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# Deletion at 12q12 increases the risk of developmental delay and intellectual disability

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## Introduction

Deletions at 12q12 are extremely rare chromosomal imbalances; only four cases involving a deletion of this type have previously been reported. Here, we identified a Chinese girl with a 3.18 Mb deletion at 12q12 (human genome build 19: 43,418,911-46,601,627), who showed postnatal growth delay, low-set ears, small hands and feet, widely spaced nipples and blue sclerae. In these five sporadic cases, all of the patients exhibited developmental issues accompanied by different degrees of intellectual disability.

## Method

This study was approved by ethics committees of our hospital and consent was obtained from the patient's parents. Chromosomal microarray analyses (CMAs) was performed on a CytoScan 750K Array (Affymetrix, CA) in accordance with the manufacturer's instructions. Genomic DNA was extracted from peripheral blood and isolated via standard procedures using a QIAamp DNA Blood Mini Kit (Qiagen, Hilden). Polymerase chain reaction (PCR) was performed on a 9700 thermal cycler (AB, Singapore).

## Results & Conclusions

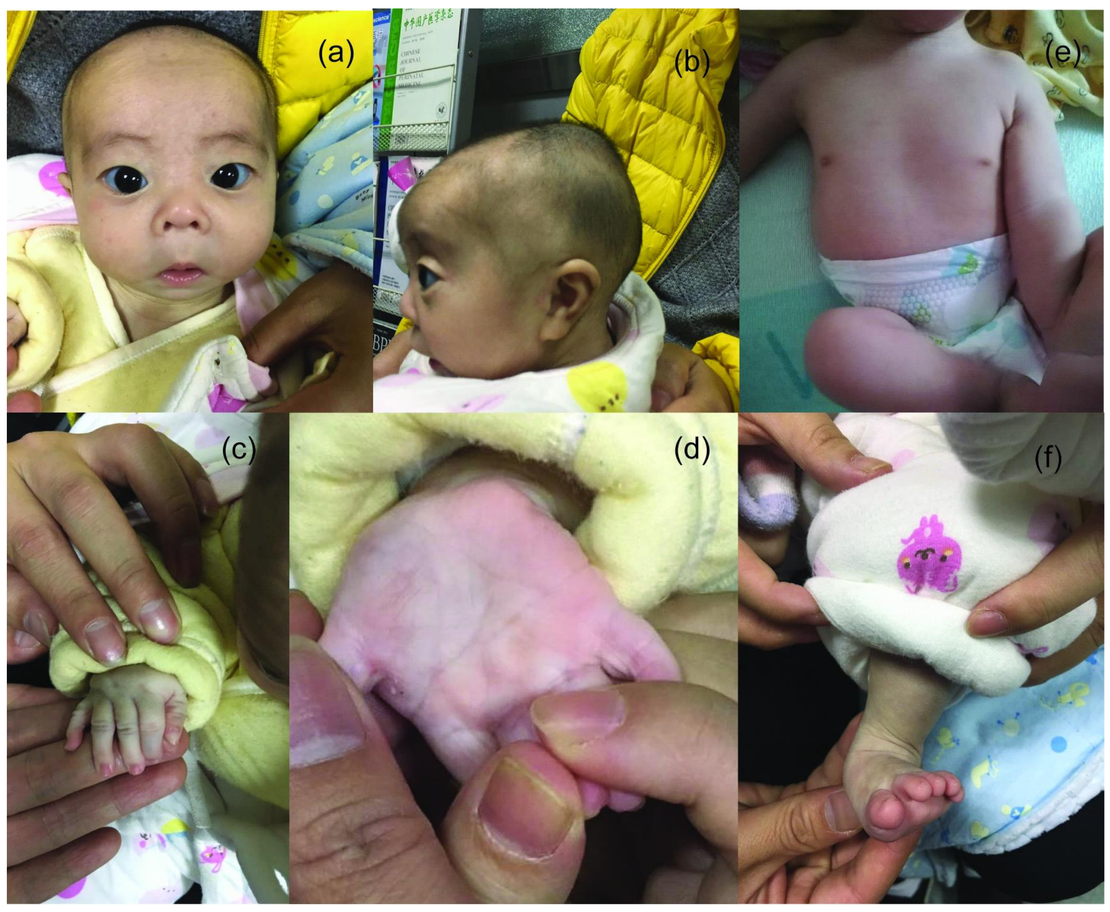


Figure 1. Appearance of the patient at the age of 3 months. a: Facial features including; upslanting palpebral fissures, a broad nasal bridge with anteverted nares, and the blue sclerae; b: Laterral view showing short neck, low-set and large ears; c: Small hands and 5th finger clinodactyly; d: Intersecting palms; e: Widely spaced nipples; f: Small feet.

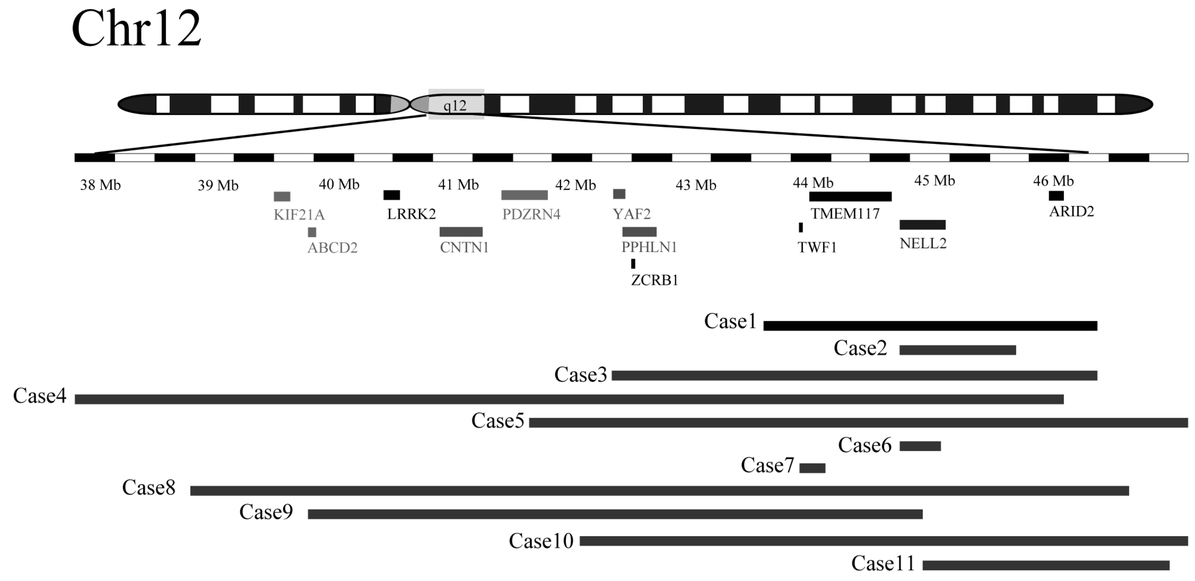


Figure 2. Genes with high HI scores in the deleted 12q12 regions (modified from the DECIPHER genome browser: https://decipher.sanger.ac.uk) in our patient and 10 other patients. Case 1 is the girl we have reported; case 2 was reported by Carlsen in 2015; case 3 was reported by Failla in 2008; and cases 4 and 5 involved patients 1 and 2 (firstly reported by Tonoki et al., 1998), respectively, of the patients reviewed by Miyake in 2004. Cases 5-11 were obtained from the DECIPHER database.

Table 1. Summary of clinical features of five previously reported patients compared with those of the new patient described in this report

| | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|---|---|---|---|---|---|
| **Patient information** | Current case | Carlsen et al., 2015 | Failla et al., 2008 | Miyake et al., 2004 (1) | Miyake et al., 2004 (2) Tonoki et al., 1998 |
| **Sex** | Female | Male | Male | Male | Male |
| **Deleted cytoband** | 12q12 | 12q12 | 12q12 | 12q11-q13 | 12q12-q13.2 |
| **Age at evaluation** | 3 m | 10 y | 10 y | 20 m | 2 y |
| **IUGR** | – | – | – | – | + |
| **Growth retardation** | + | + | + | + | + |
| **ID** | Moderate | Moderate | Moderate | Moderate | Severe |
| **OFC (<3rd centile)** | + | – | + | NA | + |
| **Small hands/feet** | + | + | + | + | + |
| **Large/low-set ears** | + | + | + | + | + |
| **Eye abnormalities** | Blue sclerae | Strabismus | Strabismus, myopia | Strabismus, myopia | Strabismus, blepharoptosis |
| **Palpebral fissures** | Up | Down | Horizontal | Up | Down |
| **Nose (broad nasal bridge/anteverted nostrils)** | +/+ | +/+ | +/– | +/+ | +/+ |
| **Mouth** | Small, downturned corners, long philtrum | Wide mouth, long flat philtrum | Downturned corners, long flat philtrum | Small, downturned corners | Small, downturned corners, long philtrum, cleft palate |
| **Fifth finger clinodactyly** | + | + | – | NA | + |
| **Widely spaced nipples** | + | + | + | + | + |
| **Cardiologic anomalies** | + | + | + | + | – |

IGR: intrauterine growth retardation; ID: intellectual disability; NA: not assessed.

Table 2 Clinical features of ten reported cases involving genomic loss at 12q12 in the DECIPHER database

| | Case 6 | Case 7 | Case 8 | Case 9 | Case 10 | Case 11 |
|---|---|---|---|---|---|---|
| **ID** | 139 | 250361 | 257543 | 259419 | 285576 | 349958 |
| **Size of 12q12/ inheritance** | 497.5 kb/ unknown | 166.44 kb/ inherited | 8.08 Mb/ unknown | 5.34 Mb/ de novo | 6.49 Mb/ de novo | 2.22 Mb/ de novo |
| **Coordinates (hg19)** | 44866421-45363917 | 44126853-44293297 | 38805678-46882370 | 39933990-45269105 | 42264141-48750492 | 45161827-47383364 |
| **Additional CNVs** | Loss chr12: 16851561-22736846 | None | None | None | None | Gain chr15: 22770421-23288350 |
| **Developmental features** | Speech and language development delay | No information | Proportionate short stature | Delayed speech and language development, motor delay | Delayed speech and language development | Mild global development delay, short stature |
| **Intellectual disability** | + | + | + | No information | No information | No information |
| **Facial /Cranial dysmorphisms** | Prominent nasal bridge | Facial abnormality | No information | No information | No information | Mild microcephaly |
| **Other clinical features** | No information | Abnormal hair pattern | Autism, precocious male puberty | No information | Cleft palate | No information |

We presented 11 individuals with 12q12 deletion, including one new subject. Our analysis suggested that a 12q12 microdeletion increases risk for developmental delay and intellectual disability. In conclusion, 12q12 deletion could be added to the database of pathophysiological genomic alterations that induce developmental delay, which will be helpful for counselling and management of the patients with developmental delay.

## References

1. Capalbo, A.; Rienzi, L., & Ubaldi, F. M. (2017). Diagnosis and clinical management of duplications and deletions. Fertil Steril 107, 12-18.
2. Carlsen, E. Ø., Frengen, E., Fannemel, M., & Misceo, D. (2015). Haploinsufficiency of ANO6, NELL2 and DBX2 in a boy with intellectual disability and growth delay. Am J Med Genet Part A 167A, 1890-1896.

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Growth and syndromes (to include Turner syndrome)

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