The *Annals of Saudi Medicine* welcomes letters from readers that comment on recent articles published in the journal. They should be received within six weeks of the publication of the article and be not more than approximately 500 words. Send letters to *jtcathey@kfshrc.edu.sa*. They should not be submitted as manuscripts on the journal's online manuscript submission site.

Re: EIF2AK3 Mutations in Patients with Wolcott-Rallison Syndrome

To the Editor: I read with interest the report of a new case of Wolcott-Rallison syndrome by Marafie et al[1] and would like to further highlight the molecular basis of this syndrome.

Wolcott-Rallison syndrome (WRS) is a rare autosomal recessive disorder characterized by early-onset permanent diabetes mellitus, multiple epiphyseal dysplasia, growth retardation, and variable other systemic manifestations. Delepine et al[2] mapped WRS to chromosome 2p12, and identified in two consanguineous families with WRS two mutations in EIF2AK3, the gene encoding the eukaryotic translation initiation factor 2-alpha kinase.[3] The mutations segregated with the disorder of each of the families. These results provided evidence for the role of EIF2AK# deficiency in WRS at the molecular level. They describe a homozygous missense serine 877 proline mutation of EIF2AK3 gene in a 5-year-old girl with WRS, and found that the mutated kinase was unable to phosphorylate its natural substrate, eukaryotic initiation factor 2alpha (eIF2alpha). A comprehensive clinical, genetic, and functional study of EIF2AK3 mutations in WRS was recently published.[4] Twelve families with WRS, totaling 18 cases were studied. With the exception of one case, all patients carried EIF2AK3 mutations resulting in truncated or missense versions of the protein. The patient with no EIF2AK3 involvement did not have any of the variable clinical manifestations associated with WRS, suggesting both genetic and clinical heterogeneity between this variant form of WRS[5,6] were included in this study;[4] two different EIF2AK3 mutations were identified in these families [560GA and del (184bp) in exon 15/intron 15]. Another novel EIF2AK3 mutation was recently described in a child with WRS.[7]

In summary, EIF2AK3 mutations have been identified in at least 18 WRS cases from 12 families. This demonstrates that EIF2AK3 gene plays a major role in the pathophysiology of WRS. In addition, EIF2aK3 kinase activity appears to be essential for pancreatic islet cell function and bone development in humans.

Doris Taha, MD
King Faisal Specialist Hospital & Research Centre
Division of Pediatric Endocrinology,
Department of Pediatrics
MBC J58
P.O. Box 40047
Jeddah 21499
Saudi Arabia
dtaha@kfshrc.edu.sa

References

1. Marafie MJ, Redha MA, Al-Naggar RL. Wolcott-Rallison syndrome in a Bedouin boy. *Ann Saudi Med.* 2004;24(6):476-9.
2. Delepine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM, Julier C. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nat Genet.* 2000;24(4):406-9
3. Biason-Lauber A, Lang-Muritano M, Vaccaro T, Schoenle EJ. Loss of kinase activity in a patient with Wolcott-Rallison syndrome caused by a novel mutation in the EIF2AK3 gene. *Diabetes.* 2002;51(7):2301-5.
4. Senee V, Vattem KM, Delepine M, et al. Wolcott-Rallison Syndrome: clinical, genetic, and functional study of EIF2^{a}K3 mutations and suggestion of genetic heterogeneity. *Diabetes.* 2044;53)7):1876-83.
5. Bin-Abbas B, Shahib S, Hainau B, Al-Ashwal A. Wolcott-Rallison syndrome: Clinical, radiological, and histological findings in a Saudi Child. *Ann Saudi Med.* 2001;21:73-74.
6. Bin-Abbas B, Al-Mulhim A, Al-Ashwal A. Wolcott-Rallison syndrome in two siblings with isolated central hypothyroidism. *Am J Med Genet.* 2002;111(2):187-90.
7. Iyer S, Korada M, Rainbow L, Kirk J, Brown RM, Shaw N, Barett TG. Wolcott-Rallison syndrome: a clinical and genetic study of three children, novel mutation in EIF2AK3 and a review of the literature. *Acta Paediatr.* 2004;93(9):1195-201.

Reply

To the Editor: We thank Dr. Doris Taha for her valuable updating of the molecular genetics information for Wolcott-Rallison syndrome, and the EIF2AK3 gene mutations found recently in further cases from different ethnic families.

Our patients' ancestors are originally from Arabian peninsula/Saudi region, therefore the possibility of carrying a mutation in EIF2AK3 gene is high since he also expressed the majority of the disease manifestations.

Finding gene mutations in affected families would help in offering genetic screening options for their members and encourage the geneticist and these individuals to decide together which is the best approach for them in future pregnancies; either to arrange for prenatal diagnosis or to offer PGD (pre-implanation genetic diagnosis) especially when termination of pregnancy is prohibited in some cultures and taking into account that cousin marriages are popular in the Arabic region.

Dr. Makia Marafie
Kuwait Medical Genetic Centre
Maternity Hospital
P.O. Box: 5833
Safat 13059, Kuwait
Mj_marafie@yahoo.com