Cryptic Genomic Rearrangements in Three Patients with 46,XY Disorders of Sex Development

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Abstract

Background: 46,XY disorders of sex development (46,XY DSD) are genetically heterogeneous conditions. Recently, a few submicroscopic genomic rearrangements have been reported as novel genetic causes of 46,XY DSD.

Methodology/Principal Findings: To clarify the role of cryptic rearrangements in the development of 46,XY DSD, we performed array-based comparative genomic hybridization analysis for 24 genetic males with genital abnormalities. Heterozygous submicroscopic deletions were identified in three cases (cases 1–3). A ~8.5 Mb terminal deletion at 9p24.1–24.3 was detected in case 1 that presented with complete female-type external genitalia and mental retardation; a ~2.0 Mb interstitial deletion at 20p13 was identified in case 2 with ambiguous external genitalia and short stature; and a ~18.0 Mb interstitial deletion at 2q31.1–32 was found in case 3 with ambiguous external genitalia, mental retardation and multiple anomalies. The genital abnormalities of case 1 could be ascribed to gonadal dysgenesis caused by haploinsufficiency of DMR17, while those of case 3 were possibly associated with perturbed organogenesis due to a deletion of the HOXD cluster. The deletion in case 2 affected 36 genes, none of which have been previously implicated in sex development.

Conclusions/Significance: The results indicate that cryptic genomic rearrangements constitute an important part of the molecular bases of 46,XY DSD and that submicroscopic deletions can lead to various types of 46,XY DSD that occur as components of contiguous gene deletion syndromes. Most importantly, our data provide a novel candidate locus for 46,XY DSD at 20p13.

Introduction

46,XY disorders of sex development (46,XY DSD) are genetically heterogeneous conditions that result from the impaired production or function of androgens, or from defective organogenesis of external genitalia [1]. To date, several genes such as SRY, AR, SRD5A2, and SOX9 have been identified as causative genes for 46,XY DSD, although mutations in these genes account for only a minor fraction of the molecular causes of these conditions [1], [2].

Recent advances in microarray technology, including comparative genomic hybridization (CGH) analysis and single nucleotide polymorphism (SNP) genotyping, have enabled researchers to identify genomic rearrangements in individuals with apparently normal karyotypes [3]. Cryptic genomic rearrangements can lead to developmental disorders, although they can also occur as benign polymorphisms [4]. To date, CGH analysis and SNP genotyping have been carried out for patients with 46,XY DSD, identifying multiple submicroscopic deletions and duplications [5], [6], [7]. Such rearrangements frequently affected coding exons or regulatory regions of known DSD-associated genes including SF1, SOX9 and DMRT1, or exons of candidate genes including KANK1 and ZEB2 [5], [6], [7]. These data suggest that genomic abnormalities at various chromosomal loci may underlie 46,XY DSD.

To clarify the role of cryptic genomic rearrangements in the development of 46,XY DSD, we performed copy-number analyses...
Subjects and Methods

Ethics Statement
This study was approved by the Institutional Review Board Committee at the National Center for Child Health and Development. After obtaining written informed consent from the parents, peripheral blood samples were collected from the patients. When possible, blood samples were also obtained from the parents.

Patients
The study population comprised 24 patients with 46, XY DSD, including nine cases with complete female-type external genitalia, five with ambiguous genitalia and 10 with male-type external genitalia with hypospadias (Table 1). None of the 24 patients had a family history of DSD or a history of prenatal exposure to specific environmental pollutants. G-banding analysis showed a normal 46,XY karyotype in all patients. Mutations in the coding regions of known DSD-causative genes, SRY, AR, SRD5A2, SF1, WNT4, SOX9, WTI, BNC2, DMRT1, HSD17B3, and MAP3K1, were excluded by sequence analyses.

CGH Analysis
Genomic DNA samples were subjected to CGH analyses using a catalog human array (4 × 180 k format, Agilent Technologies, Palo Alto, CA), according the manufacturer’s instructions. The sizes and positions of the genomic rearrangements were analyzed using the UCSC genome browser (http://genome.ucsc.edu/; February 2009, hg19, build 37). In the present study, we focused on copy-number alterations with a physical size of more than 1.5 Mb, which have a higher probability of being associated with disease phenotypes [8]. Deletions and duplications registered in the database of genomic variants (http://projects.tcag.ca/variation/) were excluded as benign polymorphisms.

Results
CGH Analysis
We identified heterozygous submicroscopic deletions in three cases (cases 1–3; Fig. 1). The deletions affected several genes (Table 2). Case 1 harbored a ~8.5 Mb terminal deletion at 9p24.1–24.3 that encompassed DMRT1, in addition to 39 other genes. Case 2 carried a ~2.0 Mb interstitial deletion at 20p13 that included 36 genes. Case 3 had a ~18.0 Mb interstitial deletion at 2q31.1–32.1 that affected the entire HOXD cluster (HOXD 1–13), and 84 other genes. The parents of case 2 did not carry the deletion, whereas the parental samples of cases 1 and 3 were not available for genetic analyses.

Table 1. Patients analyzed in the present study.

| Cases | Karyotype | Ethnic origin | External genitalia | Additional clinical features |
|-------|-----------|---------------|--------------------|-----------------------------|
| 1     | 46,XY     | Japanese      | Female             | Mental retardation, schizophrenia |
| 2     | 46,XY     | Vietnamese    | Ambiguous          | Short stature               |
| 3     | 46,XY     | Vietnamese    | Ambiguous          | Short stature, mental retardation, multiple anomalies |
| 4     | 46,XY     | Japanese      | Female             |                             |
| 5     | 46,XY     | Japanese      | Female             | Upper limb anomalies        |
| 6     | 46,XY     | Japanese      | Female             |                             |
| 7     | 46,XY     | Japanese      | Female             | Short stature               |
| 8     | 46,XY     | Japanese      | Female             |                             |
| 9     | 46,XY     | Japanese      | Female             |                             |
| 10    | 46,XY     | Japanese      | Female             |                             |
| 11    | 46,XY     | Japanese      | Female             | Agenesis of the corpus callosum, short palpebral fissures |
| 12    | 46,XY     | Japanese      | Ambiguous          |                             |
| 13    | 46,XY     | Japanese      | Ambiguous          |                             |
| 14    | 46,XY     | Indian        | Ambiguous          |                             |
| 15    | 46,XY     | Japanese      | Male with HS       |                             |
| 16    | 46,XY     | Japanese      | Male with HS       |                             |
| 17    | 46,XY     | Japanese      | Male with HS       |                             |
| 18    | 46,XY     | Japanese      | Male with HS       |                             |
| 19    | 46,XY     | Japanese      | Male with HS       |                             |
| 20    | 46,XY     | Japanese      | Male with HS       |                             |
| 21    | 46,XY     | Japanese      | Male with HS       |                             |
| 22    | 46,XY     | Japanese      | Male with HS       |                             |
| 23    | 46,XY     | Japanese      | Male with HS       |                             |
| 24    | 46,XY     | Vietnamese    | Male with HS       |                             |

DSD, disorders of sex development; HS, hypospadias.
doi:10.1371/journal.pone.0068194.t001
Clinical Features of Deletion-positive Patients

Case 1 was a genetic male born to non-consanguineous Japanese parents. This patient had complete female-type external genitalia and was raised as a female. This patient exhibited mental retardation and behavioral problems and was diagnosed as having schizophrenia. At 17 years of age, this patient was referred to our clinic because of primary amenorrhea. Clinical analysis detected no dysmorphic facial features or cardiac/renal abnormalities. Abdominal ultrasonography delineated a uterus. Blood endocrine tests indicated primary hypogonadism (Table 3). At 17 years of age, the patient underwent gonadectomy. Histological analyses showed bilateral streak gonads with ovarian ducts. The parents were clinically normal.

Case 2 was a genetic male born to non-consanguineous Vietnamese parents. At birth, this patient exhibited a micropenis, cryptorchidism, and distal hypospadias. Abdominal ultrasonography detected bilateral testes (12×6 mm) in inguinal canals. The uterus and ovaries were absent. This patient was raised as a boy and underwent surgical intervention for hypospadias and cryptorchidism at 4 years and 2 months and at 4 years and 3 months of age, respectively. On his visit at 4.5 years of age, he showed a penis with a stretched length of 3 cm, and left testis (12×9 mm) in the scrotum and right testis (13×6 mm) in the inguinal canal (Fig. 2). He had no dysmorphic facial features (Fig. 2). He showed short stature (89 cm, –2.9 SD) and delayed bone age (equivalent to 2 years of age). His mental development was normal. Blood endocrine tests at 4.5 years of age showed low levels of luteinizing hormone and testosterone (Table 3). His growth hormone levels were within the normal range at the baseline, but remained low after physical exercise. His parents were clinically normal and had normal statures.

Case 3 was born to non-consanguineous Vietnamese parents at 40 weeks of gestation with a birth weight of 2.0 kg (–2.3 SD). At birth, this patient manifested severe micropenis and hypospadias (Fig. 2). Bilateral testes were palpable in the scrotum, and uterus and ovaries were absent. Thus, this patient was raised as a boy. In addition to genital abnormalities, he exhibited multiple anomalies of the fingers and toes, i.e., camptodactyly and flexion contracture of the proximal interphalangeal joint of the right index and left ring fingers, cutaneous syndactyly of the 2nd and 3rd toes and medial deviation of the 4th toe in the right foot, lateral deviation of the 2nd toe and medial deviation the 4th toe in the left foot, and overriding of the 4th toe on the third toe in both feet (Fig. 2). Furthermore, he showed dysmorphic facial features such as ptosis and micrognathia (Fig. 2). His blood testosterone level at birth was within the normal range (Table 3). On examination at 11 months of age, he showed obvious growth retardation (body weight; 6.0 kg, –3.0 SD) and developmental delay (DQ <30). At one year of age, he presented with an episode of febrile convulsion. Brain magnetic resonance imaging detected delayed myelination, hypogenesis of the corpus callosum, and prominent ventricular and CSF spaces (Fig. 2). His parents were clinically normal.
Discussion

We identified cryptic heterozygous deletions with physical sizes of more than 1.5 Mb in three of the 24 patients with 46,XY DSD. The results support the notion that submicroscopic genomic rearrangements constitute a portion of causative mechanisms for 46,XY DSD [5], [6], [7]. Furthermore, molecular and clinical data of the three cases imply that cryptic deletions can cause DSD as components of contiguous gene deletion syndromes. Since array-based CGH analysis and SNP genotyping can detect copy-number alterations across the entire genome in a single assay,

Table 2. Genes affected by the cryptic deletions.

| Case 1       | Case 2       | Case 3       |
|--------------|--------------|--------------|
| C9orf66      | EBF4         | BB55         |
| DOCK8        | CPXM1        | K8TBD10      |
| KANK1        | C2orf141     | FASTKD1      |
| DMRT1        | FAM113A      | PPIG         |
| DMRT3        | TEMEM239     | CCDC173      |
| DMRT2        | VPS16        | SSB          |
| SMARCA2      | PTPRA        | C2orf77      |
| FLJ35024     | GNRH2        | PHOSPHO2     |
| VLDLR        | MRPS26       | KLHL23       |
| KCNV2        | OXT          | METTL5       |
| RFX3         | LOC100134015 | MYO3B        |
| GLIS3        | UBOX5        | LOC440925    |
| C9orf68      | FASTKD5      | LOC285141    |
| SLC1A1       | SLC4A11      | SP5          |
| SPATA6L      | C20orf194    | NR_046248    |
| AK3          | DDRGK1       | GAD1         |
| CDC37L1      | ITPA         | GORASP2      |
| RCL1         | SLC4A11      | TLK1         |
| C9orf46      | C20orf194    | METTL8       |
| JAK2         | ATRN         | DCAF17       |
| INSL6        | GFRA4        | CYBRD1       |
| INSL4        | ADAM33       | DYNCIi2      |
| RNL2         | SIGLEC1      | SLC25A12     |
| RNL1         | HSPA12B      | HAT1         |
| C9orf46      | C20orf27     | METAP1D      |
| CD274        | CDC25B       | DLX1         |
| PDCD1LG2     | C20orf29     | DLX2         |
| KIAA1432     | SPEF1        | ITGA6        |
| ERMP1        | CENPB        | PDK1         |
| MLANA        | MAV5         | RAPGEF4-A51  |
| KIAA2026     | PANK2        | RAPGEF4      |
| RANBP6       | RNF24        | ZAK          |
| IL33         | SMOX         | MLK7-A51     |
| TPD5L2L3     | LOC728228    | CDC4A7       |
| UHRF2        | ADRA1D       | SP3          |
| GLDC         | OLA1         | NCKAP1       |
| KDM4C        | LOC285084    | PDE1A        |
| C9orf123     | CIR1         | DUSP19       |
| PTPRD        | SCRN3        | NUP35        |
|              | GPR155       | ZNF804A      |
|              | WIPF1        | FSIP2        |
|              |              | CHRNA1       |

doi:10.1371/journal.pone.0068194.t002
these methods should be considered for patients with 46,XY DSD, particularly for those with additional clinical manifestations.

Case 1 had a ∼8.5 Mb heterozygous deletion at 9p involving 40 genes. Of the 40 genes, DMRT1 is known to encode a male specific transcriptional regulator with a conserved zinc finger-like DNA-binding domain [9], [10]. Since mouse Dmrt1 has been implicated in testicular differentiation [11], and intragenic deletions of human DMRT1 have been identified in 46,XY patients with gonadal dysgenesis [6], [12], it appears that DSD in case 1 results from haploinsufficiency of DMRT1.

Furthermore, our results provide additional information about other disease-associated loci. First, deletions at 9p22.3–23 are associated with mental retardation [13]. Second, terminal deletions at 9p have previously been reported in two patients harboring 20p terminal deletions is ascribed to growth hormone deficiency. With 20p deletions is ascribed to growth hormone deficiency. In addition, the deletion of case 2 seems to harbor a gene that is indispensable for growth, because short stature was observed in case 2, as well as in most patients with partial monosomy of 20p [16], [17], [18], [19]. It might also be possible that the 20p13 and/or the 2q31.1–32 deletion has unmasked a recessive mutation of the testis development gene(s) on the structurally normal homologous chromosome, leading to DSD. In addition, the deletion of case 2 seems to harbor a gene that is indispensable for growth, because short stature was observed in case 2, as well as in most patients with partial monosomy of 20p [16], [17], [18], [19]. It might also be possible that the 20p13 and/or the 2q31.1–32 deletion has unmasked a recessive mutation of the testis development gene(s) on the structurally normal homologous chromosome, leading to DSD. In addition, the deletion of case 2 seems to harbor a gene that is indispensable for growth, because short stature was observed in case 2, as well as in most patients with partial monosomy of 20p [16], [17], [18], [19]. It might also be possible that the 20p13 and/or the 2q31.1–32 deletion has unmasked a recessive mutation of the testis development gene(s) on the structurally normal homologous chromosome, leading to DSD.

### Table 3. Clinical and laboratory findings of cases 1–3.

| Cases | Case 1 | Case 2 | Case 3 |
|-------|--------|--------|--------|
| **Molecular analyses** | | | |
| Karyotype (G-band) | 46,XY | 46,XY | 46,XY |
| Genomic rearrangement | Deletion | Deletion | Deletion |
| Genomic position of the deletion | 9p24.1–24.3 | 20p13 | 2q31–32 |
| Size of the deletion | ∼8.5 Mb | ∼2.0 Mb | ∼18.0 Mb |
| Parental origin of the deletion | Unknown | de novo | Unknown |
| **Clinical features** | | | |
| External genitalia | Female-type genitalia | Ambiguous | Ambiguous |
| Mental retardation | Yes | No | Yes |
| Growth failure/Short stature | No | Yes | Yes |
| Dysmorphic facial appearance | No | No | Yes |
| Additional features | Schizophrenia | Delayed bone age | Skeletal anomalies |
| | | | Brain anomalies |
| | | | Convulsion |
| **Endocrine data** | | | |
| Age at examination | 17 y | 4.5 y | at birth |
| LH (mIU/mL) | 17.4 (0.2–2.2) | 0.01 (0.2–1.9) | 0.01 (0.2–0.5) |
| FSH (mIU/mL) | 101.1 (0.6–4.8) | | |
| Testosterone (nmol/L) | 0.71 (9–32) | 0.01 (0.2–0.5) | 4.9 (<12) |
| GH after physical exercise (ng/mL) | 1.5 (3.0–28.3) | | |

DSD, disorders of sex development; MP, micropenis; HS, hypospadias; CO, cryptorchidism.

The hormone values below the reference range are boldfaced, and those above the reference range are italicized.

*Reference values of the age-matched control individuals are shown in the parenthesis.

doi:10.1371/journal.pone.0068194.t003
a role in social behavior [21]. Lack of social dysfunction in case 2 indicates that haploinsufficiency of OXT and AVP permits normal psychosocial development at least in childhood. However, this notion awaits further investigation.

Case 3 had a ∼18.0 Mb interstitial deletion at 2q31.1–32.1. Clinical manifestations of case 3 including finger/toe anomalies, mental retardation and facial dysmorphism are compatible with the 2q31 microdeletion syndrome, a well-established contiguous gene deletion syndrome [22]. Notably, abnormal formation of the external genitalia has been reported in both male and female patients carrying 2q31 deletions [23], [24]. Previous studies have attributed the skeletal anomalies of 2q31 microdeletion syndrome to haploinsufficiency of the HOXD cluster [22], [25], and mental retardation and craniofacial abnormalities to deletions of certain genes located within the genomic interval spanning 174–175 Mb from the 2q telomere [22] (Fig. 3C). In this regard, while skeletal abnormalities are obviously milder in case 3 than the previously reported patients with deletions involving HOXD genes [25], this would be consistent with the assumption that haploinsufficiency of developmental genes is frequently associated with a broad phenotypic spectrum [26]. Since mouse Hoxd genes have been shown to play a role in the formation of external genitalia by regulating multiple target genes, genital abnormalities of 2q31 microdeletion syndrome could be associated with haploinsufficiency of HOXD genes [25], [27]. Indeed, the phenotype of case 3, such as hypomasculinized external genitalia without cryptorchidism and a normal blood testosterone value at birth, is indicative of perturbed organogenesis of the external genitalia rather than impaired hormone production in the gonads. However, since DSD has been described for only a small subset of males with 2q31 deletions [22], [23], [24], [25], impaired sex development in case 3 may be caused by other unknown genetic or environmental factors.

In summary, we identified cryptic genomic rearrangements in three of 24 individuals with 46,XY DSD. It appears that the genital abnormalities of case 1 result from gonadal dysgenesis due

Figure 2. Clinical features of cases 2 and 3. A. Clinical findings of case 2 at 4.5 years of age. Images of the craniofacial region and external genitalia (after surgical intervention) are shown. B. Clinical findings of case 3 at 11 months of age. Multiple facial dysmorphisms and limb anomalies including syndactyly and camptodactyly are shown. Brain magnetic resonance imaging indicates delayed myelination, hypogenesis of the corpus callosum and prominent ventricular and CSF spaces. The parents of cases 2 and 3 have given written informed consent, as outlined in the PLOS consent form, to publication of the photographs of the patients.

doi:10.1371/journal.pone.0068194.g002
to haploinsufficiency of DMRT1, while those of case 3 can be ascribed to perturbed organogenesis due to the deletion of the HOXD cluster. These data suggest that submicroscopic deletions can lead to various types of 46,XY DSD that occur as components of contiguous gene deletion syndromes. Moreover, the results obtained from case 2 provide a novel candidate locus for 46,XY DSD at 20p13. Further copy-number analyses on patients with 46,XY DSD and functional assays for genes involved in the genomic rearrangements will help to clarify novel causative mechanisms for 46,XY DSD.

Author Contributions
Conceived and designed the experiments: VCD KK YK TO MF. Performed the experiments: MI ES KN. Analyzed the data: MI ES TO MF. Contributed reagents/materials/analysis tools: VCD SI MN KM YH KK YK. Wrote the paper: TO MF.

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Figure 3. Schematic representation of the genomic regions around the deletions. A. Terminal part of the short arm of chromosome 9. The black arrow denotes the deletion identified in case 1. The dotted arrows indicate the genomic intervals associated with DSD and for 9p- syndrome [13]. The black box indicates the position of DMRT1 that is likely to be associated with DSD in case 1. B. Terminal part of the short arm of chromosome 20. The black arrow denotes the deletion in case 2. The dotted arrow indicates the genomic region associated with facial dysmorphism and mental retardation [20]. C. The 2q24.3–2q32.2 region. The black arrow denotes the deletion in case 3. The dotted arrow indicates the genomic region associated with facial dysmorphism and mental retardation [22]. The black box indicates the position of the HOXD cluster possibly associated with DSD in case 3.

doi:10.1371/journal.pone.0068194.g003
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