difficult. Most locations of the missing fragments are different, and 21q partial deletion is always combined with other abnormalities, such as ring chromosome,

gene duplication and dystopy, and deletion of other chromosomes. Sgardioli *et al.* (7) reported a female characterized by mild deformities of the face and limbs, mental retardation, seizures, and mitral valve prolapse. Genetic testing found a terminal 4.7Mb deletion at the 21q22.3 region (43310796-48097372 GRCh37/hg19) and duplication at the 20q region. While this deletion region overlaps with our patient in most areas, the brain morphology and reproductive system of the Sgardioli *et al.* patient were normal, suggesting chromosome 20q duplication may interfere with the phenotype.

We searched for the genome location 21q22.3 in the DECIPHER database (/www.deciphergenomics.org) and found 142 cases with deletion in 21q22.3 region, and the phenotype was described in 103 cases. After filtering out 42 cases (40.8%) which carried concurrent mutations on some other chromosome regions, among the remaining 61 cases, 60 (detailed information in Table S1) showed an overlapped deletion region with the present patient. Notably, among them, 10 cases showed the 16.49 Mb deletion of chr21:31578129-48119895 (GRCh37/hg19), and 25 cases showed the 5.59 Mb deletion of chr21:42478130-48119895 (GRCh37/hg19), suggesting that these were two commonly deleted regions of pure partial 21q. The phenotypes of these patient's varied greatly, ranging from mild to severe, even among patients carrying the same deletion region. So it is difficult to identify the 21q22.3 deletion in the case. However, patients with neurological and gonadal dysplasia are at increased risk of chromosome 21 abnormalities, attention should be paid to screening genes and chromosomes.

We focused on the 21q22.3 deletion-related abnormality in the genital and central nervous systems, as our patient had a buried penis, small testes and brain anomalies. We cannot explain this phenotype by a specific gene since the relationship between genotype and genital abnormality is still not well defined. Chen *et al.* (8) reported a male with 21q deletion (42543932-48119895) who showed a concealed penis and corpus callosum dysgenesis, while Oegema *et al.* (9) reported a case of cryptorchidism whose 21q deleted in chr38131848-42180291. The DECIPHER database contains only a few 21q deletion patients with a genital abnormity of decreased testicular size, oligospermia, delayed publication and/or cryptorchidism. Zeng *et al.* (10) reported a female with premature ovarian insufficiency with 21q deletion (14539866-28673235) and speculated it could result from the haploinsufficiency of some dosage-sensitive genes or genes with unclear function, or from environmental factors. We hypothesize that a combination of genetic and environmental factors resulted in the buried penis and small testes phenotypes of the patient in the present study.

Deletion of 21q is related to changes in human brain morphogenesis. Dose-sensitive genes in this region contribute to cortical development, and deletion can result in cortical dysplasia (11,12). Our patient had a widened prepontine cistern and annular cistern, hypoplasia of the pituitary gland, and deficiency of growth hormone and gonadal hormone. Ruiz-Botero and Pachajoa (13) reported on a Colombian girl of mixed race with corpus callosum hypoplasia and intellectual and mental disorders, and genetic testing found the deletion of 3.608 Mb (44482408-48090317) on chromosome 21q22.3 and a duplication on chromosome 7q. Valetto *et al.* (14) reported a boy with 21q deletion located at 38791571-43792093(GRCh37/hg19), who also suffered from hypoplasia of pituitary and corpus callosum. The overlapped region between this boy and our patient was very small (43531239-43792093), and no gene concerned with brain morphological changes was found. Oegema *et al.* (9) reported two patients with deletion of chr21:38131848-42180291 and chr21:36424426-40654602, respectively, and although their deleted regions did not overlap with our patient (*Table 2*) (2,3,8,9,14,15), they were also found to have hypoplasia of the corpus callosum. Therefore, we speculate that there are multiple gene loci regulating brain development on the long arm of chromosome 21.

We also compared the deletion region in cases with brain anomalies and/or gonadal dysgenesis reported in the literature and DECIPHER (*Figure 4* and *Table 2*) (2,3,8,9,14,15). As seen in *Table 2*, the most frequent phenotypes are of short stature, and have intellectual retardation, speech delay, epilepsy/seizures, distal limbs abnormalities, and a broad nasal bridge. As shown in *Figure 4*, most of these deletion regions were overlapped, and two recurrent microdeletion regions were identified, which may be related to gonadal and brain development. We summarized two overlapped microdeletion regions from these cases that may be related to gonadal and brain development and found 21q22.3 microdeletion 1 (chr21:43531239-43792093) and 21q22.3 microdeletion 2 (chr21:46625055-46884297) harbor seven genes and 10 genes respectively (*Table 3*). In 21q22.3 microdeletion region 1, gene *ABCG1* is highly expressed in the brain and plays a critical role in cerebrovascular function (16-18). Studies have shown that loss of *ABCG1* results in a

Table 2 Comparison of phenotype-genotype of pure 21q deletion case from the literature

Variable	The present patient	Chen *et al.* patient	Guion-Almeida *et al.* patient	Roberson *et al.* GM09868	Briegel *et al.* patient	Valetto *et al.* patient	Oegema *et al.* patient 1	Oegema *et al.* patient 2
Breakpoint	43531239-48119897	42543932-48119895	46625055-46884297	35677518-46921373	43945335-48097372	38791571-43792093	38131848-42180291	36424426-40654602
Deletion size (Mb)	4.5	5.7	219	11.2	4.5	4.9	4.1	4.2
Sex	M	M	F	F	F	M	M	F
Height	–1 SD		–1 SD		–2 SD	–3.6 SD	–3 SD	–3 SD
Microcephaly	N	Y			Y	Y	Y	Y
Hypertelorism	N	Y	Y			N		
Large ears	N	Y		Y		Y	Y	Y
Broad nasal bridge	N	Y	Y	Y		Y		Y
Abnormal vision	Y					N		
Short stature	Y		Y	Y	Y	Y	Y	Y
Distal limbs abnormalities	Y		N		Y	Y	Y	Y
Carious teeth	Y					N	Y	Y
Epilepsy/seizures	N				Y	Y	Y	Y
Speech delay	Y			Y	Y	Y		Y
Cardiac anomaly	N	Y			Y	N	Y	Y
Mental retardation	Y		N		Y	Y		Y
Intellectual retardation	Y	Y	Y		Y	Y		Y
Balance disorder	Y				N	Y		
Brain imaging	Widened prepontine cistern and annular cistern, thinned and hypoplastic pituitary gland	Corpus callosum dysgenesis, colpocephaly, ventriculomegaly, microcephaly	Sphenoethmoidal encephalocele, callosal agenesis; anterior pituitary was not visualized.			Hypoplastic of corpus callosum and pituitary stalk	Small frontal lobes, a thin corpus callosum and brain stem	Underdeveloped frontal gyri, thin corpus callosum and brain stem, loss of periventricular white matter ventricles
Genital abnormality	Concealed penis	Concealed penis					Cryptorchidism	

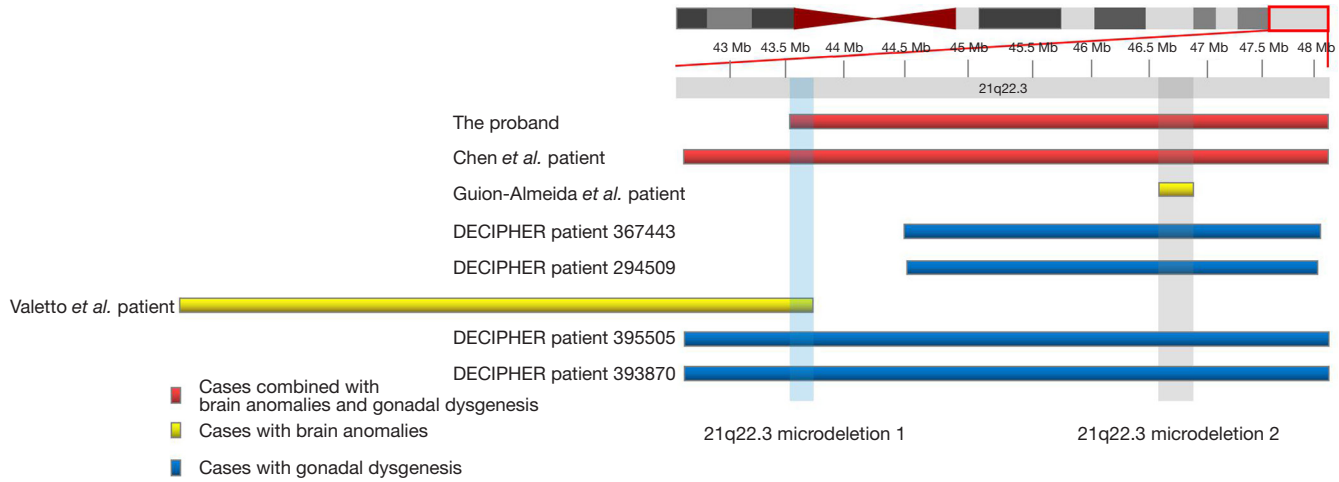

Figure 4 Comparison of the deletion region in cases about brain anomalies and gonadal dysgenesis. Red: cases combined with brain anomalies and gonadal dysgenesis; yellow: cases with brain anomalies; blue: cases with gonadal dysgenesis.

Table 3 Location and genes of 21q22.3 microdeletion 1 and microdeletion 2

Variable	21q22.3 microdeletion 1	21q22.3 microdeletion 2
Location	chr21:43531239-43792093 (GRCh37)	chr21:46625055-46884297 (GRCh37)
Genes	*ABCG1, RNA5SP492, TFF1, TFF2, TFF3, TMPRSS3, UMODL1*	*ADARB1, COL18A1, COL18A1-AS1, COL18A1-AS2, LINC00205, LINC00315, LINC00316, LINC00334, MTCO1P3, POFUT2*

chronic inflammatory response and endothelial cell injury and dysfunction. *ADARB1* is a gene related to brain development in 21q22.3 microdeletion 2, and its mutation can lead to autosomal recessive neurodevelopmental disorders with hypotonia, microcephaly, and epilepsy (19). We did not find any genes associated with gonadal dysgenesis in these two microdeletion regions.

Of the other genes in our patient's deleted region, *PRMT2* inhibits NF-kappaB-dependent transcription and promotes apoptosis (20). Abnormal regulation of PRMT2 protein, part of the arginine methyltransferase family, produced transcripts for chromatin-remodeling enzymes associated with reproductive system disease and cancer in a baboon endometriosis model (21). Abnormalities of the *WDR4* gene cause microcephaly, growth deficiency, seizures, and brain malformations, and mutation of the *TSPEAR* gene may result in ectodermal dysplasia. *DIP2A* and *S100B* in the 21q22.3 region were reported to be associated with autism spectrum disorder (6), and *DIP2A* was also shown to be related to dyslexia (22). *SIK1* mutations generate variant and truncated *SIK1* proteins that are associated with severe developmental epilepsy (23), and compared with the wild type, average neurite length and number were significantly reduced in human mutant SIK1 neurons, and the expression of synaptic activity response element genes decreased, causing epilepsy in some cases (24). However, the present case showed no signs of epilepsy. The dosage sensitivity of the deleted genes is not clear, and many of the deleted genes do not have a known function.

Partial 21q deletion is often accompanied by mental and psychological abnormalities. Our patient had difficulty in communication, and often laughed involuntarily, suggesting a mental disorder. However, mental disorders are difficult to diagnose in childhood because they may be masked by intellectual retardation and other phenotypes, so the actual prevalence may be underestimated. Therefore, we suggest regular screening for psychiatric disorders in affected children (15).

In conclusion, the similar abnormalities (hypoplasia of the corpus callosum) in different patients with non-overlapping deletion regions suggests there are multiple gene loci regulating brain development on 21q. Microdeletion 1 (chr21:43531239-43792093) and microdeletion 2 (chr21:46625055-46884297) may be related to gonadal and

brain development in 21q22.3. Chr21:31578129-48119895 and chr21:42478130-48119895 are two commonly deleted regions of pure partial 21q, and the same deletion has different phenotypes in DECIPHER cases suggesting the heterogeneity of 21q deletion. The relationship between phenotype and genotype requires further study, and more cases and molecular mechanism research are needed to clarify the effect of 21q deletion.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/tp-21-377

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tp-21-377). All authors reported that this study received the support of the major research and development program of Hainan Province (nos. ZDYF2019156), and received the support of Hainan Province Clinical Medical Center, and this study made use of data generated by the DECIPHER community. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient' parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Supplementary

Table S1 The genotype/phenotype(s) of 60 21q22.3 deletion cases that overlapped with present patient in DECIPHER

DECIPHER Patient	Sex	Location (GRCh38/hg38)	Size	Inheritance/genotype	Pathogenicity/contribution	Phenotype(s)
396146	46XX	21:30205811-46699983	16.49 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Abnormal dermatoglyphics, broad palm, bulbous nose, cubitus valgus, decreased fetal movement, dental malocclusion, downturned corners of mouth, EEG abnormality, elbow flexion contracture, hip dislocation, hypoplastic philtrum, hypotonia, incoordination, intellectual disability, keratoconus, long eyelashes, low anterior hairline, malar flattening, mandibular prognathia, myopia, nasal speech, obesity, pes planus, premature birth, round face, short metacarpal, short neck, short philtrum, spotty hyperpigmentation, synophrys, tapered finger, thin lower lip vermilion, thin upper lip vermilion, upslanted palpebral fissure
395927	46XX	21:30205811-46699983	16.49 Mb	De novo	Likely pathogenic	Abnormal aortic morphology, abnormality of prenatal development or birth, aortic valve stenosis, arrhythmia, atrial septal defect, camptodactyly of finger, cleft of alveolar ridge of maxilla, coarctation of aorta, convex nasal ridge, ectopic anus, hemivertebrae, hydrocephalus, hypertonia, hypoplasia of the corpus callosum, hypoplastic left heart, micrognathia, microphthalmia, overlapping fingers, patent ductus arteriosus, preauricular skin tag, prominent glabella, prominent nasal bridge, protruding ear, renal dysplasia, renal hypoplasia, sclerocornea, short neck, short stature, supernumerary ribs, wide intermamillary distance
398086	46XX	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Abnormal dermatoglyphics, abnormality of the dentition, abnormally low-pitched voice, blepharitis, brachycephaly, broad palm, brushfield spots, conjunctivitis, depressed nasal bridge, epicanthus, furrowed tongue, high palate, hypothyroidism, hypotonia, intellectual disability, joint laxity, myopia, narrow palate, primary microcephaly, sandal gap, short neck, short stature, single transverse palmar crease, small hand, strabismus, upslanted palpebral fissure, ventricular septal defect
396000	46XX	21:41106204-46699983	5.59 Mb	De novo, mosaic	Likely pathogenic	Abnormal hip joint morphology, abnormal thrombocyte morphology, abnormality of the pinna, breech presentation, delayed speech and language development, downslanted palpebral fissures, EEG abnormality, flexion contracture, high pitched voice, hydrocephalus, hypertonia, intellectual disability, low-set ears, macrotia, micrognathia, non-midline cleft lip, patent ductus arteriosus, primary microcephaly, recurrent infections, short neck, short stature, small for gestational age, strabismus, telecanthus, umbilical hernia, wide nasal bridge
394833	46XX	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Absent toe, breech presentation, cerebral atrophy, convex nasal ridge, cutis marmorata, fine hair, high anterior hairline, high palate, hydrocephalus, hypermobility of toe joints, hypotonia, intellectual disability, joint laxity, low-set ears, microcephaly, micrognathia, narrow forehead, prominent metopic ridge, prominent occiput, scoliosis, short foot, short nose, short toe, small for gestational age, strabismus
393928	46XY	21:38306208-46699983	8.39 Mb	De novo, mosaic	Likely pathogenic	Adducted thumb, broad neck, camptodactyly of finger, cryptorchidism, downslanted palpebral fissures, epicanthus, hypoplastic philtrum, hypotonia, inguinal hernia, intellectual disability, long neck, long philtrum, micrognathia, microtia, narrow chest, narrow forehead, narrow mouth, overlapping fingers, prominent antihelix, prominent nasal bridge, prominent occiput, proportionate short stature, thin upper lip vermilion, wide nasal bridge
398079	46XX	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Abnormal dermatoglyphics, abnormality of the helix, blepharitis, brachycephaly, broad palm, brushfield spots, depressed nasal bridge, diastasis recti, epicanthus, finger clinodactyly, furrowed tongue, high palate, hypermetropia, hypotonia, narrow palate, primary microcephaly, sandal gap, short 5th finger, short neck, short stature, small for gestational age, small hand, upslanted palpebral fissure
393304	46XY	21:30205811-46699983	16.49 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Abnormality of the pinna, abnormality of the skin, adipose tissue loss, downslanted palpebral fissures, epicanthus, facial asymmetry, high palate, hip dislocation, hypertelorism, hypertonia, hypospadias, low-set ears, micropenis, narrow chest, scrotal hypoplasia, short palpebral fissure, short stature, small for gestational age, talipes equinovalgus, torticollis, wide intermamillary distance
395104	46XX	21:30205811-46699983	16.49 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Abnormality of the pinna, coarse hair, finger clinodactyly, full cheeks, genu valgum, hallux valgus, high palate, highly arched eyebrow, hypertelorism, hypoplastic nipples, incoordination, intellectual disability, low-set ears, microdontia, short nose, strabismus, talipes equinovarus, thick eyebrow, thick nasal alae, wide intermamillary distance
395134	46XY	21:30205811-46699983	16.49 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Abnormality of the pinna, broad neck, coarse hair, flat occiput, full cheeks, genu valgum, hallux valgus, high palate, highly arched eyebrow, hypotelorism, incoordination, intellectual disability, microdontia, micropenis, prominent ear helix, round face, strabismus, talipes equinovarus, thick eyebrow, turricephaly
393029	46XX	21:30205811-46699983	16.49 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Abnormality of the helix, abnormality of the pinna, aortic valve stenosis, bulbous nose, downslanted palpebral fissures, EEG abnormality, epicanthus, facial asymmetry, intellectual disability, long philtrum, low-set ears, prominent antihelix, prominent nasal bridge, short palpebral fissure, short stature, sloping forehead, strabismus, thin upper lip vermilion, wide mouth
401735	46XY	21:40288955-45858283	5.57 Mb	De novo	Likely pathogenic	Atopic dermatitis, autistic behavior, cleft mandible, cleft palate, coarse hair, delayed speech and language development, down-sloping shoulders, downslanted palpebral fissures, feeding difficulties in infancy, hypotonia, malar flattening, nasal speech, non-midline cleft lip, pes planus, prominent nasal bridge, recurrent infections, short 5th finger, thick upper lip vermilion
393862	46XX	21:38306208-46699983	8.39 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Anteverted nares, bulbous nose, cleft palate, finger clinodactyly, hammertoe, hypotonia, intellectual disability, micrognathia, non-midline cleft lip, preauricular pit, pulmonic stenosis, recurrent infections, sacral dimple, small for gestational age, trigonocephaly, upslanted palpebral fissure, vesicoureteral reflux
393893	46XY	21:41106204-46699983	5.59 Mb	De novo	Likely pathogenic	Abnormality of the pinna, downslanted palpebral fissures, finger clinodactyly, hypertonia, inguinal hernia, intellectual disability, low-set ears, microcephaly, micrognathia, overlapping toe, plagiocephaly, prominent metopic ridge, small for gestational age, small nail, spotty hyperpigmentation, thick upper lip vermilion, thin ribs
400843	46XX	21:30205812-46699983	16.49 Mb	De novo, mosaic	Likely pathogenic	Abnormal acetabulum morphology, abnormal ilium morphology, abnormal thumb morphology, concave nail, deeply set eye, hypoplastic philtrum, joint laxity, low-set ears, micrognathia, misalignment of teeth, pectus excavatum, pes planus, preauricular pit, preauricular skin tag, slender build, stenosis of the external auditory canal, umbilical hernia
395494	46XX	21:41106204-46699983	5.59 Mb	De novo	Likely pathogenic	Brachycephaly, EEG abnormality, epicanthus, finger clinodactyly, flat occiput, intellectual disability, microcephaly, micrognathia, microtia, prominent antihelix, protruding tongue, short neck, short phalanx of finger, single transverse palmar crease, sparse hair
398081	46XY	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Abnormal dermatoglyphics, abnormality of cardiovascular system morphology, abnormality of the outer ear, blepharitis, brachycephaly, broad palm, depressed nasal bridge, epicanthus, hypotonia, protruding tongue, sandal gap, short neck, small hand, tetralogy of fallot, upslanted palpebral fissure
393936	46XX	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Downslanted palpebral fissures, EEG abnormality, finger clinodactyly, hypertonia, low-set ears, macrotia, micrognathia, primary microcephaly, prominent nasal bridge, short stature, small for gestational age, supernumerary ribs, wide nasal bridge
395590	46XX	21:41106204-46699983	5.59 Mb	De novo, mosaic	Likely pathogenic	Atresia of the external auditory canal, epicanthus, facial asymmetry, hypertelorism, intellectual disability, low-set ears, microcephaly, micrognathia, preauricular skin tag, proportionate short stature, sacral dimple, wide mouth
393891	46XY	21:41106204-46699983	5.59 Mb	De novo	Likely pathogenic	Abnormality of the skin, curly eyelashes, hypotonia, long eyelashes, low-set ears, micrognathia, narrow palate, peters anomaly, sclerocornea, small for gestational age, thin skin, wide intermamillary distance
396749	46XY	21:41106203-46699983	5.59 Mb	Unknown	Likely pathogenic	Abnormality of the pinna, EEG abnormality, highly arched eyebrow, hypertelorism, intellectual disability, macrotia, mandibular prognathia, proportionate short stature, protruding ear, thick lower lip vermilion, varicose veins, wide mouth
105	46XX	21:37784110-42396111	4.61 Mb	Unknown		Hallux valgus, intellectual disability, macrodontia, microcephaly, narrow forehead, prominent nose, seizure, short palm, short philtrum, stereotypy, wide mouth
251573	46XY	21:45714068-45755268	41.20 kb	Inherited from normal parent		Constipation, deeply set eye, delayed speech and language development, intellectual disability, microcephaly, proportionate short stature, short foot, short palm, spasticity, strabismus, wide nasal bridge
395566	46XX	21:41106204-46699983	5.59 Mb	De novo, mosaic	Likely pathogenic	Abnormal thrombocyte morphology, cleft palate, depressed nasal bridge, frontal bossing, hearing impairment, intellectual disability, non-midline cleft lip, proportionate short stature, talipes equinovarus, ventricular septal defect, wide nasal bridge
395577	46XY	21:41106204-46699983	5.59 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Brachycephaly, frontal bossing, hypoplasia of the maxilla, hypotonia, intellectual disability, microdontia, nystagmus, scoliosis, thin upper lip vermilion, upslanted palpebral fissure
393913	46XX	21:41106204-46699983	5.59 Mb	De novo, mosaic	Likely pathogenic	Anteverted nares, high palate, hypertonia, low-set ears, micrognathia, overlapping fingers, posteriorly rotated ears, prominent antihelix, prominent occiput, wide nasal bridge
401718	46XX	21:41599278-46677461	5.08 Mb	De novo	Likely pathogenic	Abnormality of finger, abnormality of the pinna, aplasia/hypoplasia of the earlobes, conductive hearing impairment, hypopigmentation of hair, long thorax, nystagmus, short neck, stenosis of the external auditory canal, vertebral segmentation defect
393875	46XX	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Carious teeth, downslanted palpebral fissures, EEG abnormality, facial asymmetry, genu valgum, microcephaly, proportionate short stature, secondary amenorrhea, talipes equinovalgus
308310	46XY	21:40520005-46142503	5.62 Mb	Unknown		Anteverted nares, delayed speech and language development, downslanted palpebral fissures, generalized neonatal hypotonia, low-set ears, macrotia, mild global developmental delay, pes planus, prominent fingertip pads
394110	46XY	21:30205811-46699983	16.49 Mb	De novo, mosaic	Likely pathogenic	Abnormal immunoglobulin level, abnormal thrombocyte morphology, dolichocephaly, epicanthus, frontal bossing, high anterior hairline, intellectual disability, pili torti, recurrent infections
396772	46XY	21:30205811-46699983	16.49 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Intellectual disability, low-set ears, micrognathia, primary microcephaly, prominent nose, short neck, short stature, small for gestational age
392570	46XY	21:30205811-46699983	16.49 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Brachycephaly, cleft palate, intellectual disability, low-set ears, non-midline cleft lip, placental infarction, small for gestational age, small placenta
395541	46XY	21:41106204-46699983	5.59 Mb	De novo	Likely pathogenic	Depressed nasal ridge, downslanted palpebral fissures, epicanthus, facial asymmetry, intellectual disability, posteriorly rotated ears, short nose
396753	46XX	21:41106203-46699983	5.59 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Abnormality of the skin, delayed speech and language development, EEG abnormality, flat occiput, gait disturbance, hyperactivity, intellectual disability
359530	46XX	21:41785816-46670405	4.88 Mb	De novo	Pathogenic	Cleft palate, conductive hearing impairment, delayed speech and language development, impaired pain sensation, intellectual disability, recurrent infections
341696	46XX	21:42336476-46673449	4.34 Mb	Unknown		Cataract, cervical c2/c3 vertebral fusion, delayed speech and language development, episodic vomiting, lingual thyroid, toe walking
278295	46XY	21:46141745-46164939	23.20 kb	Maternally inherited	Likely benign	Abnormal external genitalia, behavioral abnormality, delayed speech and language development, global developmental delay, sleep disturbance
390415	46XY	21:40296018-46567246	6.27 Mb	Unknown	Pathogenic	Intellectual disability, polymicrogyria, scoliosis, seizure
367443	46XX	21:43071168-46664244	3.59 Mb	Unknown	Pathogenic	Cleft lip, delayed puberty, short stature, specific learning disability
386959	46XY	21:36423932-46648012	10.22 Mb	Unknown	Pathogenic	Abnormal heart morphology, hypospadias, intellectual disability, scoliosis
304201	46XY	21:38208527-46699983	8.49 Mb	Unknown	Likely pathogenic	Abnormal facial shape, mild receptive language delay, pectus excavatum, unilateral cleft palate
394149	46XY	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Proportionate short stature, upslanted palpebral fissure, ventricular septal defect
331338	46XY	21:44054543-45378292	1.32 Mb	Unknown	Likely pathogenic	Intellectual disability, mild, skeletal dysplasia, spastic paraparesis
395587	46XY	21:41106203-46699983	5.59 Mb	De novo, mosaic	Likely pathogenic	Intellectual disability, microcephaly, short neck
393955	46XY	21:41106203-46699983	5.59 Mb	De novo, mosaic	Likely pathogenic	Inguinal hernia, intellectual disability, microcephaly
414037	46XY	21:43094948-46670405	3.58 Mb	De novo	Pathogenic	Hypotonia, intellectual disability, scoliosis
350149	46XY	21:44057842-44064432	6.59 kb	Maternally inherited	Likely benign	Behavioral abnormality, intellectual disability, obesity
322809	46XY	21:46511395-46603068	91.67 kb	Unknown	Uncertain	2-3 toe syndactyly, abnormality of canine, intrauterine growth retardation
395505	46XY	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Decreased testicular size, oligospermia
393870	46XY	21:41106204-46699983	5.59 Mb	Imbalance arising from a balanced parental rearrangement	Likely pathogenic	Cryptorchidism, delayed puberty
294509	46XY	21:44059454-46636538	2.58 Mb	Unknown	Pathogenic	Cognitive impairment, oligospermia
260427	46XY	21:44253374-44282764	29.39 kb	Inherited from normal parent		Autism, intellectual disability
366645	46XY	21:42955906-46648012	3.69 Mb	Unknown	Pathogenic	Autism, global developmental delay
386963	46XY	21:41855368-43204628	1.35 Mb	Unknown	Uncertain	Unilateral cleft lip
395504	46XY	21:41106204-46699983	5.59 Mb	De novo	Likely pathogenic	Umbilical hernia
289193	Unknown	21:46517395-46621026	103.63 kb	Unknown	Likely benign	Primary amenorrhea
378976	46XY	21:41855368-43204628	1.35 Mb	Unknown	Uncertain	Oral cleft
393866	46XY	21:41106203-46699983	5.59 Mb	De novo	Likely pathogenic	Oligospermia
410231	46XX	21:44720054-45262269	542.22 kb	Unknown	Uncertain	Microcephaly
384325	46XX	21:44416925-46671337	2.25 Mb	De novo	Uncertain	Hypoplastic left heart

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