Enlarged genotype-phenotype correlation for a three-base pair deletion in neurofibromatosis type 1

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Ludwine Messiaen, Ph.D., left, and Magdalena Koczkowska, Ph.D. Credit: University of Alabama at Birmingham

International collaborative research led by Ludwine Messiaen, Ph.D.,

shows that while a three-base pair, in-frame deletion called p.Met992del in the NF1 gene has a mild phenotype for people with the genetic disorder neurofibromatosis type 1, or NF1, the mutation does cause complications. These include non-optic brain tumors, mostly low-grade and asymptomatic, as well as cognitive impairment and/or learning disabilities. This study extends findings first reported in 2007 that included only 19 NF1 adults.

"Learning difficulties are clearly part of the phenotypic presentation in these individuals and will

require specialized care," said Messiaen, professor of genetics and director of the Medical Genomics Laboratory at the University of Alabama at Birmingham.

Including more adults in the new study was the key to obtaining statistically significant evidence of a mild phenotype that included absence of cutaneous and externally visible plexiform neurofibromas and symptomatic optic pathway gliomas. This is important because whether patients will have mild or severe disease cannot—in most cases—be predicted when the neurofibromatosis type 1 first appears, often only with café-au-lait skin markings in infants.

As the patients grow, they typically show a broad clinical variability, especially at the beginning of puberty, when many benign skin tumors called cutaneous neurofibromas erupt as bumps across the body and increase in number, even to thousands, over time.

Patients vary widely in their symptoms, which can include freckles in skin folds of the body, benign nodules in the iris of the eyes, tumors along the optic nerve, heart defects, bone anomalies, developmental delay, intellectual disability and learning problems. Although cutaneous neurofibromas never become malignant, they have a huge negative

impact on the quality of life due to the disfigurement and associated pruritus.

On the other hand, plexiform neurofibromas not only cause disfigurement, pain and neurological deficits, but also may become malignant, resulting in significant morbidity of these individuals. They are found in about 15 to 30 percent of NF1 patients and are usually apparent in the early years of life. Therefore, it is critical to identify as early as possible those individuals with an increased risk to develop malignancies in order to provide personalized management and genetic counseling.

"Patients and their families want to know what may happen," Messiaen said. "When a child is born with neurofibromatosis type 1, the café-au-lait spots appear early in life, sometimes as the only clinical feature of NF1. But many other problems, more specifically the development of cutaneous neurofibromas, may occur later, typically around puberty. If a genotype-phenotype correlation exists for a particular mutation, it will help these families have a better idea of what the future will bring, and it will help families cope with the disease."

Knowing what to expect from a particular NF1 mutation can help guide clinical management and genetic counseling in this complex condition, which is caused by one out of more than 3,000 different mutations found so far, distributed in every part of this large NF1 gene.

Although clinically useful genotype-phenotype correlations will not exist for the majority of the NF1 pathogenic variants, every such association between specific recurrent mutations and specific symptoms will impact many lives.

Finding a novel genotype-phenotype correlation is challenging. It is hampered by issues such as the variability of the clinical presentation,

the age-dependency of most manifestations and the vast number of different NF1 pathogenic variants. More than 2,500 of these variants have so far been identified in only one or two unrelated individuals.

Many neurofibromatosis patients develop benign skin tumors called neurofibromas that erupt as bumps across the body, beginning at puberty. Credit: University of Alabama at Birmingham

A group of pathogenic variants called missense and single amino acid deletions are promising candidates for finding additional genotype-phenotype correlations, as they typically change only a very small portion of the protein and may affect protein functionality in a more

specific way.

"My research currently prioritizes on the most recurrent missense mutations and single amino acid deletions that have a frequency of more than 0.5 percent in the UAB cohort," Messiaen said. "This approach so far has led to the identification of three clinically relevant genotype-phenotype correlations that together impact the lives of 2 to 3 percent of all NF1 patients."

Massive effort

To look for correlations, Messiaen and her team collected detailed clinical information on all symptoms found in each of 135 NF1-affected individuals from 103 unrelated families who had the p.Met992del mutation identified at the UAB Medical Genomics Laboratory and collaborating European centers. Then, these data were compared to several large clinical cohorts previously reported in the literature.

Their study, published in the journal Genetics in Medicine, involved 70 researchers and clinicians from 47 hospitals and universities in the United States, Belgium, Italy, Spain, the Netherlands, Australia, Austria and Canada.

The researchers found that none of the individuals had externally visible histopathologically confirmed cutaneous or plexiform neurofibromas, and none had complications like symptomatic optic pathway gliomas or symptomatic spinal neurofibromas. However, 4.8 percent of the study group had mostly low-grade, asymptomatic non-optic brain tumors, and 38.8 percent had cognitive impairment and/or learning disabilities.

The protein encoded by NF1 is a string of 2,818 amino acids that folds into the protein shape. Although the NF1 gene was cloned in 1990, the cellular functions performed by the huge, multi-domain protein encoded

by the gene, and called neurofibromin, are still incompletely understood. As such, the specific function of the NF1 codon 992 affected by the p.Met992del deletion remains so far unknown.

Neurofibromatosis type 1 is a common genetic disorder with highly variable symptoms, and it occurs in one out of every 2,000 to 3,000 births. The UAB Medical Genomics Laboratory has collected DNA and identified a pathogenic mutation on the more than 10,000 unrelated NF1 patients. These include more than 3,000 different mutations, and the mutational spectrum involves microdeletions, deletions or duplications of one or more exons, frameshift and nonsense mutations, and splice or missense mutations.

Although only four groups of recurrent mutations with clear genotype-phenotype correlations have been reported so far, each accounting for only a small percentage of NF1-affected individuals, they together affect between 5 and 10 percent of the neurofibromatosis type 1 population.

"This is already a significant fraction; but there is still a lot of work to do, and more remain to be identified," said first author Magdalena Koczkowska, Ph.D. "Close collaboration between NF1 clinicians and molecular geneticists is critical to achieve a timely unfolding of additional correlations that will allow genotype-driven personalized medicine."

Koczkowska is a postdoctoral fellow who joined the UAB Medical Genomics Laboratory in 2016 to work on the identification of novel genotype-phenotype correlations in NF1.

More information: Magdalena Koczkowska et al. Expanding the clinical phenotype of individuals with a 3-bp in-frame deletion of the NF1 gene (c.2970_2972del): an update of genotype–phenotype correlation, *Genetics in Medicine* (2018). DOI:

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