De Novo Microdeletion Spanning *YWHAE* and *CRK* in an Individual with Intellectual Disability and Stunted Growth

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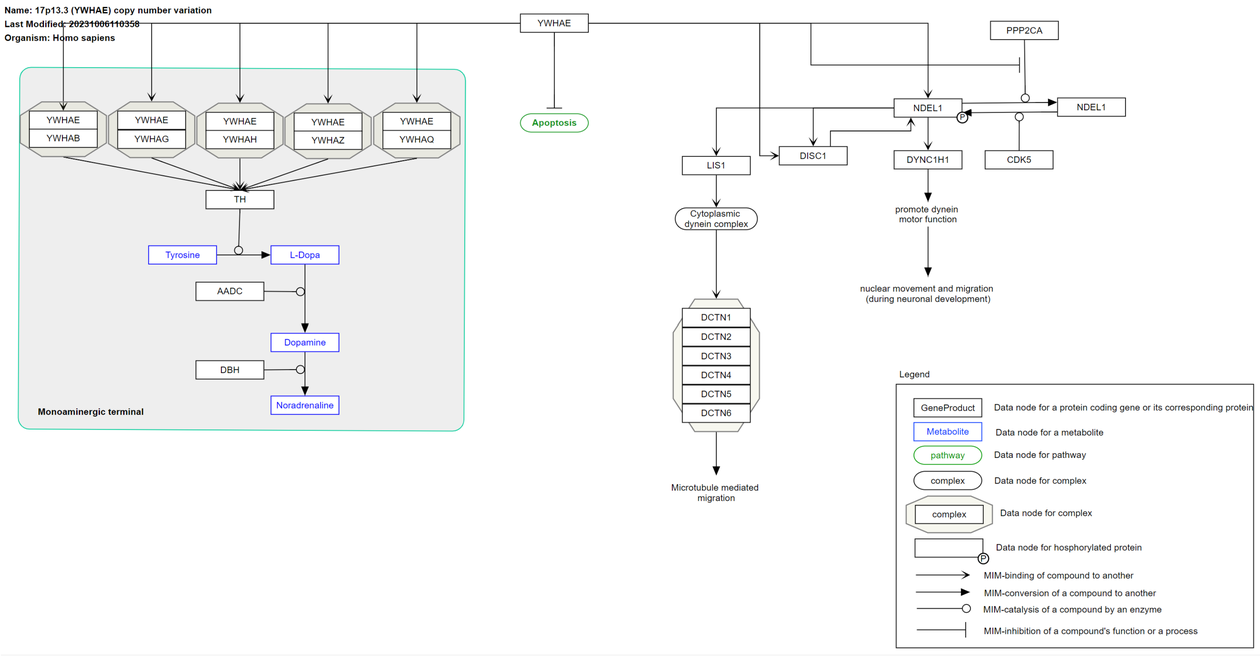
Background

In this report, we present a case of a 20-year-old female with congenital intellectual disability, stunted growth, and hypothyroidism. Competitive genetic hybridization (CHG) revealed a loss of a portion of 17p13.3 at least 195 Kb in size, not present in either parent. This area of chromosome 17 is associated with Miller-Dieker Syndrome (MDS) and Isolated Lissencephaly Sequence (ILS), but these conditions are related predominantly to PAFAH1B1, which is not included in the patient's deletion.



Picture 1. YWHAE pathway image obtained from WikiPathways.

Methods

Peripheral mononuclear cells (PBMCs) were used for karyotyping and competitive genetic hybridization (CGH) at Baylor College of Medicine. Further bioinformatic analysis was carried out using the Genome Data Viewer (ncbi.nlm.nih.gov/genome/gdv). Further confirmation of endpoints is planned using qPCR and long-range PCR. Assent was obtained from the patient and consent was obtained from the patient's parents prior to beginning the study.

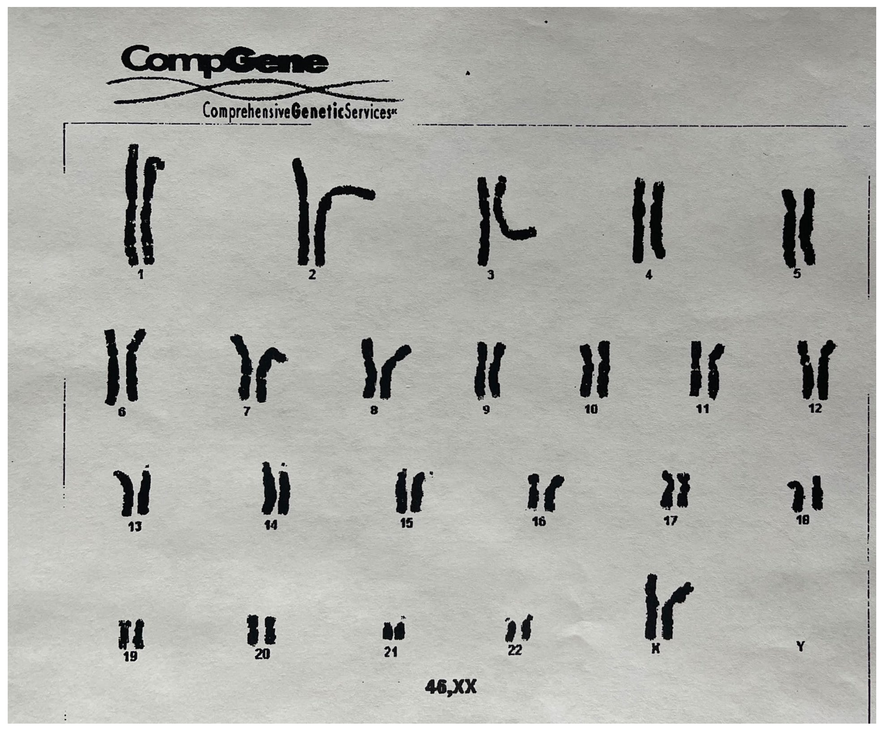


Figure 1. Scan of Karyotype results from 2003.

Results

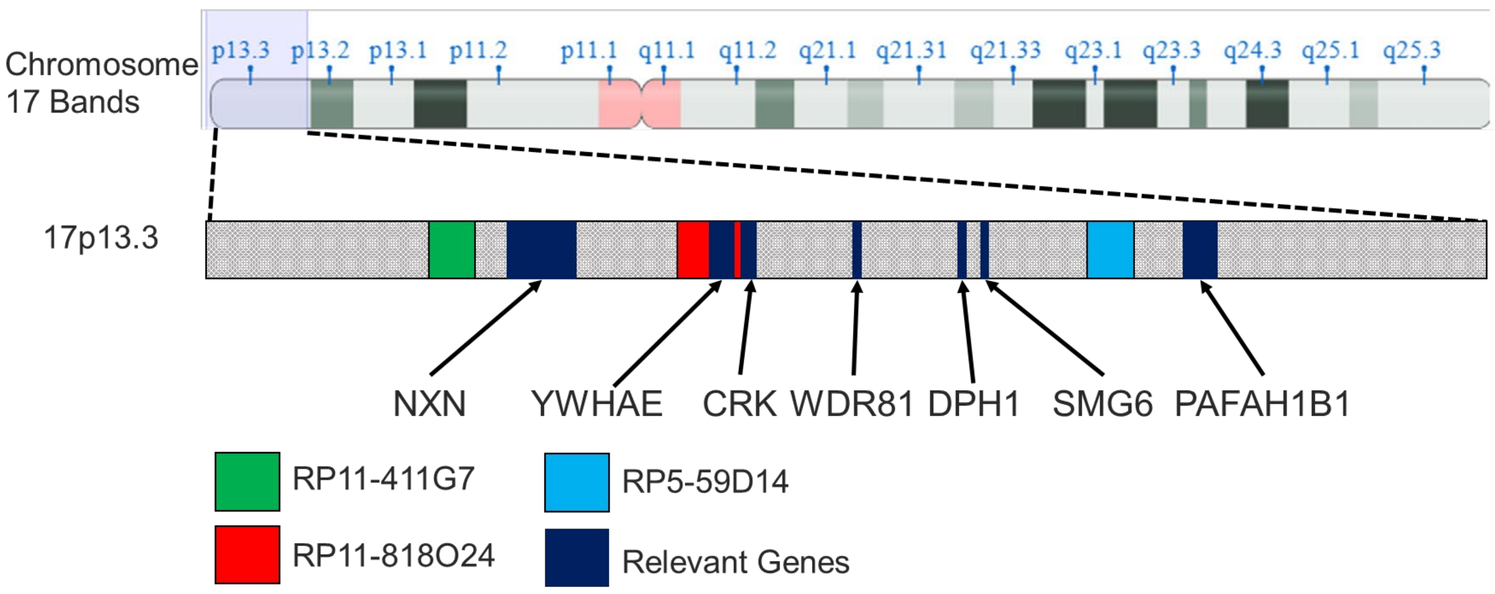


Figure 2. Representation of the relevant genes in relation to the FISH probes. *PAFAH1B1* is thought to be the main contributor to MDS and is not deleted here. *YWHAE* and *CRK* both overlap the probe of the deleted region, while *NXN*, *WDR81*, *DPH1*, and *SMG6* are located in regions that are possibly deleted.

Probe Name	NBCI Accession	HG38 Location	Status	Relevant Genes
RP11-411G7	AC027455.22	chr17:590,738-722,442	Wild-Type	
No Probe		Chr17:722,443-1,249,647	Possible Monozygous Deletion	NXN
RP11-818O24	AC032044.28	chr17:1,249,648-1,449,331	Monozygous Deletion	YWHAE, CRK
No Probe		Chr17:1,449,332-2,339,877	Possible Monozygous Deletion	WDR81, DPH1, SMG6
RP5-59D14	AC006435.7	chr17:2,339,205-2,464,878	Wild-Type	PAFAH1B1

Table 1. Position information of the FISH probes used to narrow breakpoints, along with genes likely relevant to the phenotype.

Gene Symbol	Symptoms Associated with Deletion
NXN	Robinbow syndrome with emotional disorders, recessive disorder
YWHAE	Intellectual disability with no abnormal brain structure
CRK	Deletion correlated with growth abnormalities and limb malformations
WDR81	Microlissencephaly coprus callosum agenesis and pontocerebellar hypoplasia
DPH1	Related to craniofacial abnormalities in Miller-Deiker Syndrome
SMG6	Deletion in fruit-flies causes neurodevelopmental delay, mutations common in intellectual disability

Table 2. Potentially relevant genes and phenotypes associated with deletion or mutation of these genes.

Conclusion

Microdeletions of 17p13.3 are associated with Miller-Deiker Syndrome (MDS). Here we present a patient with intellectual disability but that does not show the classic MDS phenotype. *PAFAH1B1* is not deleted, but multiple genes in the region are correlated with phenotypes presented by the patient. Deletion of *YWHAE* is the most likely cause of intellectual disability, and deletion of *CRK* is likely related to growth retardation.