327

Skeletal dysplasia gene panel with integrated enzyme follow-up for the diagnosis of lysosomal storage disorders: MPS IVA case series

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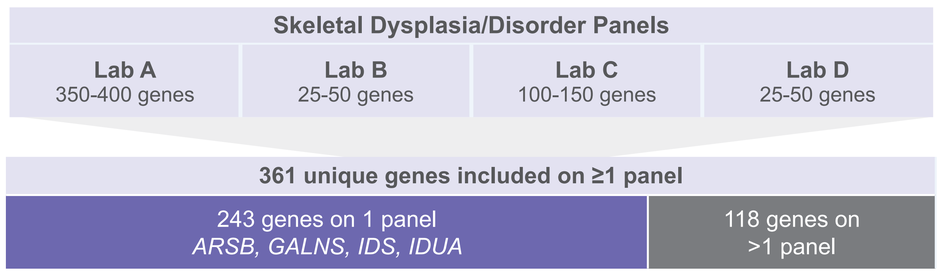
Background

- Advances in molecular genetics have led to more precise classification and diagnosis of skeletal dysplasias
- Comprehensive skeletal dysplasia/disorder (SD) gene panels can simultaneously assess hundreds of genes to identify the etiology of a patient's SD, but frequently omit genes for lysosomal storage disorders with skeletal phenotypes
  - Among 4 SD gene panels currently available in Europe/US, genes for lysosomal diseases with skeletal phenotypes (MPS I, II, IVA, VI) are only included on a single panel

Figure 1. Skeletal dysplasia/disorder gene panels frequently exclude genes for lysosomal storage disorders with skeletal phenotypes



Objective

- We sought to understand the utility of an SD gene panel for the diagnosis of MPS IVA through the evaluation of patient diagnostic journeys

Methods

- Clinicians who ordered at least one SD gene panel through a no-cost program that returned a result supporting a diagnosis of MPS IVA between 2020 and 2022 were invited to provide case history details via interview
- Deidentified data from the test requisition form and clinician interview were assessed in this analysis

Results

Summary characteristics

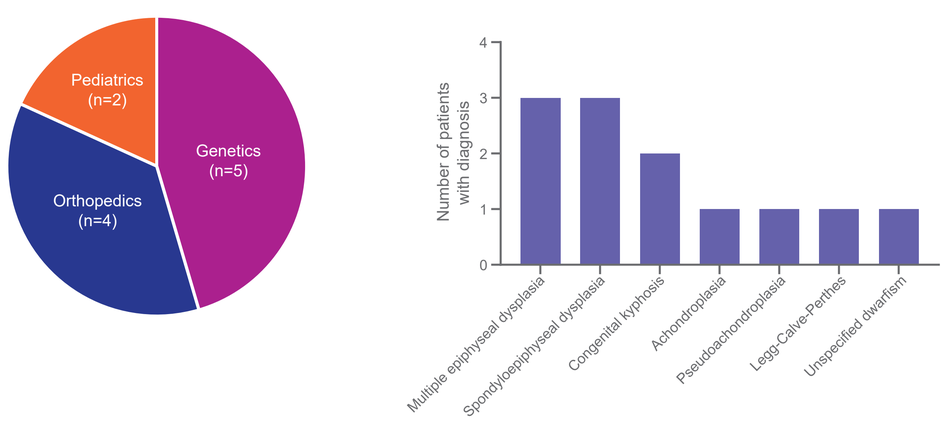
- A total of 11 MPS IVA patients who were identified through the SD gene panel were assessed; specialties of the ordering clinicians included medical genetics, pediatrics, and orthopedic surgery
- Patients ranged in age from 2-32 years at time of testing (mean, 11.2 years), with delay from symptom onset to testing ranging from 0-29 years (mean, 7.3 years)
- 10 patients (91%) had a prior diagnosis recorded before gene panel testing; a prior clinical or suspected diagnosis of spondyloepiphyseal dysplasia (SED), multiple epiphyseal dysplasia (MED), and/or Legg-Calve-Perthes (LCP) disease was noted for 7 patients (64%)
- All patients had osteoarticular involvement; most patients (n=10, 91%) had one or more spinal features
- 6 patients (67%, n=9) underwent at least one orthopedic surgery prior to testing (mean, 2.2)

Table 1. Patient characteristics

		N = 11
Age at onset, years	mean (SD)	3.9 (3.5)
Age at gene panel testing, years	mean (SD)	11.2 (9.8)
Diagnostic delay, years	mean (SD)	7.3 (9.6)
Classical features of MPS IVA[a]	n (%)	
Osteoarticular involvement		11 (100%)
Spinal features[b]		10 (91%)
Short stature		6 (55%)
Genu valgum		4 (36%)
Joint pain		6 (55%)
Facial dysmorphia		2 (18%)
Prior diagnoses	n (%)	
Any diagnosis		10 (91%)
SED, MED, pseudoachondroplasia, or LCP		7 (64%)
Prior orthopedic surgeries	n (%)	
Yes		6 (67%)
No		3 (33%)
Unknown		*2*
Number of surgeries (n=6)	mean (SD)	2.2 (1.6)

LCP, Legg-Calve-Perthes disease; MED, multiple epiphyseal dysplasia; MPS, mucopolysaccharidosis; SED, spondyloepiphyseal dysplasia; SD, standard deviation
[a]Imputed as "not present" if left blank on order form with at least one other field being completed on the form; some values backfilled from HCP interviews
[b]Includes kyphosis, scoliosis, platyspondyly, interior beaking of vertebral bodies, gibbus deformity, axial instability, cervical stenosis, lumbar lordosis, anterior wedging

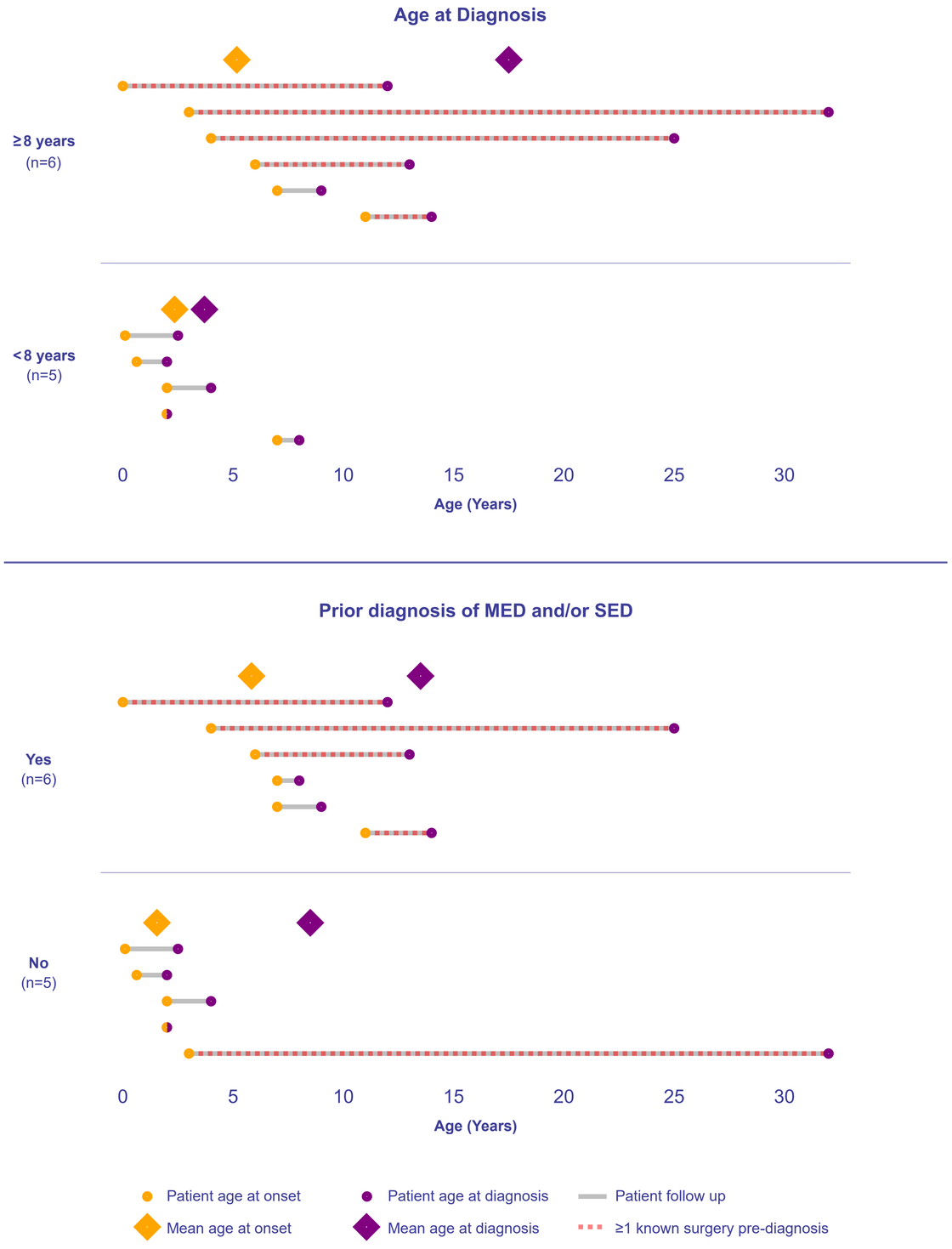
Figure 2. Ordering healthcare provider specialties and prior diagnoses



Patient diagnostic journey timelines

- Diagnostic journeys were assessed for individual patients, stratifying by either age at diagnosis or by presence/absence of a prior diagnosis of MED and/or SED
  - Patients diagnosed at >8 years of age typically had longer diagnostic delays, despite first onset of symptoms occurring within a similar age range to those diagnosed at younger ages
  - MED and/or SED is a common misdiagnosis for MPS IVA patients; patients who had received a prior MED/SED diagnosis tended to face a longer diagnostic odyssey despite early onset of symptoms, highlighting the importance of testing MED/SED patients for MPS IVA
  - Overall, patients with longer diagnostic delays were likely to have had at least one orthopedic surgery prior to diagnosis

Figure 3. Patient diagnostic journey timelines, by age at diagnosis and by prior diagnosis of MED and/or SED



Molecular genetics

- One patient had a single variant of unknown significance (VUS) identified in *GALNS*, and was confirmed to have MPS IVA by enzyme testing (diagnostic delay: 7 years)
- An additional patient received a prior gene panel for MED, which did not include *GALNS* (diagnostic delay: 7 years)
- Overall, 5 patients had variant reclassifications in *GALNS* (either VUS to pathogenic or likely pathogenic to pathogenic); other individuals had known pathogenic variants

Conclusions

- SD gene panels can be used to diagnose MPS IVA or efficiently direct non-specific suspicion toward confirmatory enzyme testing and minimize the diagnostic odyssey for patients
- Early use of gene panels can ensure accurate diagnosis before invasive, costly, and/or ineffective interventions are initiated

Disclosures

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