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Opinion Article

Simultaneous Muiti-Gene Panel Analysis for Idiopathic Disease Hypogonadotropic Hypogonadism/Kallamann Disorders Diagnosis

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DESCRIPTION

Hypogonadotropic hypogonadism and anosmia or hyposmia are characteristics of Kallmann Syndrome (KS)/Idiopathic Hypogonadotropic Hypogonadism (IHH), which is caused by aberrant migration of olfactory and gonadotropin-releasing hormone-producing neurons. The cause of KS/IHH has been linked to numerous genes. Sanger sequencing is a time and money-consuming method for evaluating these genes sequentially. A reliable method in the clinical situation has been demonstrated to be the introduction of parallel multigene panel sequencing of small gene panels for the detection of causal gene variations. We describe two cases of hypogonadotropic hypogonadism with a *PROKR2* gene and *KAL1* gene mutation using multiplex PCR for the four gene KS/IHH panel followed by NGS.

The individual who had the *PROKR2* mutation had normal sense of smell and normal odour sensors on imaging. The affected individual has a hypoplastic olfactory bulb and anosmia.

Normosmia is linked to idiopathic hypogonadotropic hypogonadism. Idiopathic hypogonadotropic hypogonadism (IHH) is a rare illness phenotype that is linked to anosmia and known as Kallmann Syndrome (KS). The pathophysiology of KS/IHH has been linked to more than 15 genes. A verified diagnosis of KS/IHH would be made possible by molecular genetic testing of the known genes, which would also aid in understanding the underlying molecular pathways.

The gold standard for genetic diagnosis has been Sanger sequencing-based sequential screening of the KS/IHH genes. However, due to the numerous genes, high expense, and drawn-out cycles of sequential testing, these technologies are challenging to apply, particularly in regard to disorders like KS/IHH with similar clinical symptoms. With its high-throughput sequencing capability, parallel multi-gene testing (also known as next generation sequencing, or NGS) can handle many genes associated with genetic diseases at once. This could help with the differential diagnosis of illnesses linked to known mutation sites and could provide information about new pathogenic pathways.

Example 1: A 22-year-old male, who was born at term to unrelated parents, had underdeveloped secondary sexual characteristics, met all of the expected developmental milestones, and displayed age-appropriate IQ. Seizures, blurred vision, color blindness, hearing loss, or mobility disorders were not present in the past. Prior to presentation, he had been getting intramuscular testosterone injections for 4 years. He had an unimpressive family background and was the oldest of eight siblings—two brothers and six sisters.

He measured 185 cm in height, 63 kg in weight, and had an upper and lower segment ratio of 0.7 (87 cm/98 cm). His neurologic examination was largely normal, and he had a high pitched voice, intact olfactory sensitivity, no facial or axillary hair, pubic hair (Tanner's stage 3), bilateral descended prepubertal testes (2 ml in volume), and extended penile length of 7 cm.

He had biochemical results that suggested hypogonadotropic hypogonadism, including LH-0.69 mIU/ml (N-0.8-7.6 mIU/ml), FSH-0.77 mIU/ml (N-0.7-11.1 mIU/ml), and Testosterone-103 ng/dl (N-270-1030 ng/dl). The olfactory bulb and other hormonal axes were visible on a typical magnetic resonance imaging scan of the brain.

Example 2: A boy, age 18, was diagnosed with delayed pubertal development. There was no sense of smell, no hearing loss, and no uncontrollable motions. With two paternal uncles and one cousin, the family had a history of possible hypogonadism. The upper and lower segment ratio was 0.75, in keeping with eunachoid body proportions, and the height and arm spread were both 163 cm. The stretched penile length was 8 cm, the testes were infantile (1 ml), there was no face or body hair, and a neurological examination revealed no abnormalities. Low testosterone levels of 115 ng/dl (N-270-1030 ng/dl), low FSH levels of 0.85 mIU/ml (N-0.7-11.1 mIU/ml), and low LH levels of 0.74 mIU/ml (N-0.8-7.6 mIU/ml) were found in laboratory tests to establish hypogonadotropic hypogonadism. An olfactory bulb that was hypoplastic and consistent with Kallmann syndrome was seen on a brain MRI.Kallmann syndrome was investigated genetically using simultaneous multigene panel testing that targeted the *KAL1*, *FGFR1*, *PROKR2*, and *PROK2*

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genes. This restricted gene panel was created as a pilot study and includes genes that are more frequently associated with the majority of IHH/KS patients.

The Qiagen gentra kit method was used to extract genomic DNA. Multiplex PCR-based target enrichment for the four genes was then performed. a proven and affordable parallel multigene panel test using multiplex PCR in the clinical context.

A library containing a 200 bp insert was produced by shearing, barcoded adaptor ligation, size selection, and barcoded adaptor ligation of 33 amplicons totaling 23,435 bp that were pooled and processed in the multiplex PCR. Ion one touch emulsion PCR was used to amp up the library, and then Ion one touch enrichment was used to get rid of extra ion beads.

For sequencing on the Ion torrent Personal Genome Machine (PGM) sequencer, the template was put into one of the 314 or 316 ion chips. we were able to sequence the samples with >1000 mean coverage and complete the target with a minimum coverage of 20. As a result, the samples' coding and splice site regions were sequenced completely.

CONCLUSION

Therefore, this strategy might help to explain why phenotypes in KS/IHH people with the same mutation differ. NGS has proven to be a different, more affordable approach for screening individual genes and small gene panels in a clinical environment with the multiplexing option. Additionally, the family members of the detected mutation can be checked, and genetic counseling can be given. In conclusion, multiplex PCR in combination with NGS provides a quick and economical method for locating mutations causing hypogonadotropic hypogonadism. These compact gene panels are adaptable and reliable screening methods for a variety of illnesses, including hypogonadotropic hypogonadism.