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When Genetic Testing Can't Find THE Answer: How Unique Clinical Presentations Challenge the Clinician

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BACKGROUND

Multi-system disorders may be difficult to differentiate between, especially as genetic causes are still being defined and in light of phenotypic variability. We present a case of a teen with multiple congenital defects for which genetic testing was inconclusive, showing features of : Noonan Syndrome (NS), Mullerian duct aplasia-renal aplasia-cervicothoracic somite dysplasia (MURCS), and VACTERL association.

CASE PRESENTATION

Table 1. Patient Clinical Presentation.

	Clinical Features
Cardiac	Myxomatous mitral valve
Oral	Cleft lip & palate, velopharyngeal incomp.
Facial Features	Slightly down slanting palpebral fissures, fullness to tip of nose, course features with square jaw and square facies
Ears	Full and fleshy, 6.2 cm bilaterally (75th%)
Endocrine	Hypoplastic anterior pituitary hypothyroidism, dysmenorrhea
Neurologic/ Development	ADHD-inattentive subtype, Anxiety, Average intelligence (FSIQ=92)
Skeletal	Head circumference > 97th%, short neck & stature, sloping shoulders, congenital scoliosis, hemivertebrae, butterfly vertebra, hydromyelia, spina bifida occulta
Skin/Hair	Thick curly hair, low posterior hairline, café au lait macules, 1 hypopigmented macule

Pregnancy/ Birth History:
- Non-contributory

Medications:
- Past: stimulant trials, Growth hormone (~13-15 years)
- Current: OCP, levothyroxine, atomoxetine, iron

Family History:
- Parents: Average height, healthy
- Full Brother: delayed bone age & puberty
- Paternal Uncle: aortic dissection
- Maternal Cousins: hip dysplasia

Genetic testing:
- Microarray—negative
- Whole Exome— negative

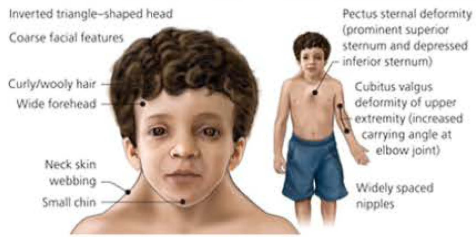

Figure 1. Clinical Features of Noonan Syndrome in child/adolescent

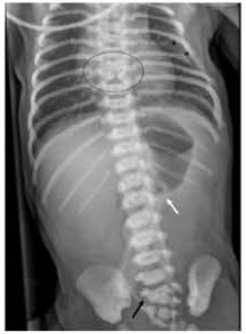

Figure 2. Chest and Abdominal Xray of a patient with VACTERL

Table 2. Phenotype Comparison of Key Genetic Disorders in the Differential.

	Noonan Syndrome	MURCS	VACTERL Association	Unique Items
Key clinical features	**Short stature, facial deformities, congenital heart defects, scoliosis, thyroid dysfunction,** hyperelastic skin, **thick curly hair** or thin sparse hair, **low posterior hairline,** webbed neck	Primary amenorrhea, genitourinary defects, **short stature,** rib anomalies, Sprengel deformities, **cervicothoracic vertebral defects,** upper limb defects	**Vertebral defects, scoliosis,** anal atresia, **cardiac defects,** tracheo-esophageal fistula, renal anomalies, limb abnormalities	Myxomatous mitral valve, spina bifida occulta, dysmenorrhea, café au laits, ligamentous laxity of fingers, flat footed
Other features	Coagulation defects, ocular abnormalities, dermatologic findings, cystic hygroma		**Hydromyelia** *3/7 defects needed for diagnosis*	
Facial features	Hypertelorism, high forehead, **short neck, relative macrocephaly, downslanting palpebral fissures**	Facial asymmetry, micrognathia, conductive hearing loss, **cleft lip and palate**	Undefined	Fullness to tip of nose, course features with square jaw and square facies
Development & Behavioral profile	Mild to **average intellectual functioning,** executive function deficits, autism spectrum disorder, **ADHD**	Undefined	Undefined	Anxiety

*Items in bold represent overlapping clinical features found in our patient case.

SUMMARY

Without definitive gene information, clinical features were used to consider diagnosis; this case presents an atypical patient presentation with features seen in NS, MURCS, and VACTERL association, as well as novel features not seen in any of those disorders.

DISCUSSION/CONCLUSIONS

- Genetic testing provides important information, but the field of genetics is still advancing and testing limitations remain.
- Clinical diagnosis of genetic disorders remains important.
- Patients benefit when identified with genetic disorders (e.g. NS, MURCS, VACTERL), which drive medical care for treatment of known issues and monitoring of highly likely features.
- Clinicians should continue to track individuals with multiple congenital anomalies and have increased suspicion of a genetic disorder even when a clear diagnosis has not presented itself.
- Atypical and novel disorder presentations continue to arise.

REFERENCES

[1] Cao H, Alrejaye N, Klein OD, et al. A review of craniofacial and dental findings of the RASopathies. *Orthod Craniofac Res.* 2017;20 Suppl 1(Suppl 1):32–38.
[2] Couser NL, Keelean-Fuller D, Davenport ML, et al. Cleft palate and hypopituitarism in a patient with Noonan-like syndrome with loose anagen hair-1. *Am J Med Genet Part A.* 2018; 176A: 2024– 2027.
[3] Fontana L, Gentilin B, Fedele L, et al. Genetics of Mayer–Rokitansky–Küster–Hauser (MRKH) syndrome. *Clin Genet.* 2017; 91: 233-246.
[4] Garg S, Brooks A, Burns A, et al. Autism spectrum disorder and other neurobehavioural comorbidities in rare disorders of the Ras/MAPK pathway. *Dev Med Child Neurol.* 2017; 59: 544-549.
[5] Perrino F, Licchelli A, Serra G, et al. Psychopathological Features in Noonan Syndrome. *European Journal of Pediatric Neurology.* 2018; 22(1): 170-177.
[6] Pierpont ME, Digilio MC. Cardiovascular disease in Noonan syndrome. *Current Opinion in Pediatrics.* 2018;30(5):601–608.
[7] Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. *Lancet.* 2013;381(9863):333–342.
[8] Solomon BD. VACTERL/VATER Association. *Orphanet J Rare Dis.* 2011;6:56.
[9] Tafazoli A, Eshraghi P, Koleti ZK, et al. Noonan syndrome - a new survey. *Arch Med Sci.* 2017;13(1):215–222.
[10] Venugopal V, Romero CJ. Endocrine Complications of Noonan Syndrome beyond Short Stature. *Pediatr Endocrinol Rev.* 2019;16(Suppl 2):465–470.
Figure 1. *American Academy of Family Physicians.*[Child/adolescent with Noonan Syndrome] (2014). Retrieved on June 2, 2020 from https://www.aafp.org/afp/2014/0101/p37.html
Figure 2. *Eurorad.* [Thoracoabdominal Radiograph] (2018). Retrieved on June 2, 2020 from https://www.eurorad.org/case/15691