The Clinical Impact of the Patient-Led Rare Disease Organization for KBG Syndrome

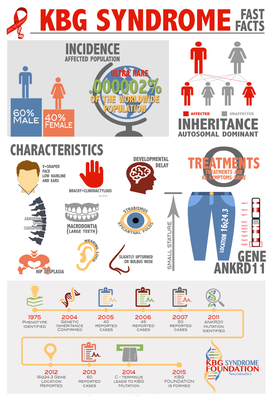
INTRODUCTION

KBG Syndrome is a rare genetic disorder caused by a mutation on the ANKRD11 gene at location 16q.24.3, associated with a spectrum of challenges, including developmental delays, cognitive disabilities, behavioral disorders, seizures, hearing loss, skeletal anomalies, autism, heart complications and gastrointestinal problems.

Most people with KBG share at least some physical traits, including a triangular face, heavy eyebrows, curved fingers and spine, and short stature.

The KBG Foundation is a 501(c)(3) nonprofit organization, dedicated to providing support, assisting in research programs and advocating to raise awareness about KBG Syndrome.

The KBG Foundation is working to better understand, and help improve, the impact of KBG on the quality of life for the affected population.



OBJECTIVES

Demonstrate the clinical importance of a patient-led organization in refuting or supporting several key findings and hypotheses including:

ANKRD11 as a co-activator for p53[1]**,** with reports of in-pipeline drugs to up-regulate ANKRD11 and probably activate p53, preventing and treating specific cancers.

ANKRD11 is a target gene in autism research[2]**.** Ankrd11 is a crucial chromatin regulator that controls histone acetylation and gene expression during neural development, thereby providing a likely explanation for its association with cognitive dysfunction and ASD.

ANKRD11 has a potential link to Alzheimer's, as well as brain atrophy. *

ANKRD11 associated with a large fontanelle and could be an early indicator of KBG Syndrome.

ANKRD11 may have an increased incidence of diagnoses of occult tethered cord syndrome.

METHODS

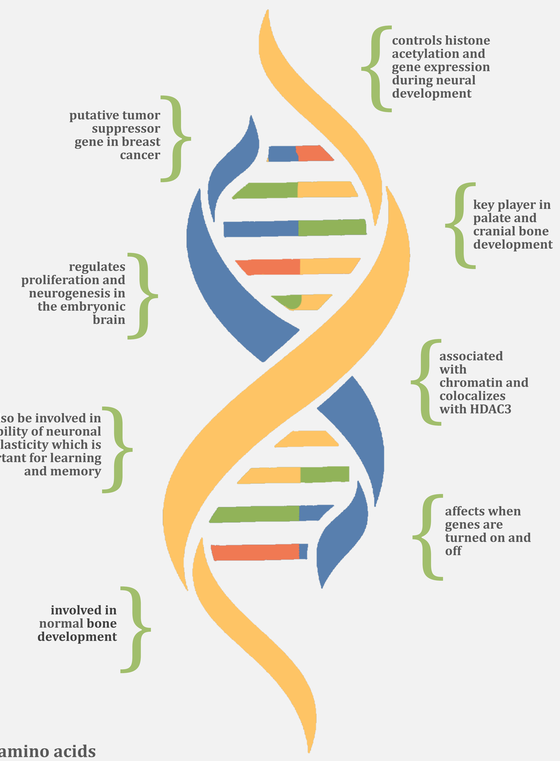
Administrators of a Foundation-owned private social group became certified researchers and polled the population based on recently published research, written requests from authors or scientific advisory board members, and patient concerns. Written requests were received from researchers with a hypothesis and/or an interest in collecting real-world patient data.

The Foundation asked the question, or set of questions, on behalf of the researcher and provided de-identified reports. Several research studies have been initiated and completed through this collaboration.

Questions asked in connection with the objectives:

1. Do you have an autism diagnosis along with KBG?
2. Did you, or your child, experience regression after hitting a developmental milestone?
3. Soft spot (Fontanel) delayed closure. We are asking about the front and the back.
4. Tethered cord poll, just simple.

ANKRD11
FUNCTION AND ASSOCIATIONS



Size: 2663 amino acids
Molecular mass: 297913 Da
Quaternary structure: Interacts with the PAS region of the p160 coactivators.

REFERENCES

1) Neilsen PM, Cheney KM, Li CW, Chen JD, Cawrse JE, Schulz RB, Powell JA, Kumar R, Callen DF. **Identification of ANKRD11 as a p53 coactivator**. *J Cell Sci. 2008 Nov 1;121(Pt 21):3541-52. doi: 10.1242/jcs.026351. Epub 2008 Oct 7.* PMID: 18840648.

2) Gallagher D, Voronova A, Zander MA, Cancino GI, Bramall A, Krause MP, Abad C, Tekin M, Neilsen PM, Callen DF, Scherer SW, Keller GM, Kaplan DR, Walz K, Miller FD. **Ankrd11 is a chromatin regulator involved in autism that is essential for neural development**. *Dev Cell. 2015 Jan 12;32(1):31-42. doi: 10.1016/j.devcel.2014.11.031. Epub 2014 Dec 31.* PMID: 25556659.

3) Roth DM, Baddam P, Lin H, et al. **The Chromatin Regulator Ankrd11 Controls Palate and Cranial Bone Development**. *Front Cell Dev Biol. 2021;9:645386. Published 2021 Apr 29.* doi:10.3389/fcell.2021.645386

4) https://www.businesswire.com/news/home/20170907005156/en/KBG-Foundation-Partners-FDNA-Children-Rare-Genetic

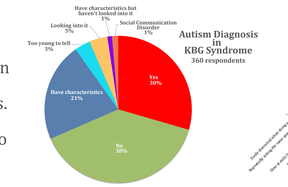
5) Bhimani AD, Selner AN, Patel JB, Hobbs JG, Esfahani DR, Behbahani M, Zayyad Z, Nikas D, Mehta AI. **Pediatric tethered cord release: an epidemiological and postoperative complication analysis.** J Spine Surg. 2019 Sep;5(3):337–350. doi: 10.21037/jss.2019.09.02. PMID: 31663045; PMCID: PMC6787363.

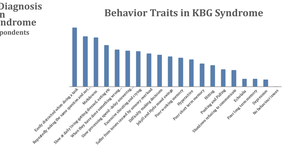
* Self-reported data collected inside the private family group

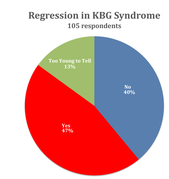
RESULTS

The KBG Foundation has been instrumental in participating in **FDNA's Face2Gene** platform [4], soliciting information from our member families, and working with our Scientific Advisory Board. Early research relied on very small patient pools. With its membership that includes approximately **600 patients**, the Foundation has, among other things, discovered or corroborated the following:

Autism or autistic traits Patient reporting* places the rate of those affected by **autism** at **30%,** with an additional 28% having strong symptoms but no official diagnosis. Ninety percent report behavioral issues, ranging from **meltdowns** to **aggressive outbursts.**

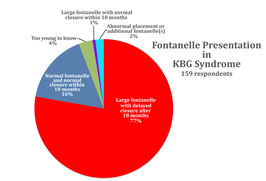


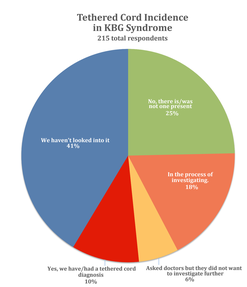




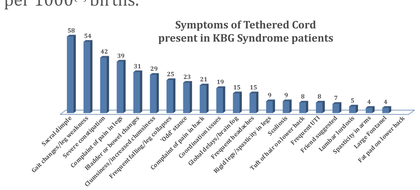
Neurodegenerative conditions - Alzheimer's, as well as brain atrophy have been reported in 7 patients, to date. With the majority of KBG syndrome patients being under the age of 20, we cannot yet determine if neurodegeneration occurs. Although, **47%** have **reported regression** stating that their child had lost skills over time.

Large Fontanelle with delayed closure - 77% identified **large fontanelle with delayed closure** in 2018; reported in medical literature in 2021[4]





Occult Tethered Cord -- 10% of 215 people reporting had positive diagnoses of **tethered cord**; and 18% are investigating the possibility. The incidence rate in the US population is reported at .25 per 1000[5] births.



CONCLUSIONS

In the instance of these five (5) objectives, the Foundation was able to support two (2) objectives: **target gene for autism** and **large fontanelle,** while also adding to the incidence rate.

One (1) **potential link to neurodegenerative conditions**, showed that regression of achieved milestones occurs at an almost 50% rate but reports of brain atrophy and Alzheimers were not confirmed to occur at a higher rate than expected (7 reports of only 7 people commenting). This objective, while not fully confirmed, did uncover the regression rate in childhood which, to date, is unreported.

One (1) we are unable to refute or support; **P53 up-regulator.**

The 5th objective, **occult tethered cord syndrome** was retroactively identified by the Foundation and supported by its patient population. No published studies or hypotheses existed. The incidence of occult tethered cord syndrome occurs at a **3600% increase** in the KBG population. The IRB-supported paper is in final development.

The KBG Foundation is well-positioned to partner in research and treatments for KBG Syndrome.