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### **MUTATIONS IN *MBTPS2* (A ZINC METALLOPROTEASE) RESULTS IN IFAP (ICHTHYOSIS FOLLICULARIS WITH ATRICHIA AND PHOTOPHOBIA) SYNDROME**

Charles E. Schwartz, PhD<sup>1</sup>, Fatima Abidi, PhD<sup>1</sup>, Patrick S. Tarpey, PhD<sup>2</sup>, Michael R. Stratton, MD<sup>2</sup>, Roger E. Stevenson, MD<sup>1</sup>, Antonie D. Kline, MD<sup>3</sup>

<sup>1</sup>Greenwood Genetic Center, Greenwood, SC, <sup>2</sup>Wellcome Trust Sanger Institute, Hinxton, UK,

<sup>3</sup>Harvey Institute for Human Genetics, Greater Baltimore Medical Center, Baltimore, MD

Ichthyosis follicularis with atrichia and photophobia (IFAP) syndrome is a rare X-linked disorder that was first described 100 years ago by MacLeod (1909). We initiated a study of three families with IFAP. Since one family had two affected boys and one unaffected boy, we utilized markers spanning the X chromosome to identify a region of "concordance". We found two such regions, Xp22.2 and Xp28, which contained 2 potential candidate genes: *STS* and *NEMO*. Both were ruled out by direct gene sequencing. We thus initiated deep sequencing of all genes in these regions using exon trapping followed by Solexa sequencing. This approach uncovered novel missense mutations in the *MBTPS2* gene in all three families. Family 1: Two affected males with a c.1286G>A, p.R429H mutation. The young boys (aged 7 and 4 at examination) had all four hallmark features of IFAP along with corneal scarring, abnormal nails, development delay, growth retardation, head tilt, corneal involvement, brain abnormalities and seizures. Family 2: One affected male with a c.1468A>G, p.K490E mutation. The boy, aged 3 at examination, has IFAP plus corneal scarring as well as developmental delay and growth retardation. His mother has several mild symptoms. Family 3: One affected male with a c.1499G>A, p.G500D mutation. The teen, age 15, had developmental delay and head tilt in addition to all findings of IFAP. *MBTPS2* (membrane-bound transcription factor protease, site 2) is a zinc metalloprotease which activates signaling proteins involved in sterol control of transcription and cholesterol homeostasis. Thus, since mutations in the *STS* gene cause another X-linked ichthyosis syndrome, ichthyosis is apparently associated with defects in lipid metabolism.