eP409

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

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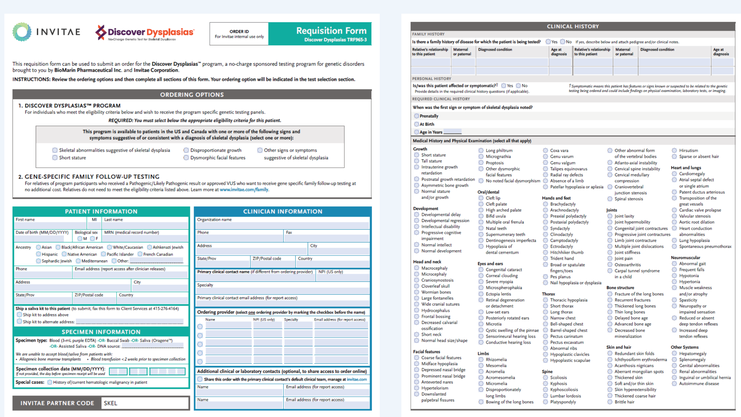
Introduction

- 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 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
- Variants were classified according to ACMG guidelines[3]
  - 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)

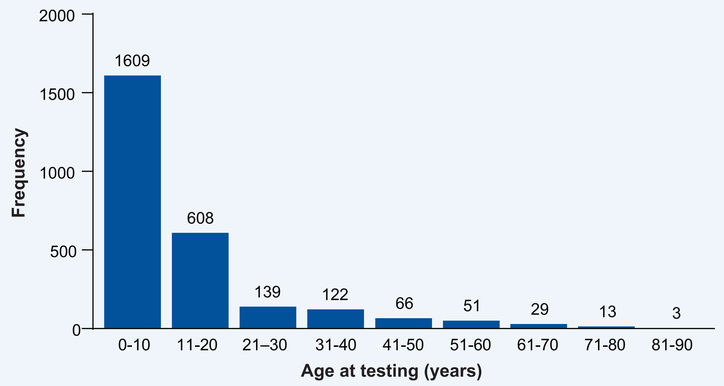
Figure 1. Discover Dysplasias® requisition form



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)**

Figure 2. Patient age at time of testing



- 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)
  - 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

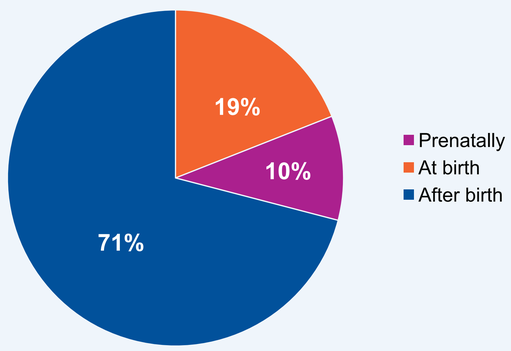


Figure 4. Age distribution of patients receiving a molecular diagnosis

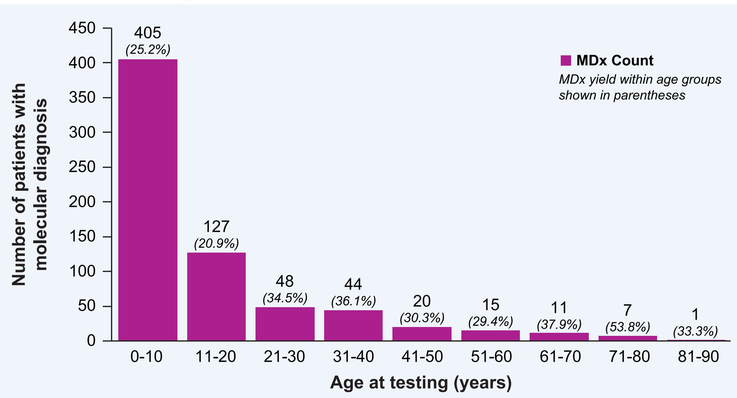


Table 1. Common diagnoses (≥ 2 patients)

MDx Gene	Count	Percent	Inheritance	Conditions
FGFR3	141	20.5%	AD/AR	Achondroplasia, CATSHL syndrome, CATSHL syndrome, Crouzon syndrome with acanthosis nigricans, *FGFR3*-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 phalangeal epiphyseal dysplasia
ALPL	78	11.3%	AD/AR	Hypophosphatasia
COL1A1	55	8.0%	AD/AR	Caffey disease, *COL1A1*-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 dysplasia
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	Atelosteogenesis, boomerang dysplasia, spondylocarpotarsal synostosis syndrome, *FLNB*-related conditions, Larsen syndrome, Piepkorn osteochondrodysplasia, clubfoot
TRPV4	12	1.7%	AD	Charcot-Marie-Tooth disease, distal hereditary motor neuropathy, 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, symphalangism
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
COL11A1	5	0.7%	AD/AR	Fibrochondrogenesis, lumbar disc herniation, Stickler syndrome
COL9A2	5	0.7%	AD/AR	*COL9A2*-related conditions, intervertebral disc disease, epiphyseal dysplasia, Stickler syndrome
EXT1	5	0.7%	AD	Hereditary multiple osteochondromatosis
FGFR2	5	0.7%	AD/AR	Bent bone dysplasia syndrome, *FGFR2*-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	*BMP2*-related condition, brachydactyly, hereditary 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
GNPTAB	3	0.4%	AR	Mucolipidosis II alpha/beta, mucolipdosis III alpha/beta
MESP2	3	0.4%	AR	Spondylocostal dysostosis
TRPS1	3	0.4%	AD	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, *EXT2*-related conditions
FLNA	2	0.3%	XLD/XLR	Congenital short bowel syndrome, frontometaphyseal dysplasia, 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
PEX7	2	0.3%	AR	Rhizomelic chondrodysplasia punctata, Refsum disease

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.

References

1. Mortier GR, Cohn DH, Cormier-Daire V, et al. Nosology and classification of genetic skeletal disorders: 2019 revision. *Am J Med Genet A*. 2019;179(12):2393-2419. **2.** Krakow D. Skeletal dysplasias. *Clin Perinatol*. 2015;42(2):301-319, viii. **3.** Richards S et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405.

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