III Treacher Collins syndrome
(TCS, Franceschetti-Zwahlen-Klein syndrome)

♦ Contact
For questions and more detailed information please feel free to contact Dagmar Wieczorek (dagmar.wieczorek@uni-duesseldorf.de)

♦ OMIM: #154500
♦ Inheritance: autosomal dominant
♦ Prevalence: 1/10.000 to 1/50.000
♦ Genes: TCOF1, POLR1C, POLR1D, others?

Summary:
Face: - malar hypoplasia
Ears: - malformation of auricle
- atresia of external auditory canal
- conductive hearing loss
- preauricular tags
Eyes: - downslanting palpebral fissures
- lower eyelid coloboma
- absence of eyelashes at lower eyelid
Mouth: - macrostomia
- cleft palate
Chin: - mandibular hypoplasia

Characteristic facial features
♦ Clinical features:
All patients with an identified mutation within the TCOF1 gene do present with downward slanting of palpebral fissures and hypoplasia of the zygomatic bones. Hypoplasia of mandibula was noted in 89% and conductive hearing loss in 88% of patients. Variable microtia was present in 78% and lower eyelid coloboma in half of the patients with TCS. Cleft palate and choanal stenosis/ataresia are less frequent with 33% and 28%, respectively. Preauricular tags were observed in 27%. Mental retardation is uncommon.

Variable microtia in TCS

♦ Diagnostic criteria
Diagnosis is based on the clinical findings. Downslanting palpebral fissures and hypoplasia of the zygomatic bones were defined as minimal diagnostic criteria, although some mutation carriers lack these minimal diagnostic criteria. A radiograph of the zygomatic bones, a Water’s projection, helps to establish the clinical diagnosis.

Water’s projection showing hypoplasia of zygomatic bone (arrow)

Without identification of the TCOF1 mutation in a patient one has to be careful to exclude the diagnosis on clinical grounds alone.

♦ Molecular genetics:
Mutations within the TCOF1 gene are causative for TCS. This gene encodes treacle, a phosphoprotein, which inhibits production of mature rRNA, inhibits rDNA gene transcription
and disturbs proliferation and differentiation of specific embryonal cells. Up to now, about 200 mutations have been identified so far with few recurrent mutations. All kinds of point mutations have been reported. There is no distinct mutational hotspot and no larger deletions/duplications have been described. Molecular genetic testing includes direct sequencing of the 26 exons of the TCOF1 gene. An MLPA kit for deletion testing (MRC Holland) is available. Very recently two new genes, causative for TCS, have been identified (Dauwerse et al.): POLR1C and POLR1D.

♦ Genotype phenotype correlation:
In about 90% of patients with typical TCS a mutation within the TCOF1 gene, which is the only known gene to be causative for TCS, is present. There is no obvious genotype phenotype correlation: Both the variation of the clinical manifestations in patients from different families (interfamilial variation) and the variation of the phenotype in patients from the same family (intrafamilial variation), are wide.

 Patients with TCS and mutation within the TCOF1 gene

The functional type of mutation, e.g. nonsense mutation or missense mutation, nor the location of the mutation within the gene is associated with severity of manifestation. Thus, one cannot give a prognosis based on the molecular findings alone. For the two new genes, no genotype phenotype correlation has been described so far.

♦ Genetic counselling
TCS based on TCOF1 and POLR1D mutations is inherited in an autosomal dominant manner. This means, that children of an affected person have a 50% risk to carrier the mutation and to present clinical features of TCS. One cannot predict the severity of the clinical findings based on the clinical findings present in the mother/father or based on the kind of mutation identified in the family. POLR1C mutations are inherited in an autosomal recessive manner with a 25% recurrence risk for siblings of affected patients.

♦ Future perspectives
The CRANIRARE consortium, especially the group in Essen, works on a detailed genotype phenotype correlation in TCS, tries to identify new genes causative for TCS and will try find out genetic modifiers responsible for the extreme variability within families. We are still collecting patients, this means clinical data and DNA or blood samples, for taking part in this project. Two new genes for TCS have been identified in collaboration with our consortium.
They have not been published yet, but mutational screening is possible. Detailed information and consent forms can be downloaded from our website: www.cranirare.eu.

♦ Parent support groups
   Germany: http://www.franceschetti.de/
   UK: http://www.treachercollins.net/index-2.html
   USA: http://www.treachercollinsfnd.org/

♦ References
   Orphanet: http://www.orpha.net/consor/

IV Acrofacial Dysostoses (AFD),
including Miller syndrome (Genée-Wiedemann syndrome) and Nager syndrome

♦ Contact
For questions and more detailed information please feel free to contact Dagmar Wieczorek (dagmar.wieczorek@uni-duesseldorf.de)

♦ OMIM: #263750 for Miller syndrome (postaxial acrofacial dysostosis, POADS, Genée-Wiedemann syndrome; %154400 for Nager syndrome (acrofacial dysostosis type I) and others

♦ Inheritance: autosomal recessive for Miller syndrome and most likely autosomal dominant for Nager syndrome

♦ Prevalence: unknown

♦ Genes: DHODH for Miller syndrome, no known causative gene for Nager syndrome

Summary:
Face: - malar hypoplasia
Ears: - malformation of auricle
- atresia of external auditory canal
- conductive hearing loss
- preauricular tags
Eyes: - downslanting palpebral fissures
- lower eyelid coloboma
- absence of eyelashes at lower eyelid
Mouth: - macrostomia
- cleft palate
Chin: - mandibular hypoplasia
Extremities: - postaxial defects in Miller syndrome, including absence of fifth digits in hands and feet; preaxial defects in Nager syndrome, including absence of radius, radioulnar synostosis, and hypoplasia or absence of the thumbs

♦ Clinical features:
Miller syndrome, or postaxial acrofacial dysostosis or Genée-Wiedemann syndrome, is characterized clinically by severe micrognathia, cleft lip and/or palate, hypoplasia or aplasia of the postaxial elements of the limbs, coloboma of the eyelids, and supernumerary nipples. The craniofacial phenotype resembles that of Treacher Collins syndrome.
Nager syndrome, or acrofacial dysostosis type I, is characterized by limb deformities consisting of absence of radius, radioulnar synostosis, and hypoplasia or absence of the thumbs. The mandibulofacial dysostosis is characterized mainly by severe micrognathia and malar hypoplasia and also resembles that of Treacher Collins syndrome.
Facial features in a patient with Miller syndrome, compound heterozygous for mutations within the *DHODH* gene

Limb anomalies in a patient with Miller syndrome, compound heterozygous for mutations within the *DHODH* gene

Facial features in a patient with Nager syndrome

Limb anomalies in a patient with Nager syndrome
♦ **Diagnostic criteria**
Diagnosis is based on the combination of mandibulofacial dysostosis in combination with postaxial defects, leading to the diagnosis of Miller syndrome, or in combination with preaxial defects, leading to the diagnosis of Nager syndrome. Other acrofacial dysostosis are much rarer.

♦ **Molecular genetics:**
The clinical diagnosis Miller syndrome can be confirmed by mutational analysis of the DHODH gene. Only few patients with mutations within the DHODH gene have been published so far (Ng et al., 2010). Further analysis is pending, especially to establish a genotype-phenotype correlation.

♦ **Genotype phenotype correlation:**
No genotype phenotype correlation are known for Miller and Nager syndromes.

♦ **Genetic counselling**
Miller syndrome is inherited in an autosomal recessive manner. This means, that children of an affected person will inherit a mutant allele but will present the phenotype only if he inherits another mutant allele from the other parent. This risk is very low, but the recurrence risk for siblings is 25%.

Nager syndrome is probably inherited in an autosomal dominant manner. Consequently, children of an affected person have a 50% risk to inherit the mutation and to present clinical features of Nager syndrome. At the moment, one cannot exclude autosomal recessive inheritance of Nager syndrome, as siblings with healthy parents have been described and the molecular basis has not been identified so far. In this case, the recurrence risk for sibs would be 25%.

♦ **Future perspectives:**
The CRANIRARE consortium, especially the group in Essen, ascertains genotype phenotype correlations in Miller syndrome and tries to identify genes causative for Nager syndrome. We are still collecting patients, this means clinical data and DNA or blood samples, for taking part in this project. Detailed information and consent forms can be downloaded from our website: www.cranirare.eu.

♦ **Parent support groups:**
Germany: None

♦ **References:**
GeneClinics: none


Orphanet: http://www.orpha.net/consor/