Phenotype expansion or multilocus variants? Additional molecular findings in patients with well-known chromosomal disorders

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INTRODUCTION

Historically, the diagnosis of congenital and developmental anomalies has predominantly relied upon conventional cytogenetic techniques, such as Chromosomal Microarray Analysis (CMA) and Karyotyping. While effective in identifying chromosomal abnormalities, these methods may fail to elucidate the complex genetic determinants responsible for observed phenotypic variations. Advanced molecular techniques, such as Genome Sequencing (GS) and Exome Sequencing (ES), are complementary to these conventional cytogenetic modalities, offering a comprehensive understanding of molecular aberrations. The integration of traditional cytogenetic methodologies and molecular approaches has been shown to significantly enhance the precision of genetic diagnostics.

METHODS

This is a retrospective evaluation of 17 patients with well-known chromosomal disorders. Demographic data, clinical history, and diagnostic findings for patients who had reportable findings in addition to the chromosomal disorders were investigated.

A combination of molecular and cytogenetic testing was performed for 9 patients either as standard of care, or if the diagnosis could not be established by a single test. In 8 additional cases, GS or ES served as the primary diagnostic tools due to the broad differential diagnoses.

RESULTS

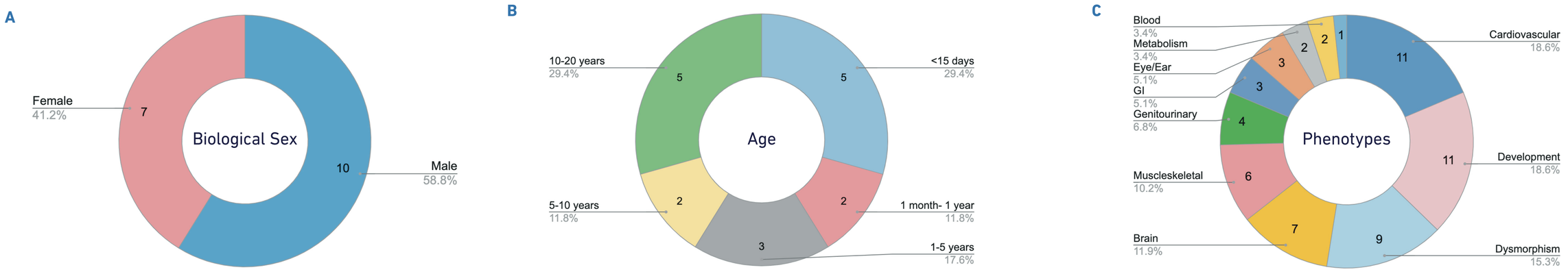

Figure 1. Distribution of biological sex, age, and phenotypes of all patients in the current study. A. Distribution of biological sex, B. Distribution of age, C. Distribution of phenotypes.

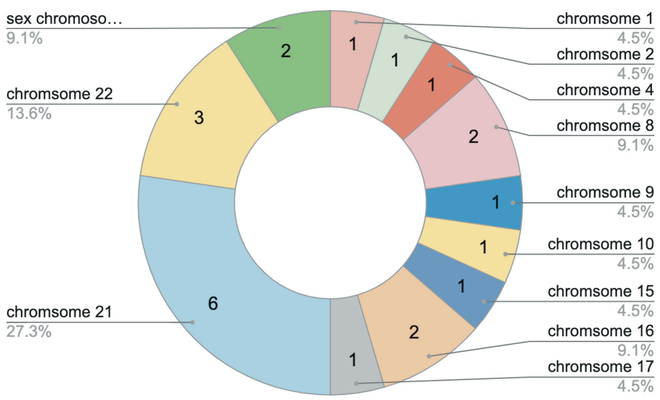

Figure 2. Distribution of Chromosomal findings in all patients

Table 1. All additional molecular findings identified in patients

Gene	Transcript	cDNA	Protein	Inheritance pattern	ACMG classification
TYMP	NM_001953.5	c.1040T>C	p.L347P	AR	Likely Pathogenic
NBEA	NM_001385012.1	c.3911dup	p.D1304Efs*11	AD	Pathogenic
SYNE1	NM_182961.4	c.18653C>A	p.S6218*	AD	Pathogenic
LZTR1	NM_006767.4	c.372C>T	p.V124=	AD	Likely Pathogenic
RPGRIP1L	NM_015272.5	c.632T>A	p.L211*	AR	Likely Pathogenic
RPGRIP1L	NM_015272.5	c.1104-2A>G		AR	Likely Pathogenic
HERC2	NM_004667.6	c.958G>A	p.G320R	AR	Likely Pathogenic
HERC2	NM_004667.6	c.7745C>T	p.A2582V	AR	Likely Pathogenic
ANKRD11	NM_013275.6	c.5659C>T	p.Q1887*	AD	Pathogenic
MECP2	NM_004992.3	c.1155_1200del	p.L386Afs*8	XL	Pathogenic
UFSP2	NM_018359.5	c.344T>A	p.V115E	AR	Likely Pathogenic
GATA1	NM_002049.4	c.159_160delinsAGTG	p.T54Vfs*84	XL	Likely Pathogenic
NPRL3	NM_001077350.3	c.189-1G>A		AD	Pathogenic
SCN5A	NM_000335.5	c.5362_5365del	p.S1787Rfs*46	AD	Likely Pathogenic
MYH7	NM_000257.4	c.3157C>T	p.R1053W	AD	Likely Pathogenic
USH2A	NM_206933.4	c.11754G>A	p.W3918*	AR	Pathogenic
WFS1	NM_006005.3	c.1523A>G	p.Y508C	AR	Likely Pathogenic

CONCLUSIONS

In summary, our results underscore the potency of integrating GS/ES and cytogenetic testing in unraveling the underlying molecular determinants responsible for specific developmental disorders, shedding light on the complexity of genetic disease etiology and the consideration of the possibility of a 'double hit' rather than prematurely attributing observed phenotypic variations to a 'phenotypic expansion' of a given gene.

For details of the patients with trisomy 21 and additional molecular findings please see Poster P297