HGG Advances

BRIEF COMMUNICATION

MGA-related syndrome: A proposed novel disorder

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Summary

MGA (OMIM: 616061) encodes a dual-specificity transcription factor that regulates the expression of Max-network and T-box family target genes, important in embryogenesis. Previous studies have linked *MGA* to various phenotypes, including neurodevelopmental disorders, congenital heart disease, and early-onset Parkinson's disease. Here, we describe the clinical phenotype of individuals with *de novo*, heterozygous predicted loss-of-function variants in *MGA*, suggesting a unique disorder involving both neurodevelopmental and congenital anomalies. In addition to developmental delays, certain congenital anomalies were present in all individuals in this cohort including cardiac anomalies, male genital malformations, and craniofacial dysmorphisms. Additional findings seen in multiple individuals in this cohort include hypotonia, abnormal brain imaging, hearing loss, sleep dysfunction, urinary issues, skeletal abnormalities, and feeding difficulties. These findings provide support for *MGA* as a gene intolerant to protein truncation with a broad phenotypic spectrum.

Introduction

At the 2023 David W. Smith (DWS) Workshop, our group reported *MGA* as a candidate gene for hearing loss, identified in a cohort of 4,657 individuals with hearing loss through next-generation sequencing (Kruska et al., 2023, DWS, poster). Although the exact function of *MGA* remains unclear, the literature suggests that the *MGA* gene encodes a dual-specificity transcription factor regulating the expression of Max-network and T-box family target genes, playing a significant role in embryogenesis.[1,2] Of note, MGA's binding partner, MAX protein (OMIM: 154950) has been reported as atypical in multiple individuals with polydactyly-macrocephaly syndrome (PDMCS) (OMIM: 620712). PDMCS is characterized by postaxial polydactyly, progressive macrocephaly, ocular and neurodevelopmental anomalies, and abnormal brain imaging. In addition, the MGA T-box domain is predicted to interact with TBXT (OMIM: 601397), genetic variants in which have been associated with neural tube, genitourinary, and skeletal anomalies in affected individuals (OMIM: 182940).

Previous studies have associated *MGA* with neurodevelopmental phenotypes including a *de novo* variant in an affected individual with intellectual disability and epilepsy, two individuals with autism, and an individual with a general neurodevelopmental disorder; however, limited clinical information was provided in these cases.[3–6] Other individuals with *de novo MGA* variants have been reported with congenital heart disease[7] and early-onset Parkinson's disease.[8] Although more evidence is needed to explore the effect of heterozygous *MGA* variants in human disease, there is promise of an underlying relationship.[9]

In this brief communication report, we present three individuals harboring *de novo* predicted loss-of-function (LoF) variants in *MGA* identified via exome sequencing (ES) and propose the possibility of a unique disorder linked to neurodevelopmental delay and multiple congenital anomalies.

Subjects and methods

Our data were derived from the GeneDx clinical exome and genome sequencing database, which includes over 665,000 individuals. We evaluated probands tested between 2014 and 2023 and identified those with heterozygous LoF variants in *MGA*. We excluded individuals with *MGA* missense and small copy-number variants. Four unrelated individuals with neurodevelopmental phenotypes and *de novo* heterozygous predicted LoF *MGA* variants were confirmed and reported during this time; three who provided research consent are included in this report.

The three individuals in the current cohort were referred to GeneDx for clinical ES, and clinical information was provided by their referring providers. All individuals and/or their guardian provided written informed consent. For individual 3, an informed written consent was obtained for the use of a photograph. The study was conducted under GeneDx protocol *Research to Expand the Understanding of Genetic Variants: Clinical and Genetic Correlations*, in accordance with all guidelines set forth by the Western Institutional Review Board (protocol 20171030).

Using genomic DNA from the proband and parents, the exonic regions and flanking splice junctions of the genome were captured

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Table 1. Clinical features and HPO terms as reported in individuals 1–3 with *de novo*, heterozygous, predicted LoF variants in the *MGA* gene (https://hpo.jax.org/)

	HPO term	Individual 1	Individual 2	Individual 3
Sex	–	male	male	female
Current age	–	26 years	8 years 7 months	2 years 8 months
Weight % percentile and age at which taken	–	50%–75% percentile (age 26 years)	10% percentile (age 8 years)	<0.01% percentile (31 months)
Height % percentile and age at which taken	–	10% percentile (age 26 years)	53% percentile (age 8 years)	<1% percentile (31 months)
Head circumference and age at which taken	–	−1 SD (age 26 years)	<2 % percentile (age 8 years)	27% percentile (23 months)
Neurodevelopmental findings				
Neurodevelopmental delay	HP:0012758	X	X	X
Autism	HP:0000717	–	X	–
Bipolar disorder	HP:0007302	X	–	–
Febrile seizure (3 months–6 years)	HP:0002373	–	X	–
Congenital malformations				
Abnormal heart morphology	HP:0001627	X	X	X
Abnormal ear morphology	HP:0031703	X	–	–
Underdeveloped supraorbital ridges	HP:0009891	X	–	–
Abnormal digit morphology	HP:0011297	X	–	–
Abnormal eye morphology	HP:0012372	X	X	X
Abnormal eye physiology	HP:0012373	X	X	–
Abnormal facial shape	HP:0001999	X	–	X
Abnormal midface morphology	HP:0000309	X	X	–
Abnormal nasal morphology	HP:0005105	X	X	X
Abnormal oral morphology	HP:0031816	X	X	X
Abnormal skull morphology	HP:0001363	X	–	X
Abnormality of the male genitalia	HP:0010461	X	X	N/A, female
Abnormality of the urinary system	HP:0000079	X	–	X
Hypospadias	HP:0000047	X	X	–
Abnormality of the skeletal system	HP:0000924	X	–	X
Abnormality of the vasculature	HP:0002597	–	X	X
Bilateral single transverse palmar creases	HP:0007598	X	–	–
Brain imaging abnormality	HP:0410263	–	X	X
Nasolacrimal duct obstruction	HP:0000579	–	X	–
Small pituitary gland	HP:0010538	–	X	–
Prominent fingertip pads	HP:0001212	X	–	–
Short stature	HP:0004322	–	–	X
Ulnar deviation of the hand	HP:0009487	X	–	–
Other findings				
Dyskinetic cerebral palsy	HP:0011445	–	X	–
Feeding difficulties (with tube feeding)	HP:0011968	–	X	X
Food allergy	HP:0500093	–	–	X
Hearing loss (bilateral)	HP:0000365	X	X	–

(*Continued on next page*)

Table 1. ***Continued***

	HPO term	Individual 1	Individual 2	Individual 3
Heart murmur	HP:0030148	X	–	–
Hypernasal speech	HP:0001611	X	–	–
Hypotonia	HP:0001252	–	X	X
Inguinal hernia	HP:0000023	–	X	–
Sleep dysfunction	HP:0002360	–	X	X
Sparse hair	HP:0008070	X	–	–
Thyroiditis	HP:0100646	X	–	–
Vertigo	HP:0002321	X	–	–

using the IDT xGen Exome Research Panel v.1.0 (Integrated DNA Technologies, Coralville, IA). Massively parallel (NextGen) sequencing was done on an Illumina system with 150 bp paired-end reads. Reads were aligned to human genome build GRCh37/UCSC hg19 and analyzed for sequence variants using a custom-developed analysis tool. Reported variants were confirmed, if necessary, by an appropriate orthogonal method in the proband and in selected relatives. Additional sequencing technology and variant interpretation protocol has been described previously.[10] The general assertion criteria for variant classification are publicly available on the GeneDx ClinVar submission page (see web resources).

Results

Clinical and genetic findings of the three individuals who consented to this study are summarized in Tables 1 and 2. The individuals ranged in age from 3 to 26 years at the time of last evaluation, and two reported sex at birth as male. The *MGA* variants reported in this study were classified as variants of uncertain clinical significance.

Individual 1 had genetic consultation for mild developmental delay, psychiatric problems, and facial dysmorphism. He was reported by his parents to have mildly delayed developmental milestones in childhood across all domains. Specific dysmorphology included bilateral congenital auricular ear abnormality, proximal thumb insertion, partial syndactyly of the 3rd and 4th toes bilaterally, clinodactyly of the 4th and 5th toes with the 4th toe overlapping the 5th toe, deep-set toenails, and scoliosis. Ocular findings included myopia, ptosis, and prominent eyes. The facial shape was asymmetrical with a short and flat forehead, turricephaly and shallow orbits, malar flattening, depressed nasal bridge, anteverted nostrils, and broad nasal root and pointed tip. He had an underbite, high arched palate, and deviated uvula. Other findings included cryptorchidism, hypospadias, reduced kidney function and size, and bicuspid aortic valve. He was motivated for the consult in the interest of family planning. Family history was reported as non-contributory. Prior genetic evaluation included microarray analysis, FISH for 22q11.2 deletion syndrome, and targeted testing for *FGD1*, which were all normal. Given the prior negative genetic testing and diverse phenotype, clinical ES was performed as a trio with his parents, with a *de novo* heterozygous variant identified: c.2679del; p.Val894Serfs*39 (NM_001164273.1).

Individual 2 had genetic consultation for bilateral sensorineural hearing loss, developmental delay, and congenital anomalies. He was reportedly diagnosed with autism at age 6 years, 5 months old. Congenital anomalies included thickened bicuspid aortic valve, patent ductus arteriosus, dysplastic pulmonary valve, micropenis, chordee, hypospadias, and right cryptorchidism. Brain imaging was atypical with the following reported: (1) punctate focus of magnetic susceptibility in the left caudothalamic groove which may represent hemosiderin deposition from remote germinal matrix hemorrhage, (2) pituitary gland markedly smaller, consistent with a partial empty sella, (3) cystic structure with fluid level in the left nasolacrimal duct consistent with a dacryocystocele measuring 0.9 × 0.5 × 1.1 cm (AP [anteroposterior] × TR [transverse] × CC [craniocaudal]), (4) right mastoid effusion, (5) moderate prominence of the ventricular system, possibly residual/secondary to previous congenital heart disease, (6) incidental note of a 1 cm large left caudothalamic cyst. Facial dysmorphism included a flat face, ocular hypertelorism, hypoplastic nasal alae with overhanging columella, and thin upper lip. Ocular findings also included hyperopia and esotropia. Family history was non-contributory. Microarray analysis showed a microduplication at 5q35.2 (arr[hg19] 5q35.2(174,147,093–174,200,503)x3) with unknown inheritance, including the *MSX2* (OMIM: 123101) and *MIR4634* genes. This was classified as pathogenic by the performing laboratory, but his clinical providers felt it was unlikely to explain his phenotype. There was no indication of a clinically relevant deletion or duplication of three or more exons in the ES data. The 5q35.2 microduplication did not meet the laboratory reporting threshold in effect at the time of analysis because it contained only two exons of the *MSX2* gene and the *MIR4634* gene is noncoding. Trio ES identified a *de novo* heterozygous variant in the *MGA* gene: c.6503dup; p.Lys2169Glufs*26 (NM_001164273.1).

Individual 3 had genetic consultation for multiple congenital anomalies including coarctation of the aorta, velopharyngeal dysfunction, possible submucosal cleft

Table 2. Details of the *de novo* variants identified in the *MGA* gene in the study individuals

Individual no.	Hg19 coordinates	Exon	cDNA change	Protein change	Effect	ClinVar ID
1	chr15:42003142	8	c.2679del	p.Val894Serfs*39	frameshift	SCV005184297
2	chr15:42042308	17	c.6503dup	p.Lys2169Glufs*26	frameshift	SCV005184164
3	chr15:41989087	3	c.1879C>T	p.Arg627*	nonsense	SCV005184296

Of note, the transcript is NM_001164273.1; all variants are absent from gnomAD v.2.1.1; all variants are *de novo* with confirmation of parentage; and all variants are predicted to result in protein truncation and/or nonsense-mediated protein decay. See the report discussion for genomic constraint data. This *MGA* transcript contains 24 exons and 3,055 amino acids. The variants reported here occur in disordered or unknown protein regions and not in any currently known functional domain (https://www.uniprot.org/).

palate, and craniosynostosis, which was later repaired. Dysmorphic features included ocular hypertelorism, high forehead, and a broad nasal bridge and tip (Figure 1). She was followed by a speech-language pathologist for speech delay and feeding concerns as well as by a physical therapist for delayed gross motor development but was discharged from both services as the concerns resolved. Other findings included hemangioma of the left upper arm, delayed bone age, and mild left unilateral pelviectasis. Brain MRI showed well-defined thin wall cystic areas along the lateral margins of the bodies and frontal horns of both lateral ventricles as well as smaller cysts along the anterior and/or posterior margins of the dominant cysts. The appearance was similar to prior imaging done at day 19 and was consistent with connatal cysts. Chromosome analysis was normal and SNP microarray analysis was normal and female [arr(X,1–22)x2]. Trio ES identified a *de novo*, heterozygous variant, c.1879C>T; p.Arg627* (NM_001164273.1) in the *MGA* gene.

Discussion

Published evidence suggests an important role for the *MGA* gene in embryonic development. MGA protein (Max's giant associated protein) is part of the Max-interacting transcription factor network. It contains a basic-helix-loop-helix leucine zipper (bHLHZip) domain and interacts with Max, which mediates the transcription function of other bHLHZip proteins. Max is required for sequence-specific DNA binding to regulatory E-box sequences important for regulation of gene expression leading to cell growth and proliferation.[1,11]

In addition to the bHLHZip domain in its N-terminal half, MGA also contains a T-box DNA-binding domain (T domain) in its C-terminal half. A similar T domain is present in the Brachyury protein, which plays a role in the initiation of notochord development during embryogenesis.[12] The presence of both a bHLHZip domain and T-domain in the MGA protein suggests that it may be involved in dual regulation of both gene networks during embryogenesis.[13] In mice, *MGA* has been shown to be essential for pluripotent cell survival during development and to prevent embryonic stem cells from developing into extraembryonic endodermal tissue.[2,14] In zebrafish, the ortholog of *MGA* is necessary for normal development of heart, brain, and gut in embryos, as demonstrated by expression patterns during embryogenesis and resultant lethal phenotypes when *MGA* production was blocked via morpholino injection.[15] The defects in organogenesis seen in zebrafish *mga* included severe disruption of normal brain morphology due to apoptosis, defective heart tube looping, and atypical yolk mass retention due to failed gut development.[15]

Human studies involving large cohorts have suggested a potential role for *MGA* in a variety of conditions, but details provided for the individuals were insufficient to confirm a disease relationship. In a cohort of individuals with epilepsy with and without neurodevelopmental concerns, a *de novo* frameshift variant in *MGA* was confirmed by ES in a single individual with a phenotype including intellectual disability and generalized epilepsy. However, a *de novo* variant in candidate gene *TSPAN5* was also identified in this individual, so the impact of the *MGA* variant is unclear.[3] Two additional studies each identified a single individual with reported autism or developmental disorder and a *de novo* missense or synonymous *MGA* variant identified by exome analysis, but no additional phenotypic details were provided.[5,6] Similarly, two individuals harboring *de novo* variants in *MGA* (a synonymous variant and a missense variant) were identified in a large cohort of individuals with congenital heart defects. In both individuals, a second variant in a candidate gene (*SNX9* or *ARHGEF5*) was also identified, and no additional clinical information was provided.[7] Finally, in a large cohort of individuals with sporadic early-onset Parkinson's disease but without other clinical details, a *de novo* missense variant was identified in the *MGA* gene for one individual.[8]

The individuals presented in this report suggest that variants predicted to result in protein truncation or nonsense-mediated decay in the *MGA* gene are deleterious to development and may cause congenital malformations as well as neurodevelopmental differences. In two of the three individuals, *MGA* was identified as the primary variant of interest in the ES. For individual 2, microarray analysis showed a microduplication at 5q35.2 including the *MSX2* and *MIR4634* genes. *MSX2* is known to be associated with autosomal dominant craniosynostosis and in LoF variants, parietal foramina.[16] Individual 2 did not present with either condition, and the clinical team determined that this duplication was unlikely to explain his phenotype. The overall phenotype of individual 2 did not differ substantially from the other two individuals in the study

Figure 1. Individual 3, a 2-year-old female
Note a high forehead, frontal bossing, hypertelorism, depressed and wide nasal bridge and thin upper lip. She also had craniosynostosis, hypotonia, and developmental delays.

(Figure 2). The unique clinical findings in individual 2, not seen in individuals 1 or 3, included small pituitary, seizure, and movement disorder, which are not currently known to be associated with this microduplication, However, as the *MSX2* gene does play a role in developmental processes, this case should be reviewed once additional information becomes available on the effects of *MSX2* duplication variants. The *MIR4634* gene was also included in the microduplication, but no diseases have been associated with germline *MIR4634* duplications at this time.

The variants observed in this report were not present in gnomAD (v.2.1.1) or in the population of unaffected individuals in the GeneDx exome/genome database.[9] Genomic constraint data from gnomAD (v.2.1.1) support pathogenicity for the predicted LoF *MGA* variants in this report. While the *MGA* misZ scores (Z = 1.1) indicate mixed levels of constraint on missense variants, the pLI score (1) indicates strong selection against LoF variants and suggests haploinsufficiency as a disease mechanism[9,17] (Table 2). Our observations of congenital malformations and neurodevelopmental concerns in individuals harboring predicted LoF variants in *MGA* are also consistent with haploinsufficiency.

We recognize the limitations to this concise report of early-stage findings. Our cohort included three consented individuals, as details of additional unconsented individuals with *MGA* predicted LoF variants could not be included. A larger cohort will be required to confirm the causative role of *MGA* variants in human disease and to better define the phenotypic spectrum. In addition, future experimental work will be necessary to determine the essential functional protein domains of MGA and to establish the putative disease mechanism.

In summary, the individuals harboring predicted LoF variants in the *MGA* gene reported in this study showed a broad phenotypic spectrum that includes neurodevelopmental delay and congenital malformations. All three individuals in the cohort specifically have developmental delay, and musculoskeletal, cardiac, and genitourinary malformations as well as craniofacial dysmorphisms (Figure 2). Other prevalent findings in two of the three individuals include skull malformations, hearing loss, male genitalia anomalies, mid-face flattening, hypertelorism, and speech delay as well as sleep dysfunction and feeding difficulties. While additional clinical and functional data will be necessary to confirm this proposed novel disease-gene relationship, the data presented here suggest that

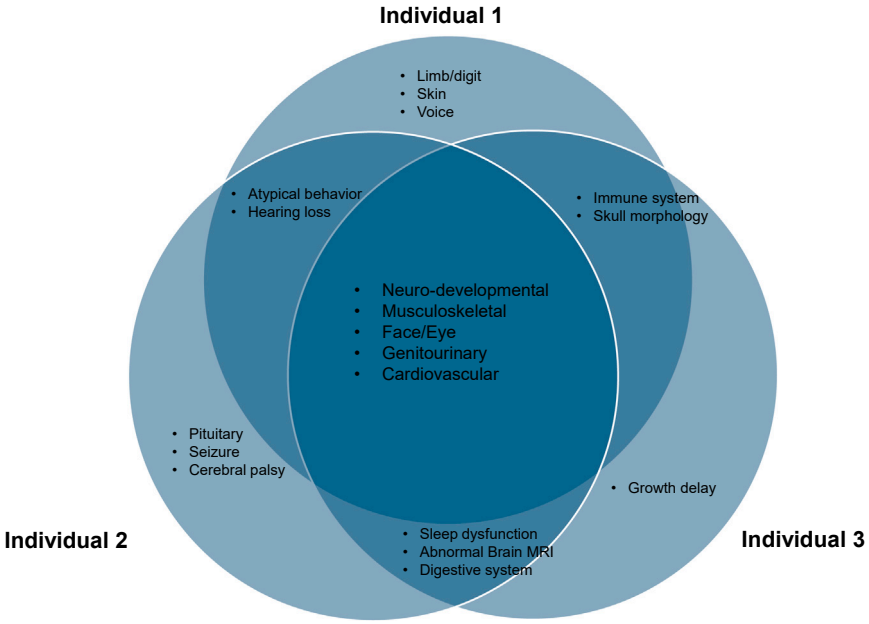

Figure 2. Venn diagram showing the shared and unique phenotypic categories of individuals 1, 2, and 3
Common features shared between all three individuals include neurodevelopmental delay, facial and eye anomalies, and musculoskeletal, genitourinary, and cardiovascular anomalies.

predicted LoF variants in *MGA* are associated with an autosomal dominant disorder characterized by neurodevelopmental delay and congenital anomalies. Individuals and families impacted by these conditions would benefit from clinical consideration of broad genetic testing, such as exome or genome, to capture variants in important genes of emerging significance including *MGA*.

Data and code availability

Exome sequence data were generated during clinical testing; study individuals were not consented for data sharing. ClinVar ID numbers can be found in Table 2.

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Author contributions

Conceptualization, B.M, K.Mc. and P.K.; genetic analysis and case identification, B.M., M.M.M., E.T., I.M.W., and K.G.M.; recruitment and clinical evaluations, A.G., L.R., D.C., C.B., S. J., and P.L.; writing – original draft, B.M. and M.M.M.; writing – review & editing, B.M, M.M.M, E.T., K.Mc. I.M.W., K.G.M. and P.K.; All authors reviewed and approved the final manuscript.

Declaration of interests

B.M., M.M.M., E.T., K.Mc., I.M.W., K.G.M., and P.K. are employees of and may hold stock in GeneDx, LLC.

Web resources

ClinVar: http://www.ncbi.nlm.nih.gov/clinvar/submitters/26957/
Human Phenotype Ontology: https://hpo.jax.org/
gnomAD: https://gnomad.broadinstitute.org/
OMIM: http://www.omim.org/
UniProt: https://www.uniprot.org/

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