Van der Woude syndrome family tree
Predič M, Mujezinović F, Eberlinc A, Šurc A
Štorklja d.o.o., Slovenj Gradec, Slovenia

Objective
Van der Woude syndrome (VW syndrome) is an autosomal dominant syndrome affecting the development of the face. The cause is a mutation of the IRF6 gene, which is located on the long arm of chromosome 1 (1q32.3-q4). The gene provides information for the synthesis of a protein that has an important role in the early development. The protein is active in cells responsible for the development of tissues in the head, face, skin and genitalia. Children with VW syndrome are born with a cleft lip and/or palate and depressions (pits) near the centre of the lower lip, which are usually moist, due to the presence of salivary and mucous glands in the pits. Hypodontia (absent teeth) is the most common anomaly. They are also at an increased risk of delayed language development, learning disabilities and other mild cognitive problems, but the IQ is usually preserved. The popliteal pterygium syndrome (PPS syndrome) is an autosomal dominant genetic malformative disorder characterized by cleft lip with or without cleft palate, contractures of the lower extremities, abnormal external genitalia, syndactyly of fingers and toes, and a pyramidal skin fold over the hallux nail. The syndrome is associated with mutations in the IRF6 (1q32.2-q32.3) gene, involved in the formation of connective and epithelial tissues. Growth and intelligence are expected to be normal, corrective surgery is available. However, the prognosis for physical activity depends on the severity of the pterygium. Genital anomalies may cause infertility.

Methods
This is a case report.

Results
In our family many clinical conditions were identified as a result of the VW and PPS syndrome. Our grandmother had 6 daughters, four of which were stillborn and two were healthy. One of them had a stillborn son. The other daughter had 4 children. One of the girls died 5 days after she was born and another one was born healthy but had cognitive problems and learning disabilities. One of the boys was born healthy and the other one had pits on the lower lip, issues with the salivary gland, and speaking problems due to a healed up tongue. He has 2 children, a healthy son and a daughter with pits on the lower lip, problems with the salivary glands, hypodontia, 4 missing teeth. In both the father and the daughter VW syndrome has been confirmed with genetic tests. The daughter had three pregnancies. Her first born child (in 2011) had congenital palatoschisis, pits on the lower lip, troubles speaking and cryptorchidism. VW syndrome was confirmed. Her second pregnancy in 2013 ended with an IUD at 36 weeks due to preeclampsia and placental abruption. Given the fact of the clinical features, the foetus was likely to have had PPS. Her third pregnancy ended with a C/S at 32 weeks due to preeclampsia. The girl had cleft upper and lower lips and pits on the lower lip. VW syndrome was confirmed. At the age of 8 months she had a reconstructive operation. The development has been normal so far. Genetic tests were carried out in the previously described individuals. Mutations in the IRF6 (16C>T) gene have been confirmed in 5 of them: 4 have VW syndrome and 1 has PP syndrome.

Conclusion
Van der Woude syndrome and popliteal pterygium syndrome are autosomal dominant syndromes in which a mutation of the IRF6 gene is present. Both syndromes are characterised with a cleft lip and/or palate, pits on lower lips and palate, salivary gland and speaking problems, missing teeth, learning disabilities and other mild cognitive problems. PP syndrome can affect the extremities and the external genitalia. In our family, a hereditary mutation in the IRF6 gene has been diagnosed with genetic testing, with 5 members being positive, 4 of which have VW syndrome and 1 - PP syndrome. Facial developmental anomalies can be diagnosed early in utero with ultrasound. At 2-3 months of age, oral and maxillofacial surgeries can fix the palate, the lips and the dental anomalies. The prognosis and treatment of individuals with VW syndrome are excellent. The prognosis of individuals with PP syndrome depends on the severity of the pterygium and the genital anomalies can cause infertility. Otherwise the prognosis of the growth and the intelligence is good.