Disclosure Slide

Financial Disclosure for:

K. Rudd, G. Haskell, A. Arreola, J. Schleede, A. L. Penton, J. Tepperberg, I. K. Gadi, K. K. Phillips, R. Potluri, J. Wiley, H. Risheg, P. Papenhausen, S. Schwartz

Center for Molecular Biology and Pathology, Laboratory Corporation of America® Holdings, Durham, NC

All authors are employees of Laboratory Corporation of America Holdings ("LabCorp") and may own LabCorp stock.

EDAR deletions: Dominant or recessive?

K. Rudd, G. Haskell, A. Arreola, J. Schleede, A. L. Penton, J. Tepperberg, I. K. Gadi, K. K. Phillips, R. Potluri, J. Wiley, H. Risheg, P. Papenhausen, S. Schwartz

Center for Molecular Biology and Pathology, Laboratory Corporation of America® Holdings, Durham, NC

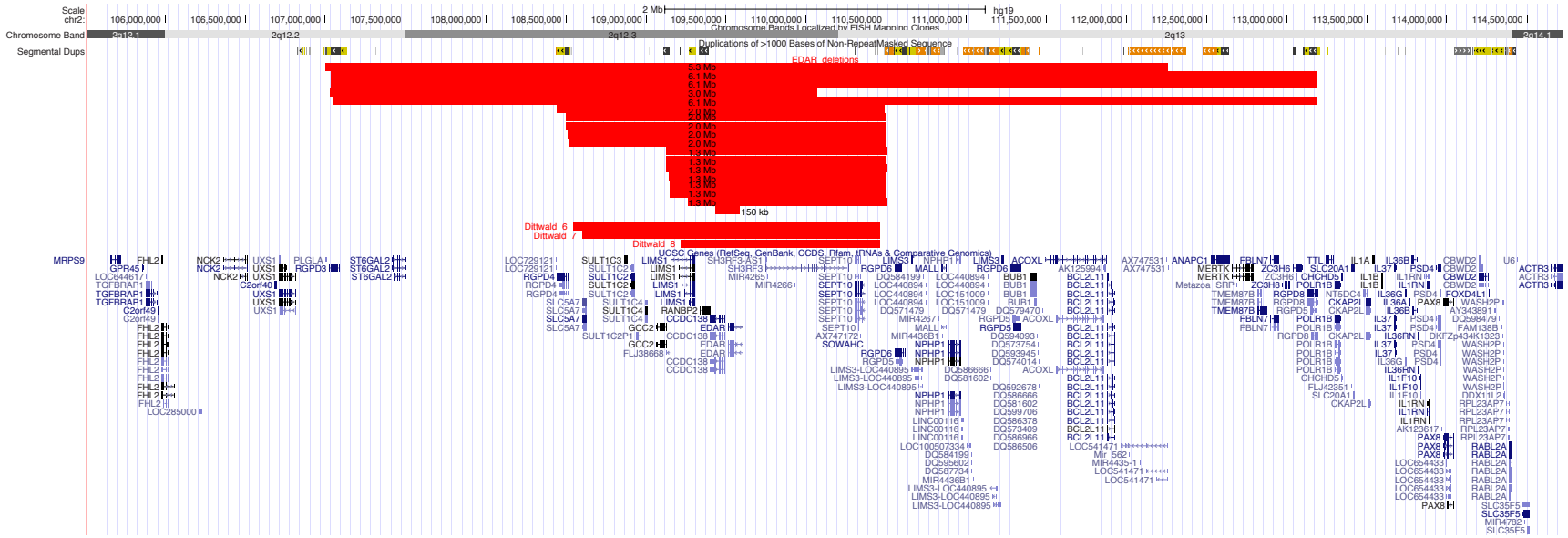
Introduction

Pathogenic variants in EDAR are responsible for ~10-15% cases of Hypohidrotic Ectodermal Dysplasia (HED), which is characterized by sparse hair, a reduced ability to sweat, and congenital absence of teeth. EDAR variants are associated with both dominant and recessive forms of HED, and most are missense changes. One nonsense variant in exon 12, p.Arg358*, is predicted to have a dominant-negative effect. Few EDAR deletions have been reported in the literature, and the dominant and recessive forms of the disease complicate interpretation of copy number variants .

Results

To better understand the phenotypic consequences of EDAR deletions, we leveraged our dataset of patients referred for chromosomal microarray analysis (CMA). In the last seven years, we have reported 18 heterozygous 2q12-q13 deletions that include EDAR; five were prenatal and 13 were postnatal. The deletions range in size from 150 kb to 6.2 Mb. The 150-kb deletion includes only the 3' end of EDAR and the 3' end of CCDC138. All of the other deletions include the entire EDAR gene, plus other genes, and are flanked by paralogous segmental duplications. These larger deletions are 1.3 Mb (n=7), 2.0 Mb (n=5), 3.0 Mb (n=1), 5.3 Mb (n=1), and 6.1 Mb (n=3). For eight probands, we performed parental testing and determined that two were de novo (150 kb, 1.3 Mb), three were maternal (2.0 Mb, 6.1 Mb, 6.1 Mb), and three were paternal (1.3 Mb, 3.0 Mb, 5.3 Mb).

Figure 1: Deletions (red) are shown relative to segmental duplications and gene content. Deletion size is indicated.



Conclusions

The 1.3-Mb and 2.0-Mb deletions have been reported in patients without features of HED (Dittwald et al. PMID: 23657883). Though we do not have detailed clinic notes for patients referred for CMA, we reviewed the indications for testing in our cases. The most common postnatal indications were intellectual disability, autism spectrum disorder, and seizures. None of the patients had phenotypes involving abnormalities of hair, skin, teeth, or sweating. These results suggest that whole-gene EDAR deletions do not follow an autosomal dominant mode of inheritance. Future clinical follow up is necessary to resolve genotype-phenotype correlations with genomic disorders of chromosome 2q12-q13.