Clinical utility of a sponsored, no-charge skeletal dysplasia gene panel testing program: Results from >2600 tests

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Introduction

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- Skeletal dysplasias, a heterogeneous group comprising over 450 genetic disorders, are typically diagnosed by a combination of prenatal ultrasonography, postnatal physical examination, radiography, clinical history, and/or molecular testing^{1,2}
- Some skeletal dysplasias are exceedingly rare and difficult to diagnose
- Furthermore, while examination and radiographs may lead to a diagnosis within a class of disorders (such as

Figure 2. Patient age at time of testing

2000 –



Table 1. Common diagnoses (≥ 2 patients)

MDx Gene	Count	Percent	Inheritance	Conditions				
FGFR3	141	20.5%	AD/AR	Achondroplasia, CATSHL syndrome, CATSHL syndrome, Crouzon syndrome with acanthosis nigricans, <i>FGFR3</i> - related conditions, hypochondroplasia, LADD syndrome, Muenke syndrome, SADDAN, thanatophoric dysplasia				
COL2A1	94	13.7%	AD/AR	Achondrogenesis, Czech dysplasia, epiphyseal dysplasia, avascular necrosis of the femoral head, Kniest dysplasia, Legg-Calve-Perthes disease, otospondylomegaepiphyseal dysplasia, osteoarthritis with mild chondrodysplasia, platyspondylic skeletal dysplasia, SMED Strudwick type, SED congenita, spondyloepiphyseal dysplasia, spondyloperipheral dysplasia, Stickler syndrome, vitreoretinopathy with phalangea epiphyseal dysplasia				
ALPL	78	11.3%	AD/AR	Hypophosphatasia				
COL1A1	55	8.0%	AD/AR	Caffey disease, <i>COL1A1</i> -related conditions, Ehlers-Danlos syndrome, osteogenesis imperfecta, thoracic aortic aneurysm and dissection, Ehlers-Danlos syndrome				
COMP	44	6.4%	AD	COMP-related conditions, epiphyseal dysplasia, pseudoachondroplasia				
RUNX2	28	4.1%	AD	Cleidocranial dysplasia, craniosynostosis, metaphyseal dysplas				
COL1A2	20	2.9%	AD/AR	Ehlers-Danlos syndrome, osteogenesis imperfecta				
LMX1B	15	2.2%	AD	Focal segmental glomerulosclerosis, nail-patella syndrome				
SLC26A2	14	2.0%	AR	Diastrophic dysplasia				
FBN1	13	1.9%	AD	Lipodystrophy syndrome, Marfan syndrome, Shprintzen- Goldberg syndrome, stiff skin syndrome, thoracic aortic aneurysm and dissection, vitreoretinopathy, Weill-Marchesani syndrome				
FLNB	13	1.9%	AD/AR	Synostosis syndrome, <i>FLNB</i> -related conditions, Larsen syndrome, Piepkorn osteochondrodysplasia, clubfoot				
TRPV4	12	1.7%	AD	Charcot-Marie-Tooth disease, distal hereditary motor neuropath spondylometaphyseal dysplasia				
PTPN11	10	1.5%	AD	Hypertrophic cardiomyopathy, metachondromatosis, Noonan syndrome, Noonan syndrome with multiple lentigines				
GALNS	10	1.5%	AR	Mucopolysaccharidosis type IVA (Morquio A syndrome)				
GDF5	7	1.0%	AD/AR	Brachydactyly, chondrodysplasia, osteoarthritis, symphalangisr				
MATN3	7	1.0%	AD	Epiphyseal dysplasia, osteoarthritis, spondyloepimetaphyseal dysplasia				
RMRP	7	1.0%	AR	Cartilage-hair hypoplasia anauxetic dysplasia (CHH-AD) spectrum disorders				
SOX9	6	0.9%	AD	Campomelic dysplasia				
ACAN	5	0.7%	AD/AR	Lymphoma, spondyloepimetaphyseal dysplasia, short stature				
COL10A1	5	0.7%	AD	Metaphyseal chondrodysplasia Schmid type				
COLOA2	5	0.7%		COL9A2-related conditions, intervertebral disc disease,				
FXT1	5	0.7%		epiphyseal dysplasia, Stickler syndrome Hereditary multiple osteochondromatosis				
FGFR2	5	0.7%	AD/AR	Bent bone dysplasia syndrome, <i>FGFR2</i> -related conditions, gastric cancer, LADD syndrome				
LEMD3	5	0.7%	AD	Autism spectrum disorder, Buschke-Ollendorff syndrome, melorheostosis with osteopoikilosis, osteopoikilosis				
MMP13	5	0.7%	AD/AR	Metaphyseal anadysplasia, metaphyseal dysplasia Spahr type				
PLS3	5	0.7%	XLD	Osteogenesis imperfecta, osteoporosis				
BMP2	4	0.6%	AD	hemochromatosis, thoracic ossification of the ligamentum flavum, tooth agenesis				
ACP5	3	0.4%	AR	Spondyloenchondrodysplasia with immune dysregulation				
ANKH	3	0.4%	AD	Chondrocalcinosis, craniometaphyseal dysplasia				
DLL3	3	0.4%	AR	Spondylocostal dysostosis				
GIVE IAB MESDO	3	0.4%		Spondylocostal dysostosis				
TRPS1	3	0.4%		Trichorhinophalangeal syndrome				
ARSB	3	0.4%	AR	Mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome)				
COL27A1	2	0.3%	AR	Steel syndrome				
CUL7	2	0.3%	AR	3-M syndrome 1				
EBP	2	0.3%	XLD/XLR	Chondrodysplasia punctata, MEND syndrome				
EXT2	2	0.3%	AD/AR	Hereditary multiple osteochondromatosis, <i>EXT2</i> -related conditions				
FLNA	2	0.3%	XLD/XLR	Congenital short bowel syndrome, frontometaphyseal dysplasi myxomatous valvular dystrophy, otopalatodigital spectrum disorders, periventricular heterotopia, terminal osseous dysplasia with pigmentary defects				
IDS	2	0.3%	XLR	Arthrogryposis, mucopolysaccharidosis II, tetralogy of Fallot				
LRP5	2	0.3%	AD/AR	High bone mass syndromes, osteoporosis-pseudoglioma syndrome, osteoporosis with retinopathy, polycystic liver disease 1				
NPR2	2	0.3%	AD/AR	Acromesomelic dysplasia, epiphyseal chondrodysplasia, short stature				
OBSL1	2	0.3%	AR	3-M syndrome 2				
PAPSS2	2	0.3%	AR	Brachyolmia with mild epiphyseal and metaphyseal changes				
PFX7	2	0.3%	AR	Rhizomelic chondrodysplasia punctata. Refsum disease				

dysostosis multiplex leading to mucopolysacharridosis [MPS] diagnosis), diagnosing the specific subtype can be especially challenging

- Genomic alterations have been identified in the vast majority of well-delineated skeletal dyplasias
- We describe a program that provides a sponsored skeletal dysplasia gene panel to eligible US patients, with the goal of achieving accurate and timely diagnoses

Methods

- Patients eligible for testing through the program must have one or more of the following characteristics: skeletal abnormalities, dysmorphic facial features, or other signs suggestive of skeletal dysplasia, short stature, or disproportionate growth (Figure 1)
- The program uses a panel of genes associated with skeletal dysplasia (initially 109 genes, expanded to 150 genes in November 2020, and further expanded to 320 genes in April 2021)
- Genetic counseling is provided for all patients as part of the program

- Initial symptom onset was noted prenatally for 10% of patients and at birth for 19%; for the remaining 71% of patients with initial symptom onset after birth, the median age at first sign was 5 years (Figure 3)
- Genetic diagnosis was established for 678 patients (68 genes), giving an overall molecular diagnostic (MDx) yield of 25.7%
 Age distribution of patients who received a molecular diagnosis
 - and MDx yield by age group are shown in Figure 4
- Overall, the most common MDx genes were FGFR3 (20.5%), COL2A1 (13.7%), ALPL (11.3%), COL1A1 (8.0%), COMP (6.4%), RUNX2 (4.1%), COL1A2 (2.9%), LMX1B (2.2%), and SLC26A2 (2.0%) (Table 1)
- FGFR3 variants were identified in 141 patients (of which 93 were associated with achondroplasia and 35 with hypochondroplasia)
- Other commonly identified variants were COL2A1 (94 patients), associated with conditions in the type 2 collagen group, and ALPL (78 patients), associated with abnormal mineralization conditions (hypophosphatemia)
- Variants were classified according to ACMG guidelines³
- Positive molecular diagnosis (MDx) was defined as two pathogenic/likely pathogenic variants in genes associated with autosomal recessive disorders, and one pathogenic/ likely pathogenic variant in genes associated with autosomal dominant disorders, X-linked dominant disorders, or X-linked recessive disorders (male only)

Figure 1. Discover Dysplasias[®] requisition form

ΙΝΥΙΤΛΕ		ver Dysplasias netic Test for Skeletal Dysplasics	ORDER ID For Invitae internal use only	Req	uisition Form cover Dysplasias TRF965-:
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TRUCTIONS: Review the order	ring options and the	en complete all sections of this for	n. Your ordering option will be in	dicated in the te	est selection section.
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				CLINICAL	. HISTORY						
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Relative's relationship Maternal to this patient or paternal		Diagnosed condition		Age at diagnosis	t Relative's relations to this patient		Maternal or paternal	Diagnosed condition			Age at diagnosi
PERSONAL HISTORY								1		ſ	
Is/was this patient affect Provide details in the requi	ted or symp red clinical hi	tomatic?† OYes ONo story questions (if applicable).		† te	Symptomatic means t sting being ordered an	his p d co	atient has featu uld include findi	res or signs known or ngs on physical exam	susp inatio	ected to be related to th on, laboratory tests, or	he genetic imaging.
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 A total of 10 patients with MPS IVA (GALNS) and 3 with MPS VI (ARSB) were identified; of these, diagnosis was confirmed by reflex enzyme testing for 5 patients

Figure 3. Timing of symptom onset



Figure 4. Age distribution of patients receiving a molecular diagnosis



patients Ir diagno:

of

Number c molecu MDx Count MDx yield within age groups shown in parentheses Table shows genes identified in ≥2 cases. Additional genes with <2 identified cases were: CANT1, COL9A3, CSGALNACT1, DDR2, DONSON, DYM, EVC, EVC2, FN1, GLB1, GNPTG, IDUA, IFITM5, KAT6B, KIF22, KMT2A, ROR2, SGSH, SMAD4, TRAPPC2, WISP3, WNT1.

Individuals with diagnoses associated with more than one gene are counted for each gene.

Conclusions

These data demonstrate the clinical utility of gene panel testing in identifying the genetic etiology of skeletal dysplasia, which in turn could facilitate earlier and timely implementation of disease-specific management strategies to improve clinical outcomes.



Results

 Between December 2019 and June 2021, 2,641 patients with suspected skeletal dysplasia were tested through the program

 Median patient age at time of testing was 8 years (range 0–90 years) (Figure 2)



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