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Pangenia Genomics' tailor-made genetic testing service provides peace of mind to family affected by Osteogenesis Imperfecta

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Pangenia Inc.

Pangenia Genomics offers tailor-made genetic testing service to meet customers' needs across different diseases, genetic causes and family structures. In this series, we will share stories of families that we helped with by employing different testing methods and customized counselling service.

Problem

Joe and Amy are expecting their first child. Amy is 10-week pregnant. In addition to common anxieties shared by all parents-to-be, this couple is particularly concerned about a condition called Osteogenesis Imperfecta. They first heard about this name when Joe's 5-year-old nephew Sam was diagnosed of this disease after suffering bone fractures several times. Sam is the only one affected in this big family.

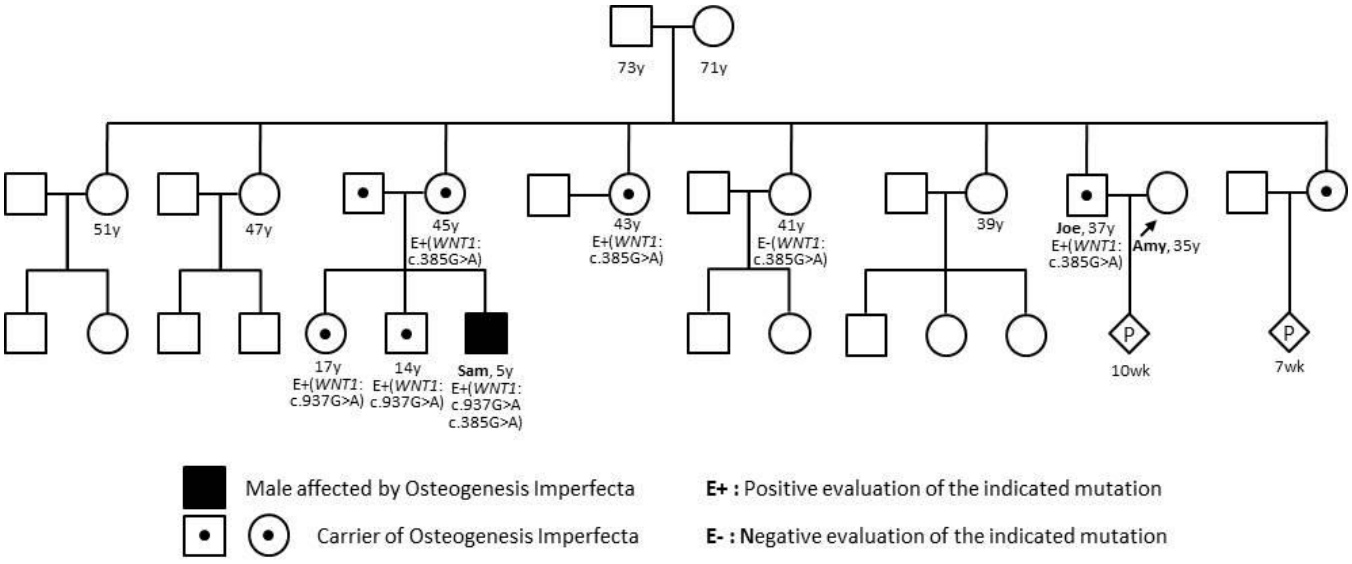

Figure 1 Pedigree of Joe and Amy's family.

It was later found that Sam's disease was caused by defects in a gene called *WNT1*. Each of Sam's healthy parents happens to have one different mutation in *WNT1*. While their first two children only inherited the mutation from their father and are unaffected, their youngest one Sam, unfortunately, inherited both mutations, one from the father and the other from the mother (Joe's sister).

Now, Joe and Amy are worried that the same thing might happen to their child, as Joe also carries the same mutation in *WNT1* as his sister does (Sam's mother), although Amy's side of the family has no history of the disease. They came to Pangenia Genomics, hoping to assess their risk.

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Solution

Osteogenesis imperfecta (OI) is a group of genetic disorders that mainly affect the bones. The term "osteogenesis imperfecta" means imperfect bone formation, and the condition is also known as brittle bone disease (1). People with this condition have bones that break easily, often with no obvious cause or injury. There are more than 20 types of OI, caused by mutations in different genes with varying inheritance pattern (2). In this family's case, the disease is autosomal recessive, requiring two defective copies of the *WNT1* gene to develop (OMIM: 615220).

Based on information initially collected over the phone, scientists at Pangenia Genomics decided that sequencing the entire coding region of the *WNT1* gene in Amy's DNA would be the most cost-effective and efficient method to assess their risk of having a child affected by *WNT1*-related OI.

An appointment was made with Joe and Amy for a pre-test genetic counselling. At the counselling, a PhD-trained genetic counsellor first discussed with the couple about their concerns, reviewed their family history and pedigree together, and introduced basic concepts of genetics, such as DNA, gene, and protein. Based on the family's case, the counsellor further explained the autosomal recessive pattern of inheritance, and introduced the test plan. With the couple's consent, a buccal swab sample was collected from each of them to extract DNA.

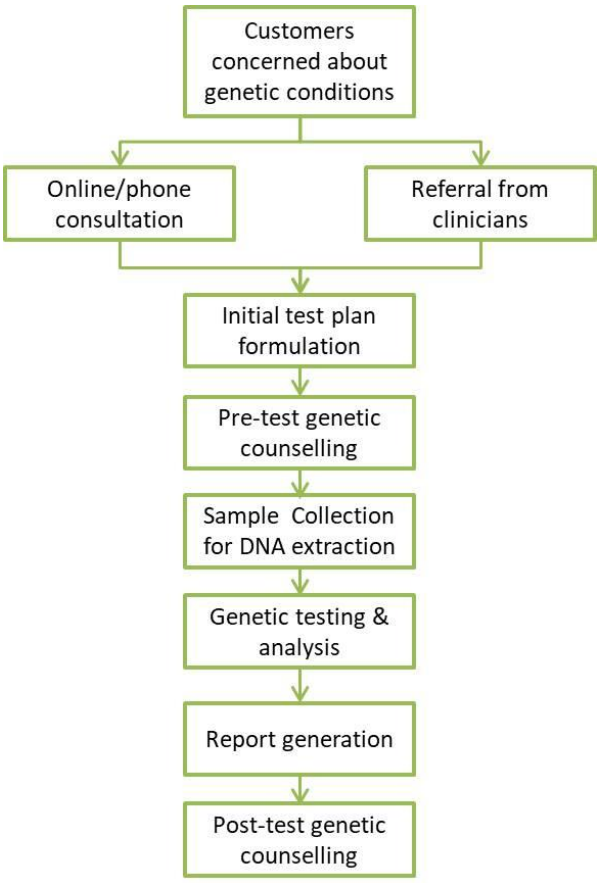

Figure 2 Pangenia Genomics' individualized genetic testing service flowchart

The entire coding region of *WNT1*, including all four exons, 5' and 3' UTR, was amplified from the DNA samples by specifically designed primers, followed by Sanger sequencing. Genetic variants in the targeted regions were identified from each sample by aligning the sequencing result to the reference sequence. A comparison was further made with all known pathogenic mutations in the *WNT1* gene identified through a comprehensive literature and database search. Luckily, no known pathogenic variant in *WNT1* was found in Amy's DNA, and it was confirmed that Joe indeed has the same pathogenic

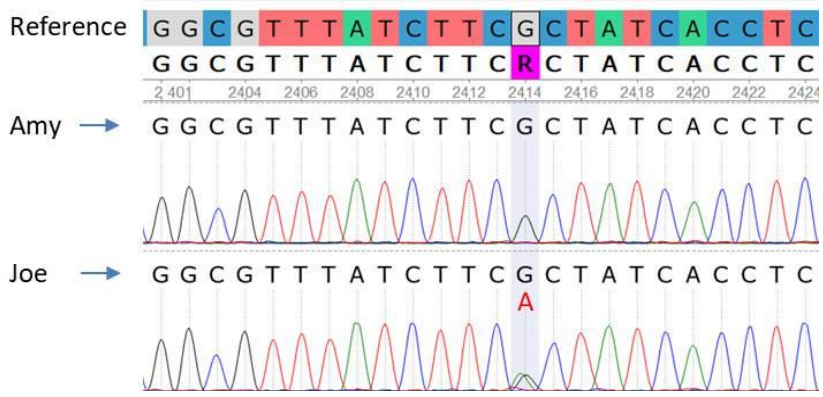

Figure 3 Alignment of Amy and Joe's DNA sequence to the reference sequence shows that Joe has a heterozygous mutation (c.385G>A) in the WNT1 gene while Amy is wildtype at this position.

variant as his sister's.

A post-test genetic counselling was scheduled with Joe and Amy to explain the result. The couple were reassured to know that with a negative result, the residual risk of Amy to carry a pathogenic mutation in *WNT1* is very low, and the risk of their child to be affected by *WNT1*-related OI is even lower, although not completely zero. The child still has a 50% chance of inheriting the pathogenic variant from Joe and becoming an unaffected carrier. It would be his/her decision whether to get tested after he/she grows up, and Pangenia Genomics would be ready to help again then.

References

1. Marini JC, Forlino A, Bächinger HP, Bishop NJ, Byers PH, Paepe AD, et al. Osteogenesis imperfecta. Nat Rev Dis Primer. 2017 Aug 18;3(1):1–19.

2. Etich J, Leßmeier L, Rehberg M, Sill H, Zaucke F, Netzer C, et al. Osteogenesis imperfecta—pathophysiology and therapeutic options. Mol Cell Pediatr. 2020 Aug 14;7(1):9.