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ORIGINAL ARTICLE

Utility of whole-exome sequencing for patients with multiple congenital anomalies with or without intellectual disability/developmental delay in East Asia population

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Abstract

Background: Congenital anomalies (CAs) with or without intellectual disability (ID)/developmental delay (DD) comprise a heterogeneous spectrum of diseases that affect approximately 3% of live births worldwide. Recently, whole-exome sequencing (WES) demonstrated the highly heterogeneous genetic causes of CAs. The purpose of this study was to evaluate a referral system to increase the yield of WES for CAs.

Methods: From August 2018 to July 2019, patients with CAs, with or without ID/DD, after excluding gross chromosomal aberrations, were referred to geneticists in two medical centers. Variant prioritization was conducted with an AI-assisted tool for whole exomes or a CA-related gene panel.

Results: Forty patients (27 males and 13 females) with CAs were enrolled in the study with a mean age of 4.71 years (range, 0.01–18.2). Pathogenic variants in 14 genes were discovered in 16 patients (three patients with CHD7 and 13 patients with one gene each of ATP6V1B2, TAF6, COL4A3BP, ANKH, BMP2, SMARCA4, CUL4B, PGAP3, SOX11, FBN2, PTPN11, SOS1, or PROKR2), with a positive diagnostic rate of 40%. Among the 16 positive cases, 13 (81%) also had ID/DD. The inheritance was autosomal dominant in 13 (81%), autosomal recessive in two (13%), and X-linked in one (6%). Only five patients received a correct clinical diagnosis before WES. The analyses of patients with a negative genetic diagnosis revealed a phenotype and gene mutation load similar to those of the positive-finding patients but with a lower percentage of ID/DD.

Conclusions: The careful selection of patients by experienced geneticists and the exclusion of chromosomal aberrations raises the positive rate of the molecular diagnosis for CAs to 40%. However, more than half of the patients with CAs still do not have a genetic diagnosis by current technologies.

Rai-Hseng Hsu and Chen-Hao Lee contributed equally.

KEYWORDS
chromosomal aberration, developmental delay, intellectual disability, multiple congenital anomalies, whole-exome sequencing

1 | INTRODUCTION

Congenital anomalies (CAs) with or without intellectual disability (ID)/developmental delay (DD) comprise a heterogeneous spectrum of diseases (Centers for Disease Control and Prevention, 2022). CAs, such as hearing impairments, occur during intrauterine life and can be identified either at birth or later in life (World Health Organization, 2022). CAs affect approximately 3% of newborn babies worldwide. The cause of CAs can be divided into genetic and nongenetic causes. Nongenetic causes include maternal drug abuse during pregnancy, prenatal infection, birth complications, extreme malnutrition, and environmental factors (Grayton et al., 2012). Approximately, a quarter of CAs have a genetic cause; the most common genetic causes are single gene disorders and chromosome aberrations. Chromosome aberrations represent a major cause of CAs with or without neurodevelopmental disorders (Grayton et al., 2012; Menten et al., 2006). ID is defined as significant limitations in both intellectual functioning and adaptive behavior that originate before the age of 18, according to the American Association on Intellectual and Developmental Disabilities (Tassé et al., 2013). The prevalence of ID is estimated to be 1%–3% in the general population worldwide (Maulik et al., 2011). The etiology of ID is also heterogeneous and has been associated with chromosomal aberrations, single gene disorders, and CAs (Moeschler, 2008; Roselló et al., 2014; Shaffer, 2005). When children are too young to be evaluated for intelligence, we describe the impairment in physical, learning, language, or behavior areas as DD.

The diagnostic yield of various genetic approaches in patients with unexplained developmental delay or mental retardation is not high (Rauch et al., 2006). Recently, whole-exome sequencing (WES) was used to capture and sequence all coding regions. These regions include approximately 180,000 exons, which is 1%–2% of the human genome (Choi et al., 2009). The exons contain 85% of disease-causing mutations (Biesecker & Green, 2014). WES is useful to identify variants in known disease-associated genes and to discover novel disease-causing genes in highly genetically heterogeneous disorders, including CAs/ID/DD. In the Deciphering Developmental Disorders (DDD) study, WES and microarray analyses were performed for more than 10,000 children with undiagnosed developmental disorders (with recruitment criteria of severe undiagnosed neurodevelopmental disorder and/or congenital anomalies, abnormal growth parameters, dysmorphic features, and unusual behavioral phenotypes), and the diagnostic yield was 27% (Wright et al., 2015). One WES study of 127 patients affected with ID and/or DD found pathogenic or likely pathogenic genetic variants in 27% of patients (Bowling et al., 2017). In a cohort from Hong Kong that included 102 families with suspicious monogenic disorders, 31% obtained a molecular diagnosis by WES (Chung et al., 2020). However, because of the high cost and variable yield, the clinical application of WES for CAs/ID/DD is still limited. The purpose of this study was to evaluate a referral system to increase the yield of WES for CAs in East Asia population.

2 | MATERIALS AND METHODS

2.1 | Patients

During the period from August 2018 to July 2019, patients with CAs/ID/DD were referred to National Taiwan University Hospital and E-Da Hospital for molecular diagnosis. The medical history that was collected included prenatal/birth history, family history with three-generation pedigree, congenital anomaly features, brain imaging, electroencephalography, a metabolic survey, and a complete cognitive evaluation. This study was approved by the Institutional Review Board of both National Taiwan University Hospital and E-Da Hospital. Written informed consent was obtained from the parents or guardians of all patients. The presence of chromosomal aberration was either excluded or not suspected according to clinical presentation.

2.2 | Exome sequencing

Genomic DNA was extracted from peripheral blood leukocytes. Exome enrichment library preparation was carried out with an Illumina TruSeq® library preparation kit (Illumina, Inc., San Diego, CA, USA), and sequencing was conducted on a HiSeq4000 or NovaSeq6000 machine (Illumina, Inc.). Sequences were aligned to the human reference genome build (hg38) followed by variant calling according to the GATK 4.0 best practice pipeline. Copy number variation analysis was conducted with gCNV-caller (GATK).

2.3 | Variant prioritization

Variants with a heterozygous percentage ≥20% were first annotated by ANNOVAR (Wang et al., 2010). Allele frequencies were obtained from the 1000 Genomes Project (www.1000genomes.org), GnomAD database (gnomad.broadinstitute.org), and Taiwan Biobank. Functional prediction was conducted in multiple ways, including Polyphen2 (http://genetics.bwh.harvard.edu/pph2/), SIFT (http://sift.jcvi.org/), and SpliceAI (Illumina). The significance of variants was obtained from both the Human Gene Mutation Database (HGMD, www.hgmd.cf.ac.uk) and ClinVar (Landrum et al., 2014). A customized filter was applied to multiple parameters, including quality score, allele frequency, severity of variant, and inheritance. Candidate genes were searched using Phenomizer (compbio.charite.de/phenomizer/) by the Human Phenotype Ontology (HPO) terms. Searching was also conducted using an in-house developed AI-assisted variant prioritizer by user-defined keywords (Wu et al., 2019). Variants were interpreted by the ACMG guidelines (Rehm et al., 2013) either manually or with the help of Varsome (https://varsome.com/).

2.4 | Mutation load analysis

Mutation load analysis, defined as the number of deleterious variants, was performed for patients with either positive or negative molecular findings. Variants with VCF files were filtered according to the following rules. Variants in intronic regions, except for splice junctions, were excluded. Variants predicted as not damaging by both SIFT and Polyphen2 or predicted not damaging by less than half of the 13 prediction tools included in ANNOVAR (SIFT, PolyPhen2 HDIV, PolyPhen2 HVAR, LRT, MutationTaster, MutationAssessor, FATHMM, PROVEAN, MetaSVM, MetaLR, M-CAP, fathmm-MKL, and CADD) were excluded. The maximal minor allele frequency of the variant from ExAC, GnomAD, and Taiwan Biobank must be lower than 0.02. The remaining deleterious variants were calculated. A hypothetical gene panel for MCAs with a total of 3025 genes exported from the human phenotype ontology (HPO) and collected from previous literatures was also tested both for the diagnosis and for the evaluation of the mutation load as the same algorithm as described above. The variant lists from two filtering algorithm were further separated into two groups, respectively, the patients with positive or negative findings. The top frequent gene variants were reviewed. We also compared the mutation loads between the patients with or without ID/DD.

2.5 | Statistics

The comparison of the presence of ID/DD employed the chi-square test, and the comparison for mutation load employed the *t* test with tools from Excel.

3 | RESULTS

3.1 | Demographic features

A total of 40 patients were enrolled in the study, including 27 males and 13 females. These patients had a mean age of 4.71 years (range: 0.01–18.2). Their clinical diagnoses included CHARGE syndrome, Cornelia de Lange syndrome, Smith–Lemli–Opitz syndrome, Paget disease/McCune–Albright syndrome, Noonan syndrome, Kallmann syndrome, etc. Their associated CAs included congenital heart disease, hearing impairment, nail dysplasia, preauricular skin tag, facial dysmorphism, cleft palate, hemivertebrae, scoliosis, camptodactyly, syndactyly, etc.

3.2 | Genetic outcome

Disease-causing variants in 14 genes were identified in these 16 patients, with a diagnostic rate of 40% (Table 1). The inheritance modes were autosomal dominant in 13 patients (81%), autosomal recessive in two (13%), and X-linked in one (6%). The involved genes included three patients with *CHD7* and 13 patients with one gene, each of *ATP6V1B2* (deafness, congenital, with onychodystrophy, autosomal dominant), *TAF6* (Alazami-Yuan syndrome), *COL4A3BP* (mental retardation, autosomal-dominant 34), *ANKH* (craniometaphyseal dysplasia), *BMP2* (short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies), *SMARCA4* (Coffin–Siris syndrome 4), *CUL4B* (mental retardation, X-linked, syndromic 15, Cabezas type), *PGAP3* (hyperphosphatasia with mental retardation syndrome 4), *SOX11* (Coffin–Siris syndrome 9), *FBN2* (contractural arachnodactyly, congenital), PTPN11 (Noonan syndrome 1), *SOS1* (Noonan syndrome 4), and *PROKR2* (hypogonadotropic hypogonadism 3 with or without anosmia). Thirteen of the 16 patients (81%) with a molecular diagnosis had ID/DD. Chromosomal aberration was excluded in 11 patients by karyotyping and/or array CGH and in two patients by noninvasive prenatal testing. It was not suspected in the other three patients. Copy number analysis by gCNVcaller did not detect clinically significant CNVs in any of the 40 patients.

TABLE 1 Mutations found in patients with congenital anomalies.

No	Clinical manifestations	Molecular diagnosis	Gene	Zygosity	Inheritance	Karyotype/array CGH
1	CHD, HCM, hypospadias, deafness, hypotonia, ID	Alazami-Yuan syndrome	*TAF6*	Het/Het	AR	Normal
2	Coloboma, CHD, choanal atresia, cryptorchidism, outer ear anomaly, ID	CHARGE syndrome	*CHD7*	Het	AD	Normal
3	Facial palsy, laryngomalacia, deafness, ID	CHARGE syndrome	*CHD7*	Het	AD	Normal
4	CHD, choanal stenosis, deafness, ID	CHARGE syndrome	*CHD7*	Het	AD	Normal
5	Facial dysmorphism, cerebellar vermis hypoplasia, deafness, CHD, ID	Coffin–Siris syndrome 4	*SMARCA4*	Het	AD	Normal
6	Hypogonadotropic hypogonadism, ID	Coffin–Siris syndrome 9	*SOX11*	Het	AD	Normal
7	Ptosis, cleft palate, CHD, scoliosis, camptodactyly, growth retardation, ID	Contractural arachnodactyly, congenital	*FBN2*[a]	Het	AD	Normal
8	Choanal stenosis, sclerosis of cranial bones, facial dysmorphism, ID	Craniometaphyseal dysplasia	*ANKH*	Het	AD	Normal (NIPT)
9	Nail dysplasia, deafness	Deafness, congenital, with onychodystrophy, autosomal dominant	*ATP6V1B2*	Het	AD	nd
10	Elevated alkaline phosphatase, brain atrophy, microcephaly, ID	Hyperphosphatasia with mental retardation syndrome 4	*PGAP3*	Het/Het	AR	Normal
11	Hypogonadotropic hypogonadism, syndactyly	Hypogonadotropic hypogonadism 3 with or without anosmia	*PROKR2*	Het	AD	nd
12	Syndactyly, ptosis, seizure, ID	Mental retardation, autosomal-dominant 34	*COL4A3BP* (*CERT1*)	Het	AD	Normal
13	Short stature, small hands, ID	Mental retardation, X-linked, syndromic 15 (Cabezas type)	*CUL4B*[a]	Hem	XL	Normal
14	Facial dysmorphism, short stature, CHD, ID	Noonan syndrome 1	*PTPN11*	Het	AD	nd
15	CHD, microtia, ID	Noonan syndrome 4	*SOS1*[a]	Het	AD	Normal (NIPT)
16	Vertebral column anomaly	Short stature, facial dysmorphism, and skeletal anomalies with or without cardiac anomalies	*BMP2*[a]	Het	AD	nd

Abbreviations: CHD, congenital heart disease; HCM, hypertrophic cardiomyopathy; ID, intellectual disability.

[a]Likely positive.

3.3 | Statistical analysis

We tried to analyze the differences between patients with a positive ($n = 16$) or negative ($n = 24$) molecular diagnosis. The presence of ID/DD was higher in the positive group (13 out of 16, 81%) than in the negative (13 out of 24, 54%) groups ($p < 0.05$). We then calculated the mutation load. The number of deleterious variants was not different ($p = 0.28$) between the positive group (229 per person) and the negative group (274 per person). Nine of the 10 genes with the highest number of deleterious variants were identical between the two groups. Interestingly, in the top 50 genes in the mutation load analysis, eight genes in the negative group and seven genes in the positive group were related to autism spectrum disorder (ASD). However, there was no difference between the two groups.

4 | DISCUSSION

This study of WES analysis for patients with CAs/ID/DD resulted in a higher diagnostic rate, 40%, than most previous studies (Bowling et al., 2017; Chung et al., 2020; Wright et al., 2015). The success of this study could be attributed to the referral system, the exclusion of chromosomal aberration, and a high-performance variant prioritizer. The current AI-assisted variant prioritizer was trained by both local data and databases. It was updated regularly and was successfully applied to our previous studies (Wu et al., 2019). We also relied on the scoring system based on different prediction tools. In the medical centers where our cases were recruited, doctors including pediatrician and pediatric surgeon were very keen to even subtle clinical manifestations and would always refer patients to geneticists when etiologies of CAs/ID/DD were considered to be of genetic causes. The evaluation of patients by an experienced geneticist before ordering WES should be an effective way to increase the diagnostic rate of WES. The exclusion of chromosomal aberrations by karyotyping, an array CGH or a clinical geneticist should increase the positive rate in this study. However, because of the rapid development of CNV analysis for WES (Gabrielaite et al., 2021) and the continuous decrease in sequencing cost, the exclusion of chromosomal aberrations before ordering WES may not be necessary in the future.

We compared the previous clinical diagnoses and current molecular diagnoses of 16 patients with a positive diagnosis. We found that only five patients had a correct clinical diagnosis before testing, including the three patients with CHARGE syndrome and the two patients with Noonan syndrome. These are two well-known diseases that both have characteristic CAs or facial dysmorphism. The other 11 patients, all with different diagnoses, had rare and heterogeneous diseases that are unlikely to be diagnosed clinically. Therefore, our data demonstrate the importance of establishing a molecular diagnosis for patients with CAs/ID/DD. A recent review supports the clinical utility and desirable effects of exome or genome sequencing on the active and long-term clinical management of patients with CAs/ID/DD and recommends that sequencing be considered a first- or second-tier test for patients with CAs/ID/DD (Manickam et al., 2021).

There were 24 patients (60%) who did not have a molecular diagnosis after WES analysis. Among them, five patients were suspected to have VACTERL association. Although the genetic etiologies of VACTERL association have recently emerged (Kolvenbach et al., 2021), most of the cases still do not have a definite molecular cause. There was no significant difference between the positive and negative groups in mutation load, which was calculated by counting the deleterious variants in all genes. Mutation load is a valuable index in cancer because of defects in DNA repair, which does not occur in CAs or ID/DD. We have also tried to narrow the scope of the analysis. However, we could not find a published gene panel that covered the 14 genes identified in this study. Nevertheless, our analysis did demonstrate the prevalence of deleterious variants in a large number of ASD-related genes, which could explain the complexity and high prevalence of ID/DD in humans. Interestingly, the negative finding group did have a lower percentage of ID/DD, which might suggest a lower genetic effect in their etiologies.

The major limitation of this study is the small case number compared to the previous cohorts, so the discovery of new diseases or the comparison of the prevalence of specific diseases are impossible. However, our study did support our approaches for the molecular diagnosis of CAs/ID/DD, from the patient referral system to the bioinformatics workflow. This study also did not involve chromosome structure variation (SV) analysis. SVs can cause both chromosomal aberrations or single gene diseases, which may explain a portion of the patients with negative molecular diagnosis.

In conclusion, this study demonstrates that WES is beneficial for identifying the etiology for patients with CAs/ID/DD in East Asia population.

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AUTHOR CONTRIBUTIONS

Rai-Hseng Hsu and Chen-Hao Lee contributed equally. Rai-Hseng Hsu, Chen-Hao Lee, and Shuan-Pei Lin collected patient data. Rai-Hseng Hsu, Wuh-Liang Hwu, Yin-Hsiu Chien, and Ni-Chung Lee wrote the manuscript. Miao-Zi Hung, Nai-Chi Chen, Yi-Lin Lin performed molecular genetic analyses. Ni-Chung Lee and Chen-Hao Lee conceived the study design.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of both National Taiwan University Hospital (201803016RINA) and E-Da Hospital (EMRP03107N). Written informed consent was obtained from the parents or guardians of all patients.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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