999 04 Rar

You or a loved one has received a diagnosis. Now what? Gaining knowledge, connecting with advocacy organizations, and learning about treatment at places like the Centers for Excellence are the next steps. We pioneered Patient Assistance Programs in 1987. Today, NORD programs include free drug, co-pay and premium assistance, travel/lodging assistance for clinical trials, expanded or emergency access, and more. NORD believes in the power of collaboration. It is the foundation upon which NORD was built. NORD works with partners in the patient community, government, academia, and industry who share the ultimate goal of identifying, treating, and curing rare diseases. In addition to the partnerships listed below, NORD works with many national partners to achieve its advocacy goals. NORD is a registered 501(c)(3) charity organization. Please note that NORD provides this information for the benefit of the rare disease community. NORD is not a medical provider or health care facility and thus can neither diagnose any disease or disorder nor endorse or recommend any specific medical treatments. Patients must rely on the personal and individualized medical advice of their qualified health care professionals before seeking any information related to their particular diagnosis, cure or treatment of a condition or disorder. **Warranty**

The warranty for new as well as unworn and used items is 24 months from delivery of the goods to the buyer. Claims for damages are excluded from this and are governed by the statutory provisions. Otherwise, the claims of the buyer against the seller for defects are governed by the statutory provisions.

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Before used watches are put back on sale, they are subjected to a detailed inspection and if necessary, a comprehensive service by our watchmaker. We always strive to maintain the excellent

reputation in the industry that we have earned over the years. * compared to the manufacturer's recommended retail price.
All prices incl. VAT in Euro plus shipping costs. Used items are taxed according to § 25 A UStG, VAT is not shown.
Gross prices may vary depending on the destination country.
Gross pricing with the surcharge of the VAT charge in the respecting destination country.
** Information on the calculation of the delivery time **The site is secure.**
The **https://** ensures that you are connecting to the official website and that any information you provide is encrypted and transmitted securely. 1Sorbonne Universités, UPMC Université Paris 06, CNRS, Laboratoire de Biologie du Développement de Villefranche-sur-Mer, Observatoire Océanologique de Villefranche-sur-Mer, 181 Chemin du Lazaret, 06230 Villefranche-sur-Mer, France During vertebrate development, the RA degrading enzymes of the CYP26 subfamily play critical roles in the formation of an anterior-posterior (A-P) RA gradient as well as in the compensation of RA level fluctuations by oxidizing RA into biologically inactive compounds [17]. They are thus characterized by dynamic, yet highly specific, developmental expression patterns in vertebrates [18], with CYP26A1, for example, being expressed in the anterior ectoderm in the early embryo and subsequently becoming localized, amongst other tissues, to the hindbrain, the pharyngeal arches, and the tail bud. Similarly, both CYP26B1 and CYP26C1 are detectable in specific rhombomeres of the hindbrain and in pharyngeal arches as well as in fin and limb buds of the developing embryo [18]. Concomitantly, the loss of CYP26 function has been associated both with A-P patterning defects, most prominently in the developing central nervous system (CNS) and the mesoderm, and an increased sensitivity to

RA teratogenicity [19]. For instance, CYP26A1 knockout mice are characterized by a posteriorization of the hindbrain and the vertebral column, and CYP26B1 genetic ablation leads to craniofacial and limb malformations [20]. Interestingly, while the loss of CYP26C1 alone does not result in overt anatomical abnormalities [21], the combined removal of CYP26C1 with either CYP26A1 or CYP26B1 induces phenotypes that are more severe than those aforementioned, thereby suggesting that CYP26C1 plays an important cooperative role in the CYP26-mediated control of endogenous RA levels during vertebrate development [19, 21]. In line with this cooperative action of CYP26 enzymes, the vertebrate RA signaling system in general is characterized by complex feedback mechanisms that are mediated, either indirectly or directly, by RAR/RXR-dependent signaling. As an example of an indirect regulation, it has been shown that, in the vertebrate trunk, RA, generated by RALDH activity, represses and confines FGF8 expression to rostral and caudal domains (i.e. to the heart- and tail bud-associated progenitor fields) [16]. This action is mediated by RAR/RXR heterodimers binding to a repressive DR2 RARE located upstream of the FGF8 gene [22, 23] that, in turn, activates CYP26 expression both anteriorly and posteriorly to limit the extent of RA activity [16, 24, 25]. In addition, the expression of CYP26A1 and CYP26B1 have been shown to be dependent on RA activity, thereby generating a CYP26-controlled negative feedback loop in RA sensitive tissues to reduce the overall amount of available RA [9, 18, 26, 27]. For CYP26A1, this regulation is directly mediated by RAR/RXR heterodimers binding to DR5 RAREs in the promoter region, while for CYP26B1 this control seems to be indirect [26, 27]. Note further that the vertebrate CYP26C1 gene is likely to contribute differently than its paralogs to this negative feedback system, as

CYP26C1 expression is actually downregulated following RA stimulation [9]. The intricate molecular mechanisms controlling the catabolism of endogenous RA during vertebrate development likely arose at the base of this lineage following the whole genome duplication (WGD) events that took place during early vertebrate diversification [28, 29]. Therefore, the evolutionary elaboration of the RA signaling system in general seems to be tightly linked to the duplication of RA metabolism genes. The so-called DDC model (for Duplication-Degeneration-Complementation) predicts three possible outcomes following duplication of a gene: non-functionalization (i.e. the loss of one of the duplicates), neo-functionalization (i.e. one of the copies retains the ancestral role, while the other duplicate assumes a novel functionality) or sub-functionalization (i.e. both duplicates assume a part of the function of the single ancestral gene) [30, 31]. While the model predicts that the most likely outcome following duplication of a gene is the loss of one of the duplicates (i.e. non-functionalization), very clear examples for the neo-functionalization and the sub-functionalization of duplicated genes remain scarce [32, 33]. Within vertebrates, we found three CYP26 paralogs in both cyclostomes (CYP26A1, CYP26B1/C1a, and CYP26B1/C1b) and gnathostomes (CYP26A1, CYP26B1, and CYP26C1). Multiple CYP26 paralogs were also identified in most invertebrates species studied (two in Capitella teleta, Ciona intestinalis, Lottia gigantea, Priapulus caudatus, and Saccoglossus kowalevskii, three in B. lanceolatum, B. floridae, B. belcheri, Crassostrea gigas, and Ptychodera flava, and four in Lingula anatina), with the notable exceptions of the cephalopod Octopus bimaculoides and the sea urchin Strongylocentrotus purpuratus, each of which possesses only a single CYP26 gene (Additional file 1). The results of the phylogenetic analysis (Fig. 1 and Additional file 2), obtained

with both the Bayesian Inference (BI) and the Maximum Likelihood (ML) methods, suggested an early phylogenetic separation of the vertebrate CYP26A1 sequences from the vertebrate CYP26B1/C1 sequences. Vertebrate CYP26A1 and CYP26B1/C1 thus formed two independent clades within the CYP26 subfamily, both of which being strongly supported: 0,91/96 (posterior probability/bootstrap percentage) for CYP26A1 and 1/99 for CYP26B1/C1. Within these two vertebrate CYP26 clades, the cyclostome sequences consistently branched at the base: Lethenteron japonicum CYP26A1 at the base of the vertebrate CYP26A1 (0,96/98) and CYP26B1/C1a and CYP26B1/C1b from L. japonicum and Petromyzon marinus at the base of the vertebrate CYP26B1/C1 (0,7/58). Within the vertebrate CYP26B1/C1 clade, the association of the gnathostome CYP26B1 sequences (0,73/58) was less robustly supported than that of the gnathostome CYP26C1 sequences (1/95), which might be related to the presence of chondrichthyan-specific CYP26B1 duplicates (CYP26B1 and CYP26B2 from Callorhinchus milii and Leucoraja erinacea) disrupting the base of the CYP26B1 branch. Of note, while our analysis revealed the general presence of CYP26A1, CYP26B1, and CYP26C1 paralogs in chondrichthyans, we were unable to identify a CYP26A1 gene in C. milii and a CYP26C1 gene in L. erinacea. Altogether, these data suggest that the diversification of vertebrate CYP26 genes was a highly complex process, involving WGD, lineage-specific duplications as well as secondary gene losses. Phylogenetic analysis of the CYP26 subfamily. Diagrammatic summary of Bayesian Inference (BI) and Maximum Likelihood (ML) analyses of the phylogenetic relationships within the CYP26 subfamily, with CYP51 used as outgroup. The detailed tree is shown in Additional file 2 and sequence information is given in Additional file 1. Branch

lengths are representative of the amino acid substitution rate and branch support is indicated at each major node as posterior probabilities (PP) for the BI tree and as bootstrap percentages for the ML tree. Furthermore, the total number of sequences (seq.) and species (sp.) is provided for the CYP26 subfamily

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